



HAL
open science

Pathogens, microbiome and the host: emergence of the ecological Koch's postulates

Pascale Vonaesch, Mark Anderson, Philippe Sansonetti

► **To cite this version:**

Pascale Vonaesch, Mark Anderson, Philippe Sansonetti. Pathogens, microbiome and the host: emergence of the ecological Koch's postulates. *FEMS Microbiology Reviews*, 2018, 42 (3), pp.273-292. 10.1093/femsre/fuy003 . pasteur-02305645

HAL Id: pasteur-02305645

<https://pasteur.hal.science/pasteur-02305645>

Submitted on 4 Oct 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

Pathogens, microbiome and the host: emergence of the ecological Koch's postulates

Pascale Vonaesch, Mark Anderson, Philippe J. Sansonetti

Abstract

Even though tremendous progress has been made in the last decades to elucidate the mechanisms of intestinal homeostasis, dysbiosis and disease, we are only at the beginning of understanding the complexity of the gut ecosystem and the underlying interaction networks. We are also only starting to unravel the mechanisms that pathogens have evolved to overcome the barriers imposed by the microbiota and host to exploit the system to their own benefit. Recent work in these domains clearly indicates that the “traditional Koch's postulate”, which state that a given pathogen leads to a distinct disease, are not valid for all “infectious” diseases, but that a more complete and complex interpretation of the Koch's postulate is needed in order to understand and explain them.

This review summarizes the current understanding of what defines a healthy gut ecosystem and highlights recent progress in uncovering the interplay between the host, its microbiota and invading intestinal pathogens. Based on these recent findings, we propose a new interpretation of the Koch's postulate, that we term “ecological Koch's postulate”.

One sentence summary

This review summarizes the current understanding of what defines a healthy gut ecosystem, highlights recent progress in uncovering the interplay between the host, its microbiota and invading intestinal pathogens and, based on the most recent findings in this field, proposes a new interpretation of the Koch's postulate, the “ecological Koch's postulates”.

Introduction

Traditionally, pathogens have been viewed as armed warriors, fighting against the host (Sansonetti 2004). However, it is well established that not everyone that has ingested a typical infectious dose of a given pathogen, for example *Salmonella* Typhimurium, *Helicobacter pylori* or *Campylobacter jejuni*, will develop disease. There also is increasing evidence for asymptomatic carriage of enteric pathogens (Kotloff *et al.* 2013; Breurec *et al.* 2016; Rendremanana *et al.* 2016). In addition, it is also known that antibiotic use leads to an increased susceptibility to infection by enteropathogens (BOHNHOFF, DRAKE and MILLER 1954; MILLER, BOHNHOFF and DRAKE 1954; Barthel *et al.* 2003; Sekirov *et al.* 2008; Van der Waaij, Berghuis-de Vries and Lekkerkerk-van der Wees 2009). These observations led to an extended concept that acknowledged the role of the microbiota in protecting the host against pathogens, referred to first as “microbial barrier” and later as “colonization resistance” (Ducluzeau and Railbaud 1989).. Bacteria can have an inhibitory effect on phylogenetically unrelated species/groups of bacteria (“interspecies barrier effect”). This was demonstrated as early as the late 1970s through work showing that pre-colonization of axenic mice with *Escherichia coli* could inhibit the colonization of *Shigella flexneri* (Ducluzeau *et al.* 1977). Further, bacteria from the same species/group can have an inhibitory effect on the installation of their peers (“intra-species barrier effect”). This concept was shown in the 1980s in studies using closely related *Clostridium* species (Corthier and Muller 1988). Several studies have also assessed the role of the prokaryotic microbiota on

42 the susceptibility to viral infections. Indeed, susceptibility to rota- and norovirus seems to depend, at least in part,
43 on the composition of a host's prokaryotic microbiota (Rodríguez-Díaz *et al.* 2017), as do sexually transmitted
44 diseases, such as for example Human Immunodeficiency Virus (HIV, (Nunn *et al.* 2015)), Cervical Human
45 Papillomavirus (HPV, (Shannon *et al.* 2017b)) or Herpes Simplex Virus (Shannon *et al.* 2017a), in the context of a
46 changed vaginal microbiota. For many years, the exact mechanisms underlying the phenomenon of colonization
47 resistance remained unclear. However, work over the last decades has demonstrated that the microbiota forms a
48 complex ecosystem and interacts with the host and invading pathogens in a dynamic manner.

49
50 The intestinal microbiota is composed of trillions of organisms belonging to hundreds of different species (Eckburg
51 *et al.* 2005; Yatsunenko *et al.* 2012), reviewed in (Cho and Blaser 2012). While the majority belongs to the
52 prokaryota (bacteria and *archae*), it also comprises viruses (including phages) and different eukaryotes, especially
53 yeasts and protists (Parfrey, Walters and Knight 2011; Ursell *et al.* 2012; Clemente *et al.* 2012; Parfrey *et al.* 2014;
54 Hamad, Raoult and Bittar 2016). Members of the gram-negative *Bacteroidetes* and the gram-positive *Firmicutes*
55 dominate the bacterial community residing in the gut. Less abundant groups include members of the
56 *Proteobacteria*, the *Verrucomicrobia*, the *Tenericutes*, the *Defferibacteres* and the *Fusobacteria* (Eckburg *et al.*
57 2005; Yatsunenko *et al.* 2012). In areas of the world without developed water supplies, the intestinal microbiota can
58 also include multicellular organisms, for example helminths (Giacomin, Agha and Loukas 2016).

59
60 Several different ecosystems formed by microbial communities in and on the body (e.g. the skin microbiota, the
61 gastric microbiota, the vaginal microbiota), engage in a constant crosstalk with the human host (Costello *et al.*
62 2009). The microbes belonging to each of these communities are often specific and adapted to living in their
63 particular environment (e.g. anaerobic bacteria in the gut). This review will focus on the interactions found in the
64 intestine, relying mainly on data gathered in laboratory mice. Even though similar mechanisms are at work in all
65 ecosystems found in and on the human host, a complete description would go beyond the scope of this review. In
66 this review, we will summarize the current understanding of what defines a healthy gut ecosystem and highlight
67 recent progress in uncovering the interplay between the host, its microbiota and invading intestinal pathogens.

68

69 **The gut ecosystem- species abundance, chance, and the environment**

70 It has been hypothesized that at least some of the gut microbes have co-evolved and/or co-speciated with
71 mammals (Groussin *et al.* 2017). However, co-occurrence of microbes and their host, even if they affect each
72 others fitness, does not necessarily mean a shared evolutionary history but can also be forged by numerous other
73 mechanisms, including unidirectional selection (Moran and Sloan 2015). Regardless of their evolutionary origin,
74 most mammals have a distinct assembly of microorganisms organized into a complex social network, which is
75 remarkably robust and resilient to aggressions from, for example, allogenic/pathogenic intruders.

76 Two major competing ecological theories have been proposed to explain how microbial communities are organized
77 and maintained, i.e. how communities are assembled. The first, termed niche theory (Chase and Leibold 2004), is
78 based on deterministic processes and assumes that each species occupies a given realized niche (i.e. a particular
79 position in the abiotic and biotic space) due to its species-specific properties that define its fundamental niche. The
80 grounding of this theory for microbes lies in the work of Martinus Willem Beijerinck (1851–1931) and in the famous
81 statement: "Everything is everywhere, but the environment selects" (O'Malley 2007).

82 On the other hand, the "neutral theory" is based only on stochastic processes and was proposed at the beginning
83 of the century by Hubbell (Hubbell [2001. The Unified Neutral Theory of Biodiversity and Biogeography, Princeton
84 University Press, Princeton, NJ]). The theory suggests that local communities are assembled independently of

85 species fitness differences, hence assuming that all individual have the same fitness. Further, the neutral theory
86 claims that the fitness differences between species are not larger than the fitness differences within a given
87 species. Competition is therefore not the driving factor of the observed community structure (“all species are
88 equivalent; they have the same chance of immigration, extinction and speciation”). Of course, these two theories
89 are not mutually exclusive and can act in parallel to drive microbial community assembly at (i) different spatial
90 scales (e.g. at different locations in the intestine) or (ii) in different environments e.g. in different location on or in
91 our body.

92 Testing the fit of both theories on intestinal microbial communities has been hampered by the inability to culture
93 many of the present species and hence define the composition of the microbial communities. With the rise of
94 advanced sequencing methodologies and the decreasing associated costs, large datasets have been put together
95 that now allow testing of these theories on highly complex communities, for example the intestinal microbiota. In
96 studies conducted in the past few years, evidence is emerging that the intestine is not only an ecosystem based on
97 Hubbell’s “neutral theory” where each member has the same fitness (Costello *et al.* 2012). Indeed the Human
98 Microbiome Project, which screened several hundred stool samples from individuals residing in the United States,
99 revealed that the microbiota of only one individual showed a composition structure consistent primarily with the
00 “neutral theory” (Li and Ma 2016). Instead, modelling confirmed that the microbiota is governed mainly by
01 deterministic processes, including environmental factors (Li and Ma 2016). This, however, does not exclude that
02 both processes are shaping the communities at the same time and clearly more work is needed to elucidate these
03 questions.

04 The microbiome is shaped by different deterministic forces, including maternal transmission at birth (Dogra *et al.*
05 2015; Frese and Mills 2015; Rutayisire *et al.* 2016; Stokholm *et al.* 2016; Edwards 2017), nutrition (Turnbaugh *et al.*
06 2006; De Filippo *et al.* 2010; Muegge *et al.* 2011; David *et al.* 2014; Kashtanova *et al.* 2016; Donovan and
07 Comstock 2016; Edwards 2017; Donovan 2017; Araújo *et al.* 2017), host genetics (Leamy *et al.* 2014; Camarinha-
08 Silva *et al.* 2017), the use of different food additives or drugs (Dethlefsen *et al.* 2008; Modi, Collins and Relman
09 2014; Chassaing *et al.* 2015; 2017; Namasivayam *et al.* 2017; Pourabedin *et al.* 2017; Uebanso *et al.* 2017) and
10 infection (Hoffmann *et al.* 2009; Hill *et al.* 2010; Braun *et al.* 2017). The immune system’s dynamic IgA host
11 response to the microbiota (Suzuki *et al.* 2004; Peterson *et al.* 2007; Slack *et al.* 2012; Macpherson *et al.* 2012;
12 Pabst, Cerovic and Hornef 2016; Moor *et al.* 2017) and its action to hamper bacteria from interacting with the gut
13 tissue (“immune exclusion”) and to grow (“enchained growth”, (Moor *et al.* 2017)), as well as other innate and
14 adaptive immune mechanisms, also have an important role in controlling the microbiota and shaping the
15 community structure (Slack *et al.* 2009; Ivanov *et al.* 2009; Macpherson, Geuking and McCoy 2012; Schnupf,
16 Gaboriau-Routhiau and Cerf-Bensussan 2013; Spasova and Surh 2014; Rescigno 2014; Kato *et al.* 2014; Bang *et al.*
17 2014; Goto *et al.* 2014; Dowds, Blumberg and Zeissig 2015; Atarashi *et al.* 2015; Furusawa, Obata and Hase
18 2015; Ivanov 2017).

19 The different environments that individuals and their gut ecosystem experience therefore select for a particular set
20 of strains within the microbiota. However, a core bacterial genetic pool can be defined that is common to all
21 individuals (Ley *et al.* 2006; Qin *et al.* 2010). Scarce resources, such as nutrients and access to a given niche are
22 limiting factors for growth in this confined ecosystem (reviewed in (Stecher and Hardt 2011)). These thoughts were
23 already, in part, formulated earlier in the “nutrient niche theory”, a refined niche theory established by Rolf Freter in
24 1983 (Freter *et al.* 1983a; 1983b; 1983c). The “nutrient niche theory” or “niche co-existence theory” stresses that
25 ecological niches are defined by the available nutrients. Further, Freter asserted that a given species can only
26 establish itself if it is using at least one of the limiting nutrients in the most efficient way. He also hypothesized that
27 only a few nutrients are responsible for shaping the whole community as they limit the growth potential of the whole

28 ecological niche (Freter *et al.* 1983a; 1983b; 1983c). Although Freter's classic "nutrient niche theory" is useful to
29 understand some of the mechanisms occurring in the gut ecosystem, it is not reflective of the entire complexity
30 observed. Indeed, several cases of mixed-substrate utilization and metabolic flexibility have been described. For
31 example, *E. coli* and *Salmonella spp.*, can thrive on tetrathionate, nitrate, succinate, 1,2-propanediol, or
32 ethanolamines among others, and therefore rapidly adapt to a changing environment in the intestine during
33 inflammation (Thiennimitr *et al.* 2011; Winter *et al.* 2013; Rivera-Chávez *et al.* 2016a; Faber *et al.* 2017; Spiga *et al.*
34 2017). There are also a few examples of nutritional cooperation between gut microbes described (Rakoff-Nahoum,
35 Foster and Comstock 2016).

36
37 To date, the complexity of the gut ecosystem and the underlying interaction networks are only beginning to be
38 understood. We are also only starting to unravel the mechanisms that pathogens have evolved to overcome the
39 barriers imposed by the microbiota and host to exploit the system to their own benefit.

41 **Hallmarks of homeostasis**

42 Intestinal pathogens are mainly ingested through consumption of contaminated food or water. During their travel to
43 their preferred "niche", they encounter several obstacles and barriers imposed by the members of the ecosystem,
44 which impede colonization and invasion by intruders. Most pathogens must replicate in the gut lumen in order to
45 elicit disease (Ackermann *et al.* 2008). Below, we discuss the primary mechanisms in a healthy host that hamper
46 pathogens from overcoming these obstacles and cause disease (see Figure 1).

48 ***Stomach acidity and bile acids***

49 After ingestion and resisting salivary enzymes, the first major barrier to infection is the low pH environment of the
50 stomach. Indeed, pharmacological perturbation of stomach acidity through the use of proton-pump inhibitors leads
51 to an increased pH and greater susceptibility to enteric infections (reviewed in (Eusebi *et al.* 2017)). After surviving
52 the stomach, the pathogen then enters the duodenum, where it is exposed to the massive influx of bile acids, that
53 are produced by the liver and released by the gall bladder. The primary bile acids are involved in lipid absorption
54 from food. They also show toxicity towards given groups of bacteria. For example, in rats treated with cholic acid,
55 phylum-level alterations in the composition of the gut microbiota were observed with an increase in *Firmicutes* and
56 a concomitant decrease in *Bacteroidetes*. Cholic acid feeding also led to a less complex composition of the
57 microbiota with overrepresentation of members of the classes *Clostridia* and *Erysipelotrichi* (Islam *et al.* 2011).
58 Therefore, bile acids shape the resident bacterial community by promoting the growth of bile acid-metabolizing
59 bacteria and by inhibiting in turn, the growth of bile-sensitive bacteria. Several studies in patients suffering from
60 biliary obstruction, who display blocked bile flow into the small intestine, have shown an association with bacterial
61 overgrowth and translocation of bacteria in the small intestine (Clements *et al.* 1996). It was also shown that this
62 phenotype can be reversed by the administration of bile acids (Lorenzo-Zúñiga *et al.* 2003). Bile acids thus play an
63 important role in regulating the microbiota in the small intestine.

64 Over the length of the intestinal tract, these primary bile acids are metabolized by the microbiota to over 50
65 different secondary bile acids. One of the possible transformations is deconjugation of bile acids through
66 extracellular bile salt hydrolases (BSHs). BSHs are encoded by different members of the microbiota, especially in
67 members of the *Firmicutes*, *Bacteroidetes* and some *Actinobacteria*. The deconjugated secondary bile acids show
68 less toxicity towards the microbiota than the primary bile acids. Bile acids can also be oxidized and epimerized
69 (transformation in between two stereoisomers) at specific hydroxyl-groups through transformation by 3- α , 7- α , or
70 12- α hydroxysteroid dehydrogenases. The secondary bile acids have an important role in gut homeostasis

71 by inhibiting inflammation (reviewed in (Ridlon *et al.* 2014; Winston and Theriot 2016; Wahlström *et al.* 2016)). A
72 recent study has shown that disuccinimidyl suberate (DSS)-mediated colitis was ameliorated in the presence of
73 ursodeoxycholic acid or its taurine- or glycine-conjugated derivatives. Even though daily administration of these bile
74 acids did not restore the full diversity of the microbiota to pre-DSS levels, specific species, such as *Akkermansia*
75 *mucoiphila* and the *Clostridium* cluster XIVa, were less depleted upon DSS treatment and the ratio of *Firmicutes* to
76 *Bacteroidetes* remained normal (Van den Bossche *et al.* 2017). Secondary bile acids have also been implicated in
77 colony resistance, for example resistance against infection by *Clostridium difficile* (Winston and Theriot 2016; Van
78 den Bossche *et al.* 2017). Reducing the pool of secondary bile acids through antibiotic treatment relieves
79 colonization resistance towards *C. difficile* and enhances spore germination. A later study demonstrated that the
80 colonization resistance was mediated by a close relative, *Clostridium scindens*, through the production of the 7- α -
81 dehydroxylated bile acids lithocholic acid and deoxycholic acid (Studer *et al.* 2016).
82

Box 1- Colonization resistance

Colonization resistance describes a phenomenon observed in the human gut as well as in many other ecosystems, that invading pathogens (and other organisms) face resistance against establishing themselves in this densely populated space. This “colonization resistance” is due to several factors, namely competition for nutrients or direct inhibition by chemical compounds or “molecular weapons”, for example Type 6 secretion systems and translocated toxins or other toxins. Colonization resistance can be breached by interfering with the equilibrium of the ecosystem, for example by the administration of antibiotics or by infection.

Short-chain fatty acids and other mechanisms of colony resistance through direct inhibition

In the colon, complex carbohydrates present in the food or eaten in the form of prebiotics are metabolized by the resident microbiota into short chain fatty acids (SCFA), the three most abundant being acetate, propionate and butyrate. Acetate and propionate are produced mainly by members of the *Lactobacilli* and *Bifidobacteriae*. Butyrate is produced by bacteria of the phylum *Firmicutes*, for example *Roseburia* spp. and *Faecalibacterium*

94 *prausnitzii*, or different members of the genus *Clostridium* (Ramirez-Farias *et al.* 2009; Rivière *et al.* 2016). Acetate
95 triggers anti-inflammatory and anti-apoptotic responses in host epithelial cells, which leads to protection in the gut
96 against colonization with pathogenic bacteria like *Enterobacteriaceae* and *Clostridiae* (Fukuda *et al.* 2011).
97 Recently, butyrate production by *Clostridia* species has been implicated in colonization resistance against *S.*
98 *Typhimurium* (Rivera-Chávez *et al.* 2016b). The authors show that either through antibiotic treatment, or to a lesser
99 extent, through *Salmonella* infection and the action of the *Salmonella* Type Three secretion system (T3SS) and
00 associated virulence factors, a depletion of butyrate-producing *Clostridia* species occurs in the intestine of affected
01 mice. This then leads to an increased epithelial oxygenation and subsequently aerobic expansion of *S.*
02 *Typhimurium*. The colonization resistance against *Salmonella*, alongside an anaerobic epithelial environment, could
03 be restored through gavage of the mice with tributyrin, a butyrate metabolic precursor, clearly demonstrating the
04 inhibitory role of butyrate on *Salmonella* invasion.

Colonization resistance and maintenance of the ecosystem through competition and cooperation

In addition to direct inhibition, invading bacteria must also contend with limited available nutrient resources. Nutrient availability in the gut varies with food intake and time of day. Therefore, the microbiota faces a constantly changing environment. In a healthy, fully established intestine, all nutrient niches are occupied and incoming species must utilize methods to displace resident species from their established niches in order to create their own niche. A recent study analysing the gene expression of co-occurring human gut microbes showed that for 41% of all co-occurring species the presence of one of the organisms was associated with an altered transcriptional profile in the other, the most affected genes being involved in nutrient uptake and anaerobic respiration (Plichta *et al.* 2016).

14 This suggests that nutrient niche partitioning is prevalent within the gut ecosystem.
 15 Furthermore, early in development or after a destabilization of the equilibrium, e.g. by an infection or antibiotic
 16 treatment, the microbiota has to re-establish itself. In this context, a so called “priority effect” is observed, whereby
 17 the first re-colonizing species establish a large colony which hampers the subsequent re-establishment of
 18 otherwise fully adapted species to the other’s niche (Fukami and Nakajima 2011) (reviewed in (Pereira and Berry
 19 2017)). This leads to fierce competition for nutrients within the microbiota and by invading pathogens. It also
 20 suggests that most of the interactions in the gut are based on competition. To date, cooperation is a type of
 21 interaction only very rarely described and does not seem to be as successful as competition in a crowded and
 22 competitive environment such as the intestine (Foster and Bell 2012). In one study of cooperation within the gut
 23 microbiota, *Bacteroides ovatus* was shown to produce two outer surface glycoside hydrolases, which digest
 24 complex carbohydrates, for example inulin. However, these two hydrolases are not necessary for *B. ovatus* to grow
 25 on inulin. Rather, other members of the microbiota, such as *Bacteroides vulgatus*, grow on the inulin breakdown
 26 products produced by *B. ovatus*. *B. ovatus* then uses products produced by *B. vulgatus* and both species flourish
 27 (Rakoff-Nahoum, Foster and Comstock 2016).
 28 Despite the rare documented cases of cooperation, most microbial interactions in the intestine are indeed
 29 competitive.
 30 The metabolic landscape is shaped by a few so-called “keystone species” or “keystone taxa”, which have a large
 31 impact on the rest of the community by degrading initial substrates and making these accessible to many other
 32 species. Keystone species may only be detectable in very low relative abundance, however their outsized effect on
 33 the global microbial composition makes them a “keystone” of the microbiota (reviewed in (Pereira and Berry 2017)).
 34 One example of “keystone species” is *Akkermansia muciniphila*, which degrades secreted host mucus into
 35 products that are then accessible to other bacteria, such as *B. vulgatus* (Png *et al.* 2010). Hydrogen and
 36 sulfate/sulfite consuming species represent an example of a “keystone taxa” due to their regulatory effect on the
 37 fermentative activity of other species (Carbonero *et al.* 2012; Rey *et al.* 2013). Yet, some of these taxa, for example
 38 *Ruminococcus*, have evolved to degrade mucin without giving other species access to the degradation products.
 39 The intramolecular transsialidase produced by *R. gnavus* releases 2,7-anhydro- Neu5Ac instead of sialic acid from
 40 mucin and other glycoproteins, a product that cannot be utilized by other species (Tailford *et al.* 2015b) (reviewed
 41 in (Tailford *et al.* 2015a)).
 42 This nutritional limitation represents a strong barrier for the niche establishment of invading species.

243

244

Mucus layer

The mucus layer forms a physical barrier to the microbiota, preventing direct interaction with the epithelium (reviewed in (McGuckin *et al.* 2011; Pelaseyed *et al.* 2014)). In the gut, the goblet cells are responsible for the secretion of the mucin MUC2, which forms a disulfide cross-linked network. This network is comprised of an inner layer, which is tightly attached to the epithelium and mainly impenetrable to bacteria, as well as a looser, outer layer. This outer layer harbours a specific community of bacteria, feeding on the mucus (Li *et al.* 2015) and

Box 2- The concept of the nutritional/dietary niche

A nutritional niche describes the nutrient sources which are available to, and usable by, a given set of organisms at a given time and space. The nutritional niche therefore defines if an organism is capable of establishing itself in a given place or not. The concept of the nutritional niche is a sub-definition of the ecological concept. The concept has been first proposed by Rolf Freter (Freter’s nutritional niche theory) and has subsequently been adapted to take into account the instable flux of nutrients in open ecosystems, for example the intestine, and to take into account the co-existence of other microorganisms utilizing the same nutrients either at different geographic locations in the intestine or at different time points. The theory also has been expanded to take into account the metabolic flexibility and mixed-substrate utilization that most microorganisms exhibit.

The process by which a given organism changes its ecological niche is known as “niche construction”. (See (Pereira and Berry 2017) for an extended review of the topic.)

57 attaching to its o-glycosylated side-chains (Johansson, Larsson and Hansson 2011). Mucus production is dynamic
58 and depends on the presence of bacterial stimuli, especially LPS (lipopolysaccharide) and PGN (peptidoglycan) as
59 reported in an elegant study using germ-free mice (Petersson *et al.* 2011). It has also been known for a long time
60 that SCFAs are involved in mucus secretion from goblet cells into the gut lumen (Shimotoyodome *et al.* 2000;
61 Willemsen *et al.* 2003). Homeostasis of mucus production is regulated by two complementary bacteria, *Bacteroides*
62 *thetaiotaomicron* (stimulating mucus production through increased goblet cell differentiation) and *F. prausnitzii*
63 (inhibiting goblet cell proliferation and mucus glycosylation) (Wrzosek *et al.* 2013). A preponderance of evidence
64 shows that mucus composition and structure directly depends on the interplay between resident microbiota and
65 epithelial tissues (Jakobsson *et al.* 2015). Several studies have also linked reduced or aberrant O-glycosylation of
66 mucin to the development of intestinal inflammation (Fu *et al.* 2011; Larsson *et al.* 2011; Sommer *et al.* 2014).
67 Other studies have shown penetration of commensal bacteria into the inner mucus layer in the context of colitis
68 (Johansson *et al.* 2014). The mucus layer thickness is also related to nutrition, especially dietary intake, as it has
69 been shown recently that low-fibre diets increase mucus-eroding bacteria communities, leading to greater access
70 for pathogens at the epithelial surface and subsequently increased susceptibility to infection (Desai *et al.* 2016).
71 Furthermore, the attachment of the mucus layer to the epithelium is dependent on the microbiota. Meprin β , a host-
72 derived zinc-dependent metalloprotease induced by the microbiota, is needed to detach the mucus in the small
73 intestine and to subsequently release it into the intestinal lumen (Schütte *et al.* 2014).
74 A healthy mucus layer is therefore essential to protect the underlying epithelium from the dense bacterial
75 population and to physically separate this population from immune cells in the underlying tissue in order to prevent
76 exaggerated immune activation.

77

78 **Mucosal immune system**

79 Prokaryotic microbiota and the immune system

80 It is now well established that the immune system relies on the microbiota for proper maturation (reviewed in
81 (Schnupf, Gaboriau-Routhiau and Cerf-Bensussan 2013; Spasova and Surh 2014; Turfkruyer and Verhasselt
82 2015; Donovan and Comstock 2016; Torow and Hornef 2017)). Different bacterial species guide the development
83 of specific cell subsets; for example, Segmented filamentous Bacteria (SFB) induce the development of T_H17 cells
84 (Ivanov *et al.* 2009; Gaboriau-Routhiau *et al.* 2009; Goto *et al.* 2014)(reviewed in (Schnupf *et al.* 2017; Ivanov
85 2017), and *Bacteroides fragilis* has been shown to induce T_{reg} proliferation and to act on the T(H)1/T(H)2 balance
86 (Mazmanian *et al.* 2005; Round and Mazmanian 2010). *F. prausnitzii* increases antigen-specific T cells and
87 decreases the number of IFN- γ (+) T cells (Rossi *et al.* 2016) and other *Clostridia* species induce different T_{reg}
88 subsets (Atarashi *et al.* 2011). Additionally, short chained fatty acids derived from bacteria regulate T_{reg} numbers in
89 the intestine (Geuking *et al.* 2011; Smith *et al.* 2013; Furusawa, Obata and Hase 2015) and have a direct impact on
90 overall IgA levels (Kim *et al.* 2016) (reviewed in (Velasquez-Manoff 2015)).

91 Mucosal IgA plays a crucial role in gut homeostasis (Peterson *et al.* 2007; Macpherson and Slack 2007; Pabst,
92 Cerovic and Hornef 2016). It is known to protect the gut mucosa from access of bacteria (“immune exclusion”) and
93 to inhibit bacterial replication in the gut lumen (“enchained growth” (Moor *et al.* 2017)). Through these mechanisms,
94 IgA regulates the composition and dynamics of the gut microbiota. IgA and the microbiota therefore regulate each
95 other, leading to a delicate homeostatic balance between stimulation and control (reviewed in (Peterson *et al.*
96 2007; Macpherson and Slack 2007; Slack *et al.* 2012; Macpherson *et al.* 2012; Pabst, Cerovic and Hornef 2016)).
97 The microbiota’s effect on the mucosal immune system is not limited to regulatory T cells and IgA secretion. It also
98 plays a major role in inducing production of antimicrobial peptides (AMPs), which concentrate at the interphase
99 between the thick, tightly formed, mucus layer and the more dispersed outer layer (reviewed in (Lehrer,

00 Lichtenstein and Ganz 1993; Salzman *et al.* 2010))(Meyer-Hoffert *et al.* 2008; Vaishnav *et al.* 2011). Antimicrobial
01 peptides include the defensins, the Reg-protein family and several other proteins, which act directly on the bacteria
02 by targeting the bacterial cell wall. In addition, other host factors with antimicrobial activity include lipocalin2/NGAL,
03 which chelates bacterial siderophores involved in iron acquisition, as well as calprotectin, which leads to the
04 chelation of two other essential trace elements, zinc and manganese. .

05 06 Eukaryotic microbiota and the immune system

07 The intestinal microbiota is not only composed of bacteria, but also harbours a whole array of *archae*, viruses and
08 eukaryotes. It has been shown that the presence of helminths, through their effect on the host immune system
09 (Walsh *et al.* 2009; Finlay, Walsh and Mills 2014; Finlay *et al.* 2016; Ramanan *et al.* 2016), can have profound
10 effects on the microbiota composition in the intestine (Walk *et al.* 2010; Broadhurst *et al.* 2012; Giacomini *et al.*
11 2015; McKenney *et al.* 2015; Ramanan *et al.* 2016; Li *et al.* 2016; Guernier *et al.* 2017) , reviewed in (Gause and
12 Maizels 2016)) as well as on disease susceptibility within the intestine (Reynolds *et al.* 2017) and at distant sites,
13 e.g. the respiratory system (McFarlane *et al.* 2017). However, alterations in the microbiota composition due to the
14 presence of helminths are not generalisable, as changes were observed in a first study of 51 persons infected with
15 *Trichuris trichiuria* in Malaysia (Lee *et al.* 2014), but no changes were found in a second study in 97 children from
16 Ecuador (Cooper *et al.* 2013) nor in 8 persons living in Australia infected experimentally by *Necator americanus*
17 (Cantacessi *et al.* 2014). Helminths have also been shown to attenuate the effect of intestinal bowel disease by
18 restoring the number of goblet cells and preventing outgrowth of *B. vulgatus* in the context of *Nod2*^{-/-} mice and
19 associated intestinal inflammation (Ramanan *et al.* 2016). For some of the observed immune changes, the
20 helminth-induced changes seem to be mediated through the prokaryotic microbiota (Zaiss *et al.* 2015). For other
21 effects, they seem to be independent from the microbiota (Osborne *et al.* 2014), highlighting the complex interplay
22 found within the gut ecosystem. Very recently, a member of the eukaryome, *Tritrichomonas musculus*, was shown
23 to activate the epithelial inflammasome to induce protection against bacterial mucosal infection (Chudnovskiy *et al.*
24 2016). Other protists, such as *Giardia* (Barash *et al.* 2017) and possibly *Blastocystis* (Audebert *et al.* 2016;
25 Siegwald *et al.* 2017) have also been shown to change the resident prokaryotic microbiota. However, data remains
26 conflicting, pointing towards the fact that shifts in the microbiota through given eukaryotes might be strain-specific.
27 Due to incomplete databases, it is currently difficult to determine the exact strain of a eukaryotic organism by
28 comparison against the database. More work in curating these databases is therefore needed to better appreciate
29 the influence that specific eukaryotes might have on the prokaryotic microbiota. More work is also needed to
30 unravel the triad of eukaryotes, prokaryotes, and the immune system to better understand the mutual interactions
31 that take place.

32
33 Taken together, the microbiota and the development and proper function of the mucosal immune system are
34 exquisitely intertwined. Thus, perturbations on either side of this ecosystem can deregulate the balance and leave
35 the host open to infection or inflammatory diseases (Clarke 2014).

36 37 **Friend or foe: pathogens facing the microbiota and the host**

38 As discussed, the host and its microbiota have set-up a tightly regulated network of mutual control. Invading
39 pathogens therefore have several barriers to overcome in order to establish themselves and cause disease (see
40 Figure 2).

41 Within the last decade, much progress has been made in understanding the “ménage à trois” of the microbiota, the
42 host, and pathogens. In this section we will discuss the mechanisms that have evolved in pathogens to overcome

43 the protective environment arising from homeostasis and summarize the complex interactions that take place
44 between pathogens, the microbiota and their host.

45

46 ***Combatting the resident microbiota by direct killing or by inhibition***

47 Small antibacterial toxins

48 A number of small, mainly plasmid-encoded, antibacterial peptides termed bacteriocins or microcins, are produced
49 and secreted by a broad range of bacteria, including the *Bifidobacteria* (reviewed in (Martinez *et al.* 2013; Alvarez-
50 Sieiro *et al.* 2016)), *Lactobacilli* (Collins *et al.* 2017), *Enterococci* (Kommineni *et al.* 2015) and many more. It has
51 been demonstrated that bacteriocin production leads to a niche advantage for the bacteria expressing them (Riley
52 and Wertz 2002; Kommineni *et al.* 2015). Some of the bacteriocins and microcins have been shown to act against
53 pathogenic strains (Kommineni *et al.* 2015; Sassone-Corsi *et al.* 2016b), thereby augmenting colonization
54 resistance and mediating resistance to invading pathogens. One bacteriocin subclass produced by
55 *Enterobacteriaceae* and termed colicins are encoded by several pathogenic strains including *S. Typhimurium*
56 (Nedialkova *et al.* 2014) and *Shigella sonnei* (Anderson *et al.* 2017; Calcuttawala *et al.* 2017). It has been shown
57 recently that *S. Typhimurium* expresses colicin Ib (CollB), giving it a fitness advantage over the closely related *E.*
58 *coli*, which blooms simultaneously in the gut upon *Salmonella*-induced intestinal inflammation. CollB is regulated
59 through the SOS-response and iron-limitation and upregulated in the context of inflammation (Nedialkova *et al.*
60 2014). Therefore, the carriage and induced upregulation of colicins seems to be an evolutionary adaption of
61 enteropathogens in order to have a selective advantage in the ecological niche they share with commensal *E. coli*
62 in the inflamed gut.

63

64 Type 6 secretion system (T6SS)

65 T6SS are encoded by a substantial number of gram-negative pathogens, as diverse as *Helicobacter hepaticus*
66 (Chow and Mazmanian 2010), *S. Typhimurium* (Sana *et al.* 2016), *S. sonnei* (Anderson *et al.* 2017), *Pseudomonas*
67 *aeruginosa* (Mougous *et al.* 2006), *enteroaggregative E. coli* (Dudley *et al.* 2006), *Vibrio cholera* (Pukatzki *et al.*
68 2006) and *B. fragilis* (Hecht *et al.* 2016; Chatzidaki-Livanis, Geva-Zatorsky and Comstock 2016) to name a few.
69 Indeed, T6SS homologous have been described in up to 25% of all sequenced gram-negative genomes. While
70 some bacteria use their T6SS to interfere with host processes (Brodmann *et al.* 2017), alter the immune response
71 upon infection (Chow and Mazmanian 2010; Hachani, Wood and Filloux 2016; Aubert *et al.* 2016; Chen *et al.*
72 2017), or modulate virulence (Bladergroen, Badelt and Spaink 2003; Parsons and Heffron 2005; Pukatzki *et al.*
73 2006), growing evidence suggests that T6SS are also used to attack the resident microbiota and to confer the
74 bacteria expressing them with a competitive advantage ((Russell *et al.* 2014; Unterweger *et al.* 2014; Sana *et al.*
75 2016; Chatzidaki-Livanis, Geva-Zatorsky and Comstock 2016; Anderson *et al.* 2017; Bernal *et al.* 2017; Tian *et al.*
76 2017; Kim *et al.* 2017), reviewed in (Sana, Lugo and Monack 2017)). Indeed, *Shigella*, which encodes a T6SS had
77 a selective advantage in colonization of the mouse gut compared to *S. flexneri* or *E. coli*, a phenomenon which was
78 shown to be largely due to the T6SS (Anderson *et al.* 2017). In *B. fragilis* this could also be observed at the strain
79 level, where symbiotic, non-toxic *B. fragilis* was shown to outcompete a pathogenic strain in a T6SS-dependent
80 manner (Hecht *et al.* 2016; Chatzidaki-Livanis, Geva-Zatorsky and Comstock 2016).

81 The T6SS is also implicated in other important tasks that confer the bacterium harbouring it a selective advantage
82 over the resident microbiota. These include iron acquisition (Lin *et al.* 2017) as well as different mechanisms to
83 handle oxidative stress induced by the host (Wang *et al.* 2015; Si *et al.* 2017; Wan *et al.* 2017). It has been shown
84 recently in marine bacteria that T6SS are horizontally shared between different species (Salomon *et al.* 2015).
85 Furthermore, in *Vibrio cholera*, the T6SS was shown to be able to foster horizontal gene transfer (Borgeaud *et al.*

86 2015). Clearly, the last few years have seen strong advancements in the understanding of T6SS contributions to
87 microbial life cycles (Filloux 2013), while more work is needed in order to fully understand the full scope of T6SS
88 functions.

89

90 ***Exploiting nutrients to gain a selective advantage over the resident microbiota***

91 The most limiting nutrients in the gut are micronutrients, especially iron, as well as general energy sources, such as
92 carbohydrates. Bacterial pathogens have evolved a number of strategies to selectively acquire nutrients over the
93 resident microbiota in the race for these resources.

94

95 Iron scavenging and use of specific siderophores

96 The host has evolved sophisticated strategies termed “nutritional immunity” to limit the amount of available iron that
97 the microbiota has access to, (reviewed in (Cassat and Skaar 2013) and (Kortman *et al.* 2014)). Bacteria have
98 responded by maximizing their ability to uptake iron through the secretion of iron-scavenging molecules, termed
99 siderophores, which give them a selective advantage over strains lacking the scavenging capability (Niehus *et al.*
00 2017). Lipocalin2 (NGAL in humans) is a potent antimicrobial factor secreted by the host whose function is to
01 sequester iron bound siderophores (Flo *et al.* 2004). Bacteria do not only have to compete with the host for iron,
02 but also with the resident members of the microbiota. Indeed, many microbes encode species-specific
03 siderophores that require specific re-uptake machinery to bind and import the iron-siderophore complex (reviewed
04 in (Miethke and Marahiel 2007)). Many enteropathogens have also evolved specific strategies to more efficiently
05 scavenge any available iron. *S. Typhimurium* for example secretes Salmochelin, which is not recognized by
06 lipocalin2/NGAL (Raffatellu *et al.* 2009). Using Salmochelin, *S. typhimurium* is able to obtain enough iron to
07 overcome iron-restriction, leading to a selective growth advantage over neighbouring bacteria. This proves
08 especially important in the context of the inflamed intestine where *Salmonella* thrives amidst large quantities of
09 Lipocalin2 secreted mainly by recruited neutrophils.

10

11 Use of alternative energy sources

12 *S. Typhimurium* is a useful model pathogen to illustrate the basic mechanisms that pathogens employ to bypass
13 the metabolic environment established by the microbiota. Initial replication of *Salmonella* in the yet undisturbed gut
14 depends on hydrogen gas, an important intermediate in microbiota metabolism (Maier *et al.* 2013). Once
15 *Salmonella* has invaded the gut mucosa and induced inflammation, other energy sources become available and
16 are exploited by the pathogen. One of these is the aerobic and anaerobic respiration of 1, 2-propanediol generated
17 by the resident microbiota (demonstrated in mono-associated mice using *B. fragilis* and *B. thetaiotaomicron*)
18 through fermentation of fucose or rhamnose in the inflamed intestine (Faber *et al.* 2017). *Salmonella* can also thrive
19 by oxidative respiration on succinate, which is released by the resident microbiota (Spiga *et al.* 2017). As an
20 alternative energy source, *Salmonella* is also capable of using galactarate and glucarate, generated by the
21 microbiota after antibiotic treatment. This metabolic versatility, especially in an oxidative environment as is found in
22 the inflamed intestine, is likely the basis of the long known condition of antibiotic-mediated *Salmonella* expansion
23 (Faber *et al.* 2016). Another nutrient source is siacylic acid, liberated from the breakdown of sialyated mucins by *B.*
24 *thetaiotaomicron* and other microbiota members. *B. thetaiotaomicron* secretes a sialidase but lacks the ability to
25 use the freed siacylic acid itself. In turn, this acid is metabolized by *C. difficile* and *S. Typhimurium* as an alternative
26 nutrient source giving them a selective nutritional advantage over neighbouring bacteria (Ng *et al.* 2013; Huang *et al.*
27 *et al.* 2015). Differential energy utilization has also been recently shown in some *E. coli* species, which use
28 microbiota-derived formate as an alternative energy source to increase their advantage over other resident species

29 (Hughes *et al.* 2017).

30 Several enteropathogens, including *Citrobacter rodentium*, *Campylobacter jejuni* and *S. Typhimurium*, induce acute
31 intestinal inflammation through their virulence factors (reviewed in (Winter *et al.* 2010a)). The inflammation provides
32 these pathogens with an advantage over the resident microbiota by transforming the intestine into an aerobic
33 environment. Niche creation can be exemplified by the widely studied enteropathogen *S. Typhimurium* (reviewed in
34 (Winter, Lopez and Bäumlér 2013; Winter and Bäumlér 2014a)). It is likely that similar mechanisms that have
35 evolved in *Salmonella* have also evolved in other enteropathogens, for example *E. coli* and *Shigella* spp. and
36 together contribute to the “enterobacterial bloom” that is observed in the inflamed gut ((Lupp *et al.* 2007; Stecher *et al.*
37 *et al.* 2010) reviewed in (Winter and Bäumlér 2014a)). Inflammation leads to the production of respiratory electron
38 acceptors, for example nitrogen species and reactive oxygen species. These products are converted in the
39 intestine to nitrate. Nitrate can be used by *Salmonella* spp., *E. coli* and potentially other facultative anaerobe
40 members of the *Enterobacteriaceae* as an alternative electron acceptor, giving them a selective advantage over
41 other resident bacteria, which rely mainly on anaerobic fermentation of carbohydrates (Lopez *et al.* 2012; Spees *et al.*
42 *et al.* 2013; Winter *et al.* 2013). *Salmonella* has also been shown to use other electron acceptors, for example S-
43 oxides, ethanolamine or tetrathionate, which are present in larger amounts in the inflamed intestine (Winter *et al.*
44 2010b; Thiennimitr *et al.* 2011). In a recent study, it could be shown that *Salmonella* T3SS activation leads to a
45 depletion of *Clostridium* species, which in turn leads to a decrease in butyrate levels. Butyrate is the most important
46 energy source of colonocytes and butyrate oxidation to carbon dioxide leads to the consumption of local oxygen
47 and the generation of an anaerobic environment. The lack of butyrate therefore increases tissue oxygenation,
48 generating a favourable niche for *Salmonella*’s aerobic expansion in the gut lumen (Rivera-Chávez *et al.* 2016b).

49 Under physiological conditions, the microbiota induces expression of PPAR γ , resulting in an increase in β -oxidation
50 of the colonocytes and hence an anoxic environment. In the context of antibiotic treatment, PPAR γ -induction is
51 inhibited and the colonocytes switch to anaerobic glucose oxidation. This then leads to increased availability of
52 nitrate and allows for aerobic expansion of *Enterobacteriaceae* (Byndloss *et al.* 2017). Inflammation also leads to
53 outgrowth of other bacterial species, for example *B. vulgatus* (Huang *et al.* 2015). Through its sialidase activity, *B.*
54 *vulgatus* releases sialic acid from the intestinal tissue, supporting the growth of *E. coli*. *B. vulgatus* thereby
55 contributes to the occurrence of the “enterobacterial blooms” observed during inflammation. Conversely,
56 enterobacterial blooms during infection are abrogated when sialidase inhibitors are administered (Huang *et al.*
57 2015). Gut inflammation can also boost horizontal gene transfer, either between pathogenic and commensal
58 enteropathogens or between dense populations of enteropathogens in the context of the so-called “enterobacterial
59 booms” (see text above). This has been shown for the transfer of a colicin-carrying plasmid p2 (Stecher *et al.* 2012)
60 as well as of temperate phages (Diard *et al.* 2017). Enterobacterial blooms can therefore contribute to pathogen
61 evolution of some species.

62 **Virulence genes**

63 Once in contact with the host, pathogens have developed different strategies to influence the host and exploit it to
64 their own benefit. This is mainly achieved through so called “virulence factors”. First and foremost, pathogens
65 express “classical” virulence factors, for example toxins and the T3SS and their associated effector proteins. The
66 function and specific role of these virulence factors have been discussed in detail elsewhere ((Puhar and
67 Sansonetti 2014; Qiu and Luo 2017) and many others for specific pathogens). The expression of these virulence
68 factors can be constitutive. However, with the immense fitness cost virulence gene expression imparts on the
69 pathogen, virulence gene expression is often regulated by environmental cues. This means that the

70 bacterium only expresses the virulence genes once it is in close contact with the host and at the right location along
71 the gastrointestinal tract.

72 73 Induction of pathogen virulence genes by cues from the host

74 Different host cues allow invading pathogens to pinpoint their position within their host and to regulate virulence
75 genes only once the appropriate location has been reached. Host cues for virulence regulation include bile
76 acids (Antunes *et al.* 2012; Brotcke Zumsteg *et al.* 2014; Eade *et al.* 2016), pH (Behari, Stagon and Calderwood
77 2001), temperature (Elhadad *et al.* 2015; Nuss *et al.* 2015; Fraser and Brown 2017), nutrient availability (reviewed
78 in (Porcheron, Schouler and Dozois 2016)), and oxygen levels ((Marteyn *et al.* 2010; Fraser and Brown
79 2017) reviewed in (Marteyn *et al.* 2011; Marteyn, Gazi and Sansonetti 2012)). Oxygen levels are dynamic within
80 the intestine and even within the anoxic colon an oxygen tension gradient is present in close proximity to the
81 epithelial surface. *Shigella flexneri* has adapted to this gradient by repressing its T3SS in response to reduced
82 oxygen levels encountered in the lumen of the intestine. The key outcome is to conserve metabolic resources in
83 this energy and nutrient depleted environment. This regulation has the added benefit of more closely aligning the
84 expression of virulence factors to the site of infection at the epithelial layer, where they are actually used. The
85 suppression of the T3SS system is mediated by the oxygen sensitive regulator gene *fnr*. When oxygen pressure
86 increases near the epithelium, the anaerobic block on the master regulators of the T3SS, *spa32* and *spa33*, is
87 released and the genes of the T3SS can be expressed (Marteyn *et al.* 2010).

88 Another example of regulated virulence is the bile salt-mediated activation of virulence in *Vibrio cholerae*. It was
89 recently shown through a series of elegant in vitro experiments in a tissue model of infection that virulence genes of
90 *V. cholerae* are induced by the bile salt taurocholate, glyocholate and cholate, but not the deconjugated
91 deoxycholate or chenodeoxycholate. This virulence activation is mediated through dimerization of the transcription
92 factor TcpP by disulfide bond formation. Consequently, a *V. cholerae* strain mutated in the respective cysteine is
93 unable to respond to the bile salts, leading to a competitive disadvantage compared to the wildtype strain in an
94 infant mouse model of colonization. This colonization difference was abolished when a bile-salt sequestering
95 resine, cholestyramine, was co-administered, confirming the crucial role of bile acids in the observed colonization
96 defect (Yang *et al.* 2013).

97 A third example is the regulation of virulence genes in *Enterotoxigenic E. coli* (ETEC) and its close relative, the
98 mouse pathogen *C. rodentium* in the intestine. A recent study has shown that the two neurotransmitters
99 epinephrine and norepinephrine, that are produced by the endocrine cells localized in the intestine are needed for
00 the full expression of virulence/colonization genes (Moreira *et al.* 2016).

01 Together, these observations show that pathogens have evolved varied and complex mechanisms to tightly
02 regulate their virulence attributes. This helps pathogens avoid unnecessary energetic costs that may lead to a loss
03 of fitness in the highly competitive gut environment (see (Diard and Hardt 2017) for a recent review on the evolution
04 of bacterial virulence).

05 06 Induction of pathogens's virulence genes by members of the microbiota

07 We previously discussed the cues from the host that lead to the induction of virulence genes expression in the
08 invading pathogens. Beside this host-mediated induction, some virulence genes are also controlled by sensing
09 metabolites derived from the microbiota, for example SCFAs (butyrate, acetate, lactate and propionate). A recent
10 study has shown that microbiota-derived SCFAs modulate the expression of virulence genes in *Campylobacter*
11 *jejuni*. The authors discovered that the gradient of SCFAs butyrate, acetate, and lactate along the intestinal tract
12 guide expression of genes involved in virulence and commensalism of *C. jejuni*. Lactate, which is abundant in the

13 upper intestinal tract, suppresses production of *C. jejuni* virulence genes, while acetate and butyrate, two SCFA's
14 that are mostly produced in the lower intestinal tract, activate virulence pathways (Luethy *et al.* 2017).
15 Expression of the *Salmonella* pathogenicity island 1 (SPI-1) is inhibited in the presence of propionate, a SCFA that
16 is produced mainly by *Lactobacilli* and *Bifidobacteria* and is more abundant in the upper gastrointestinal tract.
17 Propionate acts through posttranslational modification on HilD, the master regulator of the *Salmonella* SPI-1 (Hung
18 *et al.* 2013). This inhibition ensures that the coordinated expression of SPI-1 genes starts only in the distal small
19 intestine, the main site of *Salmonella* infection. Another example of microbiota-mediated virulence gene expression
20 is the enhancement of enterohemorrhagic *E. coli* (EHEC) T3SS by *B. thetaiotaomicron*. *B. thetaiotaomicron* is an
21 abundant member of the gut microbiota metabolizing complex polysaccharides into monosaccharides that can be
22 further processed by a number of other bacteria. The presence of *B. thetaiotaomicron* leads to a local increase in
23 the levels of succinate, which is sensed by the transcription factor Cra of EHEC. Cra activation leads to an increase
24 in the expression of the genes encoding EHEC's T3SS while leaving the general growth of the pathogen unaffected
25 (Curtis *et al.* 2014).

26

27 **Induction of AMP's by pathogens to inhibit microbiota competition**

28 Some pathogens have evolved mechanisms to exploit the host's own antibacterial defenses. By developing
29 countermeasures against host AMPs, pathogens can rely on the host response to combat the resident microbiota
30 and gain a selective advantage. *Salmonella* Typhimurium for example uses an alternative siderophore
31 (Salmochelins, described above), which is resistant to chelation by Lipocalin2. *Salmonella* has also evolved
32 strategies to resist against calprotectin-induced sequestration of zinc and manganese (Liu *et al.* 2012), giving
33 *Salmonella* a selective advantage over the majority of microbiota members that do not have the necessary tools to
34 survive in the inflamed gut.

35 *Salmonella* infection induces the cytokine IL-22, which in turn activates AMP's (Behnsen *et al.* 2014). One of the
36 proteins induced is the antimicrobial peptide Reg3beta. Previously, Stelzer and colleagues showed that induction of
37 this antimicrobial peptide inhibits the competing microbiota (Miki, Holst and Hardt 2012), while having no effect on
38 the resistant *S. Typhimurium* (Stelzer *et al.* 2011). In a new study, Miki and collaborators could show that Reg3beta
39 extends gut colonization by *S. Typhimurium* through the prolonged induction of a pro-inflammatory environment
40 and changes to the microbiota, especially an inhibition of *Bacteroides* species. The alteration of the microbiota also
41 leads to profound changes in the metabolic landscape with metabolites of Vitamin B6 being the most affected. The
42 authors could show that re-insertion of *Bacteroides* species or supplementation of Vitamin B6 alone was able to
43 accelerate clearance of *Salmonella* from infected mice (Miki *et al.* 2017).

44 A recent study in *Ixodes scapularis* ticks showed a similar mechanism whereby *Anaplasma phagocytophilum*
45 infection induced *Ixodes* anti-freeze glycoprotein (lafgp), which alters biofilm formation in the *Ixodes* gut to
46 destabilize the resident microbiota and facilitate niche construction of *A. phagocytophilum*. It is likely that many
47 pathogens have evolved similar mechanisms to take advantage of host defence mechanisms to facilitate niche
48 construction and induce a host-derived selective advantage over the resident microbiota.

49

50 **Evolutionary adaptations of pathogens to overcome homeostasis: penetrating the mucus layer**

51 As described previously, the mucus layer constitutes a thick, protective layer between the gut lumen and the
52 epithelium. To get access to the epithelium, pathogens have evolved strategies to penetrate the mucus layer and
53 enter the underlying epithelium. *Porphyromonas gingivalis*, a pathogen found mostly in the oral cavity, secretes a
54 cysteine protease (RgpB), which leads to Muc2 cleavage (van der Post *et al.* 2013). Mucinases also play an
55 important role in the colonization and fitness of pathogenic *E. coli* (Valeri *et al.* 2015), an *E. coli* strain associated

56 with Crohn's disease (Gibold *et al.* 2016), and also eukaryotic pathogens such as *Candida albicans* (Colina *et al.*
57 1996) or *Entamoeba histolytica* (Lidell *et al.* 2006). It is likely that other enteropathogens also express mucinases to
58 gain access to the underlying epithelium although more research is needed to fully address the scope of mucinase
59 secretion and usage by pathogens.

60

61 ***Mechanisms established by the microbiota to clear off invading pathogen after infection***

62 The microbiota not only plays an important role in preventing the colonization of pathogens, but also in the
63 pathogen clearing from the gut upon resolution of the inflammation. The mechanisms underlying this process differ
64 from those governing colonization resistance as the mucosa and the microbiota have both been affected and
65 therefore need to return to homeostasis (Endt *et al.* 2010). In the case of *S. Typhimurium* infection it was shown
66 that recovery is mainly mediated by the microbiota and was largely independent of the IgA pool (Endt *et al.* 2010).
67 Mechanistic insights on the underlying causes of clearance were elucidated in a study on *Vibrio cholera* infection,
68 showing an increase in *Ruminococcus obeum* upon infection of mice with the pathogen. The same was also
69 observed in a cohort of infected humans from Bangladesh recovering from the disease. In elegant mouse studies,
70 the authors showed that *Ruminococcus obeum*, through the expression of the *luxS* gene (autoinducer-2 synthase),
71 promotes quorum sensing-mediated restriction of virulence gene expression in *V. cholerae*, leading to a decrease
72 in host symptoms (Hsiao *et al.* 2014)

73 **Dysbiosis: Towards a new interpretation of Koch's postulate**

74 It is now common knowledge that the gut is a complex ecosystem with different interacting entities and that
75 infections must be understood in this context rather than isolated as a pathogen and a host. In consequence, for
76 these complex diseases, neither Koch's postulate ("a pathogen, a disease") nor the molecular Koch's postulate as
77 proposed by Stanley Falkow ("a virulence gene, a disease", (Falkow 1988)) are sufficient. In a very recent review
78 by Neville and collaborators, a third interpretation of the Koch's postulates, the commensal Koch's postulate, was
79 proposed ("a beneficial microbe", "an ameliorated disease state"). The authors infer a new framework for
80 establishing causation in microbiome studies were they use the commensal Koch's postulate to test if a given
81 microorganism is able to ameliorate a disease state in a reproducible manner (Neville, Forster and Lawley 2017).
82 As in the original Koch's postulate, they propose that for inferring causation, the "beneficial" commensals need to
83 be isolated in pure cultures before they are re-introduced and tested in a host for their capacity to mitigate disease.

84

85 We propose yet another interpretation of Koch' postulate, which we have termed "ecological Koch's postulate ("a
86 gut ecosystem state, a disease"). Underlying these postulates is the fact that the gut harbours a full ecosystem,
87 rather than an isolated bacterium or pathogen. This means that rather than an isolated microorganism or group of
88 microorganisms, a whole ecosystem, including the microbiota, the genetic make-up of the host as well as nutrition,
89 age etc. form an entity, which can ultimately lead to disease (see Figure 3 and Box 3).

90

91 The ecological Koch's postulates are based on two major observations, both pointing towards the fact that the clear
92 distinction between a pathogen and a commensal are probably too simple of a model to explain complex disease
93 states.

94

Box 3- Postulates for defining a disease-promoting ecosystem (dysbiosis)

Ecological Koch's postulates

- 1 The dysbiotic microbiota is found in similar composition/ with similar characteristics in all affected individuals
- 2 The dysbiotic microbiota can be retrieved from the affected host
- 3 Gavaging of germ-free hosts with this retrieved microbiota leads, in combination with a similar environment (ex. genetic make-up of the host, nutrition, age), to similar symptoms as in the affected individual
- 4 The dysbiotic microbiota composition remains fairly stable in the newly affected host

Original Koch's postulates

- 1 The microorganism must be present in all diseased individuals
- 2 The microorganism must be isolated from the diseased host and be grown in a pure culture
- 3 The re-inoculation of a naïve host with this pure culture must lead to the same disease as in the original host
- 4 The microorganism must be recovered from the newly diseased host

(I) Not every person infected with a "pathogen" will manifest disease. Therefore, host susceptibility, from a genetic point of view, but also from the resident microbiota, the nutrition, earlier infections, or other insults to the microbiota, play as much of a role in the manifestation of disease as does the presence of given virulence factors in an aggressing pathogen. The pathogens not only need to be present and harbour the virulence genes, but they also need to express these genes and be able to establish a niche for themselves within the competitive environment of the

10 already established microbial community in order to replicate and then cause disease.

11
12 (II) In the last years, several gastrointestinal diseases have emerged, which are not associated with an overt
13 pathogen, but where the microbial community as a whole seems to mediate the disease. Examples are intestinal
14 bowel disease, colorectal cancer, obesity, and different states of malnutrition. Indeed, depending on the microbial
15 community pathogens find themselves in, bacteria, which normally do behave as commensals may become
16 invasive and cause disease. For all of these diseases, a decrease in the composition complexity of the microbiota
17 leads to dysbiosis and an oxidation of the gut environment as well as an increase in aeortolerant species such as
18 *Enterobacteriaceae* (Rivera-Chávez, Lopez and Bäumler 2017). These disturbances in the ecosystem lead to a
19 lowered resilience and increased susceptibility to pathogens and other, normally commensal, bacteria with
20 potential harmful properties (often called "pathobionts"). Indeed, these diseases are characterized by the fact that
21 the wrong bacteria are in wrong proportions, in wrong "company" (Huang *et al.* 2015) or in the wrong "place"
22 (Brown *et al.* 2015; Tomas *et al.* 2016). The presence of commensal bacteria near the epithelial surface has been
23 put in relation with the breakdown of gut homeostasis and emergence of pathological states in the context of
24 environmental enteropathy (Brown *et al.* 2015) or in a pre-diabetic state (Tomas *et al.* 2016).

25
26 In the ecological Koch's postulate, a dysbiotic community, including or not "classical pathogens" or pathobionts
27 therefore represents a disease. The entity of transmission is the complete dysbiotic microbiota rather than a
28 pathogen (Koch's postulate), a virulence gene (molecular Koch's postulate) or a commensal (commensal Koch's
29 postulate).

30 In accordance to the other Koch's postulate, the ecological Koch's postulate are proven through the fact that a
31 given entity (here the dysbiotic microbiota) from a diseased individual can provoke disease in a formerly healthy
32 individual. To prove this hypothesis, one hence has to transmit the microbiota from a diseased individual into a
33 germfree individual/ mouse and this transplanted individual subsequently has to develop the signs of the disease.
34 This transfer can either be performed in (I) "standard" conditions, using a "wild type, normally fed" germ-free host
35 (showing a direct effect of the microbiota on disease), or, else, in (II) a "pre-fragilised" host, as an example in a
36 mouse exhibiting a mutation in a given gene or eating a specific chow. In syndromes, which do need a pre-
37 fragilised host, the dysbiotic microbiota contributes to disease, without however being the only cause for it.

38 As stated earlier, several inflammatory, gastrointestinal diseases can be explained through the ecological Koch's
39 postulate, including obesity. Indeed, if a microbiota from obese mice is transplanted into lean mice, the
40 transplanted mice showed increased fat deposition (Turnbaugh *et al.* 2006; Ridaura *et al.* 2013). The same could
41 also be proven for kwashiorkor, the oedematous form of acute undernutrition (Smith *et al.* 2013) as well as for
42 environmental enteropathy (Brown *et al.* 2015). On the other hand, it is well known that mutations in *nod2* facilitate
43 and support the onset of IBD (Cho 2001). Therefore, to prove the contribution of the microbiota in IBD, a
44 susceptible host, mutated for *nod2*, should be transplanted with the dysbiotic microbiota and this transplanted
45 microbiota should worsen the disease state.

46
47 An instructive example of a "pathological dysbiosis" and hence a disease following the ecological Koch's postulates
48 is chronic and acute malnutrition coupled to associated environmental enteropathy. Several reports have shown
49 evidence that children suffering from one of these two syndromes have an altered colonic microbiota (Smith *et al.*
50 2013; Subramanian *et al.* 2014; Gough *et al.* 2015; Blanton *et al.* 2016a; 2016b) and increased abundance of
51 asymptomatic pathogen carriage, including enteroaggregative *E. coli* (Havt *et al.* 2017), *Campylobacter spp.* and
52 *Giardia spp.* (Platts-Mills *et al.* 2017). Further, a recent study sequencing cultured microbes from two Bangladeshi
53 children suffering or not of undernutrition showed that the *B. fragilis* strain found in the undernourished child is
54 enterotoxic, while the strains found within the normally nourished child were not. When transplanting the native
55 community into germfree mice and infecting with the enterotoxigenic *B. fragilis* strain, the authors could show that
56 the enterotoxigenic strain causally led to malnutrition and associated pathophysiological disturbances only in its
57 native community, but not when administered to mice harboring the microbiota of the healthy child (Wagner *et al.*
58 2016). These observations put forward the hypotheses that (I) even subclinical infections with enteropathogens can
59 have negative effects on gut health and that (II) pathogens or pathobionts, depending on the community they dwell
60 in, might have negative effects on host homeostasis or not. This indeed supports the concept of the "ecological
61 Koch's postulates", stating that the whole ecosystem, rather than an isolated element contributes to morbidity.

62
63 Overall, we are only beginning to understand the complex relationships and interactions within the gut ecosystem
64 and more research is needed in order to elucidate the origin and pathophysiological effect of the different dysbiotic
65 communities and to understand the crosstalk they have between each other as well as with the host.

66 67 **Conclusion**

68 Infection biology has been moving in the last decades from the original Koch's postulate looking at pathogens, to
69 molecular Koch's postulate looking at virulence factors, to the newly proposed ecological Koch's postulate looking
70 at dysbiosis. Indeed, infection biology has shifted towards an integrated approach of systems biology, ecology, and
71 evolution. This increasing complexity makes it more and more difficult to untangle the causative effects of disease
72 states and asks for imaginative and sophisticated designs of experiments to explain the underlying
73 pathophysiological mechanisms. Particularly, experiments need to take into account the physiological and
74 pathophysiological state of the infected host, for example the microbiota and the exact nutrition the model animals
75 are receiving. In recent years, several initiatives have been launched to standardize the microbiota of model
76 animals (Brugiroux *et al.* 2016) or at least to meticulously report, not only the exact strain of pathogen used and the
77 genetics of the mouse model, but also the microbiota composition, as well as the food composition of the animal
78 models used (Ma *et al.* 2012; Macpherson and McCoy 2015). This will prove indispensable in the future in order to
79 compare different studies and explain the pathophysiological mechanisms underlying the complex interplay
80 between pathogens, the microbiota, and their host. To date, we are only at the beginning of understanding the

81 interactions within these ecosystems, the perturbations, which can be induced, and their effect on pathogen
82 susceptibility and disease. The widely available techniques of sequencing, especially of metagenomics,
83 metatranscriptomics and metabolomics, will prove essential in this endeavour. Special attention should also be
84 paid to not forget that the microbiota harbours other organisms than prokaryotes, first and foremost viruses
85 (including phages and prophages), and eukaryotes. Only an integrated view of the gut ecosystem, including the
86 host, the pro- and eukaryome and virome as well as the pathogens will allow us to move forward in our
87 understanding of which mechanisms are governing infection.

88 The scientific community is on the verge of experiencing another revolution in understanding the complex network
89 of gut interactions. This will surely open the way for more targeted and personalized interventions to infectious
90 diseases based on interference or corrections to the imbalances in the gut ecosystem and restoration of gut
91 homeostasis. This could include siderophore-based immunization strategies (Mike *et al.* 2016; Sassone-Corsi *et al.*
92 2016a), probiotic bacteria (e.g. *E. coli* strain Nissle) using similar iron-scavenging mechanisms than the invading
93 pathogen (Deriu *et al.* 2013), probiotic strains consuming H₂ and hence restricting the use of this energy source for
94 invading pathogens (Maier *et al.* 2013), the development of probiotic strains expressing bacteriocins or microcins
95 targeting the pathogen (Kommineni *et al.* 2015; Hegarty *et al.* 2016; Sassone-Corsi *et al.* 2016b), expressing iron-
96 sequestering mechanisms to inhibit invading pathogens (Vazquez-Gutierrez *et al.* 2016), siacylidase inhibitors
97 (Huang *et al.* 2015) or inhibitors of anaerobic respiration (Winter and Bäumlér 2014b) (see Table 1). There are
98 certainly many other possible intervention strategies yet to be discovered. The generated knowledge will therefore
99 prove very important in paving the way to propose other intervention strategies, which do not rely on antibiotics. In
00 a world where antibiotic resistance is on a constant rise this aspect will be of utmost importance.

01

02

03 **Figure 1: Homeostatic gut environment (A) versus a dysbiotic gut environment (B).** Scheme of an intestine in
04 homeostasis (left) and in dysbiosis upon invasion of a pathogen (depicted in red). Upon dysbiosis, the mucus layer
05 is thinner, larger amounts of antimicrobial peptides are secreted (e.g. C-type lectins as Reg3 γ) to prevent bacteria
06 breach the barrier and get access to the underlying tissue. This leads to villous blunting, influx of inflammatory cells
07 into the lamina propria and depletion of members of the microbiota, leading to a changed composition and lower
08 diversity of the resident microbiota.

09
10

11 **Figure 2: Mechanisms evolved by pathogen to combat the resident microbiota and the host**

12 Pathogens have evolved several mechanisms to overcome the barrier imposed by the resident microbiota and the
13 host. These include direct (bacteriocins, microcins, T6SS) and indirect (nutrient restriction) inhibition of members of
14 the microbiota, the use of alternative energy sources as well as different mechanisms to overcome the barriers
15 imposed by the hosts (mucinases, T3SS and other virulence factors acting on the host).

16

17 **Figure 3: The evolution of the Koch's postulate**

18 In recent years, the original Koch's postulate ("a pathogen, a disease") have been extended to the molecular
19 Koch's postulate (Stanley Falkow, "a virulence genes, a disease") and here to the ecological Koch's postulate ("a
20 dysbiosis, a disease")

21
22
23
24
25
26
27
28
29
30

31 **Table 1: Possible new intervention strategies intervening with the gut ecosystem to target diseases related**
 32 **to dysbioses-induced enteropathogenic blooms**
 33

Intervention strategy	Evidence for intervention	References
Siderophore-based immunization strategies	<p>Mice immunized with siderophores conjugated to an immunogenic carrier protein were able to elicit a potent immune response and to protect against urinary tract infections.</p> <p>Mice immunized with a cholera toxin β-siderophore conjugate show a potent immune response and are able to protect against infection with <i>Salmonella</i> Typhimurium.</p>	(Mike <i>et al.</i> 2016; Sassone-Corsi <i>et al.</i> 2016a)
Probiotic strains with similar or more efficient iron-sequestering mechanisms inhibiting invading pathogens	<p>Oral gavage with <i>Escherichia coli</i> strain Nissle 1917 reduces <i>S. Typhimurium</i> colonization in mouse models of acute colitis or chronic persistent infection. The observed probiotic activity depends on the iron-sequestering mechanisms of <i>E. coli</i> Nissle, which is highly similar to the one found in <i>Salmonella</i> Typhimurium.</p> <p>The two bifidobacterial strains <i>Bifidobacterium pseudolongum</i> PV8-2 (Bp PV8-2) and <i>Bifidobacterium kashiwanohense</i> PV20-2 (Bk PV20-2) are able to inhibit growth of <i>S. Typhimurium</i> and <i>E. coli</i> O157:H45 (EHEC) in <i>in vitro</i> co-culture experiments and are able to displace the pathogens on mucus-producing HT29-MTX cell lines.</p>	(Deriu <i>et al.</i> 2013) (Vazquez-Gutierrez <i>et al.</i> 2016),
Probiotic strains consuming H ₂ to prevent initial ecosystem invasion	In a non-inflamed intestine, <i>S. Typhimurium</i> relies on H ₂ metabolisms for invasion. Introducing H ₂ -consuming bacteria into the microbiota reduces <i>hyb</i> -dependent <i>S. Typhimurium</i> growth.	(Maier <i>et al.</i> 2013)
Probiotic strains producing butyrate	Oral gavage of mice with tributyrin reduces growth of <i>S. Typhimurium</i> in the inflamed intestine.	(Rivera-Chávez <i>et al.</i> 2016b)
Probiotic strains expressing bacteriocins or microcins targeting the pathogen	<p>Colonization of mice with a bacteriocin-carrying <i>E. faecalis</i> strain defective for conjugation leads to clearance of vancomycin resistant enterococci.</p> <p>Microcin-producing <i>E. coli</i> Nissle is able to limit the growth of commensal <i>E. coli</i>, adherent-invasive <i>E. coli</i> and <i>Salmonella enterica</i> in the inflamed intestine.</p>	(Kommineni <i>et al.</i> 2015; Hegarty <i>et al.</i> 2016; Sassone-Corsi <i>et al.</i> 2016b)
Sialidase inhibitors	Oral administration of sialidase inhibitors decreases outgrowth of <i>E. coli</i> as well as the severity of colitis in a mouse model.	(Huang <i>et al.</i> 2015)
Inhibitors of aerobic respiration	Aerobic respiration is used by <i>Salmonella</i> spp and other <i>Enterobacteriaceae</i> to thrive in the inflamed intestine.	(Winter and Bäumlner 2014b)
Sustaining PPAR- γ signaling	PPAR- γ signaling in the homeostatic intestine leads to β -oxidation in the colonocytes and hence an anoxic environment limiting nitrate availability and outgrowth of <i>Enterobacteriaceae</i>	(Byndloss <i>et al.</i> 2017)

34

35 **Acknowledgements**

36 We would like to thank Pamela Schnupf, Kelsey Huus and Florent Mazel for fruitful discussions and critical reading
37 of the manuscript. PV was supported by an Early.PostdocMobility Fellowship form the Swiss National Science
38 Foundation, a Roux-Cantarini Postdoctoral Fellowship as well as a L'Oréal-UNESCO for Women in Science France
39 Fellowship. Work in PJS's group is supported by ERC Grant No. 339579 (DECRYPT). PJS is a HHMI Senior
40 Foreign Scholar and CIFAR scholar in the human microbiome consortium.

41

42

43 References

- 44 Ackermann M, Stecher B, Freed NE *et al.* Self-destructive cooperation mediated by phenotypic noise. *Nature*
45 2008;**454**:987–90.
- 46 Alvarez-Sieiro P, Montalbán-López M, Mu D *et al.* Bacteriocins of lactic acid bacteria: extending the family. *Appl*
47 *Microbiol Biotechnol* 2016;**100**:2939–51.
- 48 Anderson MC, Vonaesch P, Saffarian A *et al.* *Shigella sonnei* Encodes a Functional T6SS Used for Interbacterial
49 Competition and Niche Occupancy. *Cell Host Microbe* 2017;**21**:769–776.e3.
- 50 Araújo JR, Tomas J, Brenner C *et al.* Impact of high-fat diet on the intestinal microbiota and small intestinal
51 physiology before and after the onset of obesity. *Biochimie* 2017, DOI: 10.1016/j.biochi.2017.05.019.
- 52 Atarashi K, Tanoue T, Ando M *et al.* Th17 Cell Induction by Adhesion of Microbes to Intestinal Epithelial Cells. *Cell*
53 2015;**163**:367–80.
- 54 Atarashi K, Tanoue T, Shima T *et al.* Induction of colonic regulatory T cells by indigenous *Clostridium* species.
55 *Science* 2011;**331**:337–41.
- 56 Aubert DF, Xu H, Yang J *et al.* A *Burkholderia* Type VI Effector Deamidates Rho GTPases to Activate the Pyrin
57 Inflammasome and Trigger Inflammation. *Cell Host Microbe* 2016;**19**:664–74.
- 58 Audebert C, Even G, Cian A *et al.* Colonization with the enteric protozoa *Blastocystis* is associated with increased
59 diversity of human gut bacterial microbiota. *Sci Rep* 2016;**6**:25255.
- 60 Bang C, Weidenbach K, Gutschmann T *et al.* The intestinal archaea *Methanosphaera stadtmanae* and
61 *Methanobrevibacter smithii* activate human dendritic cells. Foligne B (ed.). *PLoS ONE* 2014;**9**:e99411.
- 62 Barash NR, Maloney JG, Singer SM *et al.* *Giardia* Alters Commensal Microbial Diversity throughout the Murine
63 Gut. Appleton JA (ed.). *Infect Immun* 2017;**85**:e00948–16.
- 64 Barthel M, Hapfelmeier S, Quintanilla-Martínez L *et al.* Pretreatment of mice with streptomycin provides a
65 *Salmonella enterica* serovar Typhimurium colitis model that allows analysis of both pathogen and host. *Infect*
66 *Immun* 2003;**71**:2839–58.
- 67 Behnsen J, Jellbauer S, Wong CP *et al.* The cytokine IL-22 promotes pathogen colonization by suppressing related
68 commensal bacteria. *Immunity* 2014;**40**:262–73.
- 69 Bernal P, Allsopp LP, Filloux A *et al.* The *Pseudomonas putida* T6SS is a plant warden against phytopathogens.
70 *ISME J* 2017;**11**:972–87.
- 71 Bladergroen MR, Badelt K, Spaik HP. Infection-blocking genes of a symbiotic *Rhizobium leguminosarum* strain
72 that are involved in temperature-dependent protein secretion. *Mol Plant Microbe Interact* 2003;**16**:53–64.
- 73 Blanton LV, Barratt MJ, Charbonneau MR *et al.* Childhood undernutrition, the gut microbiota, and microbiota-
74 directed therapeutics. *Science* 2016a;**352**:1533–3.
- 75 Blanton LV, Charbonneau MR, Salih T *et al.* Gut bacteria that prevent growth impairments transmitted by
76 microbiota from malnourished children. *Science* 2016b;**351**:aad3311–1.
- 77 BOHNHOFF M, DRAKE BL, MILLER CP. Effect of streptomycin on susceptibility of intestinal tract to experimental
78 *Salmonella* infection. *Proc Soc Exp Biol Med* 1954;**86**:132–7.
- 79 Borgeaud S, Metzger LC, Scignari T *et al.* The type VI secretion system of *Vibrio cholerae* fosters horizontal gene
80 transfer. *Science* 2015;**347**:63–7.
- 81 Braun T, Di Segni A, BenShoshan M *et al.* Fecal microbial characterization of hospitalized patients with suspected
82 infectious diarrhea shows significant dysbiosis. *Sci Rep* 2017;**7**:1088.
- 83 Breurec S, Vanel N, Bata P *et al.* Etiology and Epidemiology of Diarrhea in Hospitalized Children from Low Income
84 Country: A Matched Case-Control Study in Central African Republic. Ryan ET (ed.). *PLoS Negl Trop Dis*
85 2016;**10**:e0004283.

- 86 Broadhurst MJ, Ardeshir A, Kanwar B *et al.* Therapeutic helminth infection of macaques with idiopathic chronic
87 diarrhea alters the inflammatory signature and mucosal microbiota of the colon. Douek DC (ed.). *PLoS Pathog*
88 2012;**8**:e1003000.
- 89 Brodmann M, Dreier RF, Broz P *et al.* Francisella requires dynamic type VI secretion system and ClpB to deliver
90 effectors for phagosomal escape. *Nat Commun* 2017;**8**:15853.
- 91 Brown EM, Wlodarska M, Willing BP *et al.* Diet and specific microbial exposure trigger features of environmental
92 enteropathy in a novel murine model. *Nat Commun* 2015;**6**:7806.
- 93 Brugiroux S, Beutler M, Pfann C *et al.* Genome-guided design of a defined mouse microbiota that confers
94 colonization resistance against *Salmonella enterica* serovar Typhimurium. *Nat Microbiol* 2016;**2**:16215.
- 95 Byndloss MX, Olsan EE, Rivera-Chávez F *et al.* Microbiota-activated PPAR- γ signaling inhibits dysbiotic
96 Enterobacteriaceae expansion. *Science* 2017;**357**:570–5.
- 97 Calcuttawala F, Hariharan C, Pazhani GP *et al.* Characterization of E-type colicinogenic plasmids from *Shigella*
98 *sonnei*. *FEMS Microbiol Lett* 2017;**364**, DOI: 10.1093/femsle/fnx060.
- 99 Camarinha-Silva A, Maushammer M, Wellmann R *et al.* Host Genome Influence on Gut Microbial Composition and
00 Microbial Prediction of Complex Traits in Pigs. *Genetics* 2017;**206**:1637–44.
- 01 Cantacessi C, Giacomini P, Croese J *et al.* Impact of experimental hookworm infection on the human gut
02 microbiota. *J INFECT DIS* 2014;**210**:1431–4.
- 03 Carbonero F, Benefiel AC, Alizadeh-Ghamsari AH *et al.* Microbial pathways in colonic sulfur metabolism and links
04 with health and disease. *Front Physiol* 2012;**3**:448.
- 05 Cassat JE, Skaar EP. Iron in infection and immunity. *Cell Host Microbe* 2013;**13**:509–19.
- 06 Chase JM, Leibold MA. Ecological Niches: Linking Classical and Contemporary Approaches. *Biodiversity and*
07 *Conservation* 2004;**13**:1791–3.
- 08 Chassaing B, Koren O, Goodrich JK *et al.* Dietary emulsifiers impact the mouse gut microbiota promoting colitis
09 and metabolic syndrome. *Nature* 2015;**519**:92–6.
- 10 Chassaing B, Van de Wiele T, De Bodt J *et al.* Dietary emulsifiers directly alter human microbiota composition and
11 gene expression *ex vivo* potentiating intestinal inflammation. *Gut* 2017;**66**:1414–27.
- 12 Chatzidaki-Livanis M, Geva-Zatorsky N, Comstock LE. *Bacteroides fragilis* type VI secretion systems use novel
13 effector and immunity proteins to antagonize human gut Bacteroidales species. *Proc Natl Acad Sci USA*
14 2016;**113**:3627–32.
- 15 Chen H, Yang D, Han F *et al.* The Bacterial T6SS Effector EvpP Prevents NLRP3 Inflammasome Activation by
16 Inhibiting the Ca(2+)-Dependent MAPK-Jnk Pathway. *Cell Host Microbe* 2017;**21**:47–58.
- 17 Cho I, Blaser MJ. The human microbiome: at the interface of health and disease. *Nat Rev Genet* 2012;**13**:260–70.
- 18 Cho JH. Update on the genetics of inflammatory bowel disease. *Curr Gastroenterol Rep* 2001;**3**:458–63.
- 19 Chow J, Mazmanian SK. A pathobiont of the microbiota balances host colonization and intestinal inflammation. *Cell*
20 *Host Microbe* 2010;**7**:265–76.
- 21 Chudnovskiy A, Mortha A, Kana V *et al.* Host-Protozoan Interactions Protect from Mucosal Infections through
22 Activation of the Inflammasome. *Cell* 2016;**167**:444–456.e14.
- 23 Clarke TB. Microbial programming of systemic innate immunity and resistance to infection. Haldar K (ed.). *PLoS*
24 *Pathog* 2014;**10**:e1004506.
- 25 Clemente JC, Ursell LK, Parfrey LW *et al.* The impact of the gut microbiota on human health: an integrative view.
26 *Cell* 2012;**148**:1258–70.
- 27 Clements WD, Parks R, Erwin P *et al.* Role of the gut in the pathophysiology of extrahepatic biliary obstruction. *Gut*

- 28 1996;**39**:587–93.
- 29 Colina AR, Aumont F, Deslauriers N *et al.* Evidence for degradation of gastrointestinal mucin by *Candida albicans*
30 secretory aspartyl proteinase. *Infect Immun* 1996;**64**:4514–9.
- 31 Collins FWJ, O'Connor PM, O'Sullivan O *et al.* Bacteriocin Gene-Trait matching across the complete *Lactobacillus*
32 Pan-genome. *Sci Rep* 2017;**7**:3481.
- 33 Cooper P, Walker AW, Reyes J *et al.* Patent human infections with the whipworm, *Trichuris trichiura*, are not
34 associated with alterations in the faecal microbiota. Bereswill S (ed.). *PLoS ONE* 2013;**8**:e76573.
- 35 Corthier G, Muller MC. Emergence in gnotobiotic mice of nontoxigenic clones of *Clostridium difficile* from a
36 toxinogenic one. *Infect Immun* 1988;**56**:1500–4.
- 37 Costello EK, Lauber CL, Hamady M *et al.* Bacterial community variation in human body habitats across space and
38 time. *Science* 2009;**326**:1694–7.
- 39 Costello EK, Stagaman K, Dethlefsen L *et al.* The Application of Ecological Theory Toward an Understanding of the
40 Human Microbiome. *Science* 2012;**336**:1255–62.
- 41 Curtis MM, Hu Z, Klimko C *et al.* The gut commensal *Bacteroides thetaiotaomicron* exacerbates enteric infection
42 through modification of the metabolic landscape. *Cell Host Microbe* 2014;**16**:759–69.
- 43 David LA, Maurice CF, Carmody RN *et al.* Diet rapidly and reproducibly alters the human gut microbiome. *Nature*
44 2014;**505**:559–63.
- 45 De Filippo C, Cavalieri D, Di Paola M *et al.* Impact of diet in shaping gut microbiota revealed by a comparative
46 study in children from Europe and rural Africa. *Proc Natl Acad Sci USA* 2010;**107**:14691–6.
- 47 Deriu E, Liu JZ, Pezeshki M *et al.* Probiotic Bacteria Reduce *Salmonella Typhimurium* Intestinal Colonization by
48 Competing for Iron. *Cell Host Microbe* 2013;**14**:26–37.
- 49 Desai MS, Seekatz AM, Koropatkin NM *et al.* A Dietary Fiber-Deprived Gut Microbiota Degrades the Colonic
50 Mucus Barrier and Enhances Pathogen Susceptibility. *Cell* 2016;**167**:1339–1353.e21.
- 51 Dethlefsen L, Huse S, Sogin ML *et al.* The pervasive effects of an antibiotic on the human gut microbiota, as
52 revealed by deep 16S rRNA sequencing. Eisen JA (ed.). *PLoS Biol* 2008;**6**:e280.
- 53 Diard M, Bakkeren E, Cornuault JK *et al.* Inflammation boosts bacteriophage transfer between *Salmonella* spp.
54 *Science* 2017;**355**:1211–5.
- 55 Diard M, Hardt W-D. Evolution of bacterial virulence. *FEMS Microbiol Rev* 2017, DOI: 10.1093/femsre/fux023.
- 56 Dogra S, Sakwinska O, Soh S-E *et al.* Dynamics of infant gut microbiota are influenced by delivery mode and
57 gestational duration and are associated with subsequent adiposity. *MBio* 2015;**6**:e02419–14.
- 58 Donovan SM, Comstock SS. Human Milk Oligosaccharides Influence Neonatal Mucosal and Systemic Immunity.
59 *Ann Nutr Metab* 2016;**69 Suppl 2**:42–51.
- 60 Donovan SM. Introduction to the special focus issue on the impact of diet on gut microbiota composition and
61 function and future opportunities for nutritional modulation of the gut microbiome to improve human health. *Gut*
62 *Microbes* 2017;**8**:75–81.
- 63 Dowds CM, Blumberg RS, Zeissig S. Control of intestinal homeostasis through crosstalk between natural killer T
64 cells and the intestinal microbiota. *Clin Immunol* 2015;**159**:128–33.
- 65 Ducluzeau R, Ladire M, Callut C *et al.* Antagonistic effect of extremely oxygen-sensitive clostridia from the
66 microflora of conventional mice and of *Escherichia coli* against *Shigella flexneri* in the digestive tract of
67 gnotobiotic mice. *Infect Immun* 1977;**17**:415–24.
- 68 Dudley EG, Thomson NR, Parkhill J *et al.* Proteomic and microarray characterization of the AggR regulon identifies
69 a pheU pathogenicity island in enteroaggregative *Escherichia coli*. *Mol Microbiol* 2006;**61**:1267–82.
- 70 Eckburg PB, Bik EM, Bernstein CN *et al.* Diversity of the human intestinal microbial flora. *Science* 2005;**308**:1635–

- 71 8.
- 72 Edwards CA. Determinants and Duration of Impact of Early Gut Bacterial Colonization. *Ann Nutr Metab*
73 2017;**70**:246–50.
- 74 Endt K, Stecher B, Chaffron S *et al.* The microbiota mediates pathogen clearance from the gut lumen after non-
75 typhoidal Salmonella diarrhea. Stebbins CE (ed.). *PLoS Pathog* 2010;**6**:e1001097.
- 76 Eusebi LH, Rabitti S, Artesiani ML *et al.* Proton pump inhibitors: Risks of long-term use. *J Gastroenterol Hepatol*
77 2017;**32**:1295–302.
- 78 Faber F, Thiennimitr P, Spiga L *et al.* Respiration of Microbiota-Derived 1,2-propanediol Drives Salmonella
79 Expansion during Colitis. Sperandio V (ed.). *PLoS Pathog* 2017;**13**:e1006129.
- 80 Faber F, Tran L, Byndloss MX *et al.* Host-mediated sugar oxidation promotes post-antibiotic pathogen expansion.
81 *Nature* 2016;**534**:697–9.
- 82 Falkow S. Molecular Koch's postulates applied to microbial pathogenicity. *Rev Infect Dis* 1988;**10 Suppl 2**:S274–6.
- 83 Filloux A. The rise of the Type VI secretion system. *F1000Prime Rep* 2013;**5**:52.
- 84 Finlay CM, Stefanska AM, Walsh KP *et al.* Helminth Products Protect against Autoimmunity via Innate Type 2
85 Cytokines IL-5 and IL-33, Which Promote Eosinophilia. *J Immunol* 2016;**196**:703–14.
- 86 Finlay CM, Walsh KP, Mills KHG. Induction of regulatory cells by helminth parasites: exploitation for the treatment
87 of inflammatory diseases. *Immunol Rev* 2014;**259**:206–30.
- 88 Flo TH, Smith KD, Sato S *et al.* Lipocalin 2 mediates an innate immune response to bacterial infection by
89 sequestering iron. *Nature* 2004;**432**:917–21.
- 90 Foster KR, Bell T. Competition, not cooperation, dominates interactions among culturable microbial species. *Curr*
91 *Biol* 2012;**22**:1845–50.
- 92 Frese SA, Mills DA. Birth of the infant gut microbiome: moms deliver twice! *Cell Host Microbe* 2015;**17**:543–4.
- 93 Freter R, Brickner H, Botney M *et al.* Mechanisms that control bacterial populations in continuous-flow culture
94 models of mouse large intestinal flora. *Infect Immun* 1983a;**39**:676–85.
- 95 Freter R, Brickner H, Fekete J *et al.* Survival and implantation of Escherichia coli in the intestinal tract. *Infect*
96 *Immun* 1983b;**39**:686–703.
- 97 Freter R, Stauffer E, Cleven D *et al.* Continuous-flow cultures as in vitro models of the ecology of large intestinal
98 flora. *Infect Immun* 1983c;**39**:666–75.
- 99 Fu J, Wei B, Wen T *et al.* Loss of intestinal core 1-derived O-glycans causes spontaneous colitis in mice. *J Clin*
00 *Invest* 2011;**121**:1657–66.
- 01 Fukami T, Nakajima M. Community assembly: alternative stable states or alternative transient states? *Ecol Lett*
02 2011;**14**:973–84.
- 03 Fukuda S, Toh H, Hase K *et al.* Bifidobacteria can protect from enteropathogenic infection through production of
04 acetate. *Nature* 2011;**469**:543–7.
- 05 Furusawa Y, Obata Y, Hase K. Commensal microbiota regulates T cell fate decision in the gut. *Semin*
06 *Immunopathol* 2015;**37**:17–25.
- 07 Gaboriau-Routhiau V, Rakotobe S, Lécuyer E *et al.* The key role of segmented filamentous bacteria in the
08 coordinated maturation of gut helper T cell responses. *Immunity* 2009;**31**:677–89.
- 09 Gause WC, Maizels RM. Macrobiota - helminths as active participants and partners of the microbiota in host
10 intestinal homeostasis. *Curr Opin Microbiol* 2016;**32**:14–8.
- 11 Geuking MB, Cahenzli J, Lawson MAE *et al.* Intestinal bacterial colonization induces mutualistic regulatory T cell

- 12 responses. *Immunity* 2011;**34**:794–806.
- 13 Giacomini P, Agha Z, Loukas A. Helminths and Intestinal Flora Team Up to Improve Gut Health. *Trends Parasitol*
14 2016;**32**:664–6.
- 15 Giacomini P, Zakrzewski M, Croese J *et al.* Experimental hookworm infection and escalating gluten challenges are
16 associated with increased microbial richness in celiac subjects. *Sci Rep* 2015;**5**:13797.
- 17 Gibold L, Garenaux E, Dalmaso G *et al.* The Vat-AIEC protease promotes crossing of the intestinal mucus layer
18 by Crohn's disease-associated *Escherichia coli*. *Cell Microbiol* 2016;**18**:617–31.
- 19 Goto Y, Panea C, Nakato G *et al.* Segmented filamentous bacteria antigens presented by intestinal dendritic cells
20 drive mucosal Th17 cell differentiation. *Immunity* 2014;**40**:594–607.
- 21 Gough EK, Stephens DA, Moodie EEM *et al.* Linear growth faltering in infants is associated with *Acidaminococcus*
22 *sp.* and community-level changes in the gut microbiota. *Microbiome* 2015;**3**:24.
- 23 Groussin M, Mazel F, Sanders JG *et al.* Unraveling the processes shaping mammalian gut microbiomes over
24 evolutionary time. *Nat Commun* 2017;**8**:14319.
- 25 Guernier V, Brennan B, Yakob L *et al.* Gut microbiota disturbance during helminth infection: can it affect cognition
26 and behaviour of children? *BMC Infect Dis* 2017;**17**:58.
- 27 Hachani A, Wood TE, Filloux A. Type VI secretion and anti-host effectors. *Curr Opin Microbiol* 2016;**29**:81–93.
- 28 Hamad I, Raoult D, Bittar F. Repertory of eukaryotes (eukaryome) in the human gastrointestinal tract: taxonomy
29 and detection methods. Allen J (ed.). *Parasite Immunol* 2016;**38**:12–36.
- 30 Havt A, Lima IF, Medeiros PH *et al.* Prevalence and virulence gene profiling of enteroaggregative *Escherichia coli*
31 in malnourished and nourished Brazilian children. *Diagn Microbiol Infect Dis* 2017;**89**:98–105.
- 32 Hecht AL, Casterline BW, Earley ZM *et al.* Strain competition restricts colonization of an enteric pathogen and
33 prevents colitis. *EMBO Rep* 2016;**17**:1281–91.
- 34 Hegarty JW, Guinane CM, Ross RP *et al.* Bacteriocin production: a relatively unharnessed probiotic trait?
35 *F1000Res* 2016;**5**:2587.
- 36 Hill DA, Hoffmann C, Abt MC *et al.* Metagenomic analyses reveal antibiotic-induced temporal and spatial changes
37 in intestinal microbiota with associated alterations in immune cell homeostasis. *Mucosal Immunol* 2010;**3**:148–
38 58.
- 39 Hoffmann C, Hill DA, Minkah N *et al.* Community-wide response of the gut microbiota to enteropathogenic
40 *Citrobacter rodentium* infection revealed by deep sequencing. *Infect Immun* 2009;**77**:4668–78.
- 41 Hsiao A, Ahmed AMS, Subramanian S *et al.* Members of the human gut microbiota involved in recovery from *Vibrio*
42 *cholerae* infection. *Nature* 2014;**515**:423–6.
- 43 Huang Y-L, Chassard C, Hausmann M *et al.* Sialic acid catabolism drives intestinal inflammation and microbial
44 dysbiosis in mice. *Nat Commun* 2015;**6**:8141.
- 45 Hughes ER, Winter MG, Duerkop BA *et al.* Microbial Respiration and Formate Oxidation as Metabolic Signatures of
46 Inflammation-Associated Dysbiosis. *Cell Host Microbe* 2017;**21**:208–19.
- 47 Hung C-C, Garner CD, Slauch JM *et al.* The intestinal fatty acid propionate inhibits *Salmonella* invasion through the
48 post-translational control of HilD. *Mol Microbiol* 2013;**87**:1045–60.
- 49 Islam KBMS, Fukiya S, Hagio M *et al.* Bile acid is a host factor that regulates the composition of the cecal
50 microbiota in rats. *Gastroenterology* 2011;**141**:1773–81.
- 51 Ivanov II, Atarashi K, Manel N *et al.* Induction of intestinal Th17 cells by segmented filamentous bacteria. *Cell*
52 2009;**139**:485–98.
- 53 Ivanov II. Microbe Hunting Hits Home. *Cell Host Microbe* 2017;**21**:282–5.

- 54 Jakobsson HE, Rodríguez-Piñeiro AM, Schütte A *et al.* The composition of the gut microbiota shapes the colon
55 mucus barrier. *EMBO Rep* 2015;**16**:164–77.
- 56 Johansson MEV, Gustafsson JK, Holmén-Larsson J *et al.* Bacteria penetrate the normally impenetrable inner colon
57 mucus layer in both murine colitis models and patients with ulcerative colitis. *Gut* 2014;**63**:281–91.
- 58 Johansson MEV, Larsson JMH, Hansson GC. The two mucus layers of colon are organized by the MUC2 mucin,
59 whereas the outer layer is a legislator of host-microbial interactions. *Proc Natl Acad Sci USA* 2011;**108 Suppl**
60 1:4659–65.
- 61 Kashtanova DA, Popenko AS, Tkacheva ON *et al.* Association between the gut microbiota and diet: Fetal life, early
62 childhood, and further life. *Nutrition* 2016;**32**:620–7.
- 63 Kato LM, Kawamoto S, Maruya M *et al.* The role of the adaptive immune system in regulation of gut microbiota.
64 *Immunol Rev* 2014;**260**:67–75.
- 65 Kim J, Lee J-Y, Lee H *et al.* Microbiological features and clinical impact of the type VI secretion system (T6SS) in
66 *Acinetobacter baumannii* isolates causing bacteremia. *Virulence* 2017:1–12.
- 67 Kim M, Qie Y, Park J *et al.* Gut Microbial Metabolites Fuel Host Antibody Responses. *Cell Host Microbe*
68 2016;**20**:202–14.
- 69 Kommineni S, Bretl DJ, Lam V *et al.* Bacteriocin production augments niche competition by enterococci in the
70 mammalian gastrointestinal tract. *Nature* 2015;**526**:719–22.
- 71 Kortman GAM, Raffatellu M, Swinkels DW *et al.* Nutritional iron turned inside out: intestinal stress from a gut
72 microbial perspective. *FEMS Microbiol Rev* 2014;**38**:1202–34.
- 73 Kotloff KL, Nataro JP, Blackwelder WC *et al.* Burden and aetiology of diarrhoeal disease in infants and young
74 children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control
75 study. *Lancet* 2013;**382**:209–22.
- 76 Larsson JMH, Karlsson H, Crespo JG *et al.* Altered O-glycosylation profile of MUC2 mucin occurs in active
77 ulcerative colitis and is associated with increased inflammation. *Inflamm Bowel Dis* 2011;**17**:2299–307.
- 78 Leamy LJ, Kelly SA, Nietfeldt J *et al.* Host genetics and diet, but not immunoglobulin A expression, converge to
79 shape compositional features of the gut microbiome in an advanced intercross population of mice. *Genome*
80 *Biol* 2014;**15**:552.
- 81 Lee SC, Tang MS, Lim YAL *et al.* Helminth colonization is associated with increased diversity of the gut microbiota.
82 Davies SJ (ed.). *PLoS Negl Trop Dis* 2014;**8**:e2880.
- 83 Lehrer RI, Lichtenstein AK, Ganz T. Defensins: antimicrobial and cytotoxic peptides of mammalian cells. *Annu Rev*
84 *Immunol* 1993;**11**:105–28.
- 85 Ley RE, Turnbaugh PJ, Klein S *et al.* Microbial ecology: human gut microbes associated with obesity. *Nature*
86 2006;**444**:1022–3.
- 87 Li H, Limenitakis JP, Fuhrer T *et al.* The outer mucus layer hosts a distinct intestinal microbial niche. *Nat Commun*
88 2015;**6**:8292.
- 89 Li L, Ma ZS. Testing the Neutral Theory of Biodiversity with Human Microbiome Datasets. *Sci Rep* 2016;**6**:31448.
- 90 Li RW, Li W, Sun J *et al.* The effect of helminth infection on the microbial composition and structure of the caprine
91 abomasal microbiome. *Sci Rep* 2016;**6**:20606.
- 92 Lidell ME, Moncada DM, Chadee K *et al.* *Entamoeba histolytica* cysteine proteases cleave the MUC2 mucin in its
93 C-terminal domain and dissolve the protective colonic mucus gel. *Proc Natl Acad Sci USA* 2006;**103**:9298–
94 303.
- 95 Lin J, Zhang W, Cheng J *et al.* A *Pseudomonas* T6SS effector recruits PQS-containing outer membrane vesicles
96 for iron acquisition. *Nat Commun* 2017;**8**:14888.
- 97 Liu JZ, Jellbauer S, Poe AJ *et al.* Zinc sequestration by the neutrophil protein calprotectin enhances *Salmonella*

- 98 growth in the inflamed gut. *Cell Host Microbe* 2012;**11**:227–39.
- 99 Lopez CA, Winter SE, Rivera-Chávez F *et al.* Phage-mediated acquisition of a type III secreted effector protein
00 boosts growth of salmonella by nitrate respiration. *MBio* 2012;**3**:e00143–12–e00143–12.
- 01 Lorenzo-Zúñiga V, Bartolí R, Planas R *et al.* Oral bile acids reduce bacterial overgrowth, bacterial translocation,
02 and endotoxemia in cirrhotic rats. *Hepatology* 2003;**37**:551–7.
- 03 Luethy PM, Huynh S, Ribardo DA *et al.* Microbiota-Derived Short-Chain Fatty Acids Modulate Expression of
04 *Campylobacter jejuni* Determinants Required for Commensalism and Virulence. Wolfe AJ, Ruby EG (eds.).
05 *MBio* 2017;**8**:e00407–17.
- 06 Lupp C, Robertson ML, Wickham ME *et al.* Host-Mediated Inflammation Disrupts the Intestinal Microbiota and
07 Promotes the Overgrowth of Enterobacteriaceae. *Cell Host Microbe* 2007;**2**:204.
- 08 Ma BW, Bokulich NA, Castillo PA *et al.* Routine habitat change: a source of unrecognized transient alteration of
09 intestinal microbiota in laboratory mice. Mantis NJ (ed.). *PLoS ONE* 2012;**7**:e47416.
- 10 Macpherson AJ, Geuking MB, McCoy KD. Innate and adaptive immunity in host-microbiota mutualism. *Front Biosci*
11 (*Schol Ed*) 2012;**4**:685–98.
- 12 Macpherson AJ, Geuking MB, Slack E *et al.* The habitat, double life, citizenship, and forgetfulness of IgA. *Immunol*
13 *Rev* 2012;**245**:132–46.
- 14 Macpherson AJ, McCoy KD. Standardised animal models of host microbial mutualism. *Mucosal Immunol*
15 2015;**8**:476–86.
- 16 Macpherson AJ, Slack E. The functional interactions of commensal bacteria with intestinal secretory IgA. *Curr Opin*
17 *Gastroenterol* 2007;**23**:673–8.
- 18 Maier L, Vyas R, Cordova CD *et al.* Microbiota-derived hydrogen fuels *Salmonella typhimurium* invasion of the gut
19 ecosystem. *Cell Host Microbe* 2013;**14**:641–51.
- 20 Martinez FAC, Balciunas EM, Converti A *et al.* Bacteriocin production by *Bifidobacterium* spp. A review.
21 *Biotechnology Advances* 2013;**31**:482–8.
- 22 Mazmanian SK, Liu CH, Tzianabos AO *et al.* An immunomodulatory molecule of symbiotic bacteria directs
23 maturation of the host immune system. *Cell* 2005;**122**:107–18.
- 24 McFarlane AJ, McSorley HJ, Davidson DJ *et al.* Enteric helminth-induced type I interferon signaling protects
25 against pulmonary virus infection through interaction with the microbiota. *J Allergy Clin Immunol* 2017, DOI:
26 10.1016/j.jaci.2017.01.016.
- 27 McGuckin MA, Lindén SK, Sutton P *et al.* Mucin dynamics and enteric pathogens. *Nat Rev Microbiol* 2011;**9**:265–
28 78.
- 29 McKenney EA, Williamson L, Yoder AD *et al.* Alteration of the rat cecal microbiome during colonization with the
30 helminth *Hymenolepis diminuta*. *Gut Microbes* 2015;**6**:182–93.
- 31 Meyer-Hoffert U, Hornef MW, Henriques-Normark B *et al.* Secreted enteric antimicrobial activity localises to the
32 mucus surface layer. *Gut* 2008;**57**:764–71.
- 33 Miethke M, Marahiel MA. Siderophore-based iron acquisition and pathogen control. *Microbiol Mol Biol Rev*
34 2007;**71**:413–51.
- 35 Mike LA, Smith SN, Sumner CA *et al.* Siderophore vaccine conjugates protect against uropathogenic *Escherichia*
36 *coli* urinary tract infection. *Proc Natl Acad Sci USA* 2016;**113**:13468–73.
- 37 Miki T, Goto R, Fujimoto M *et al.* The Bactericidal Lectin RegIII β Prolongs Gut Colonization and Enteropathy in the
38 Streptomycin Mouse Model for *Salmonella* Diarrhea. *Cell Host Microbe* 2017;**21**:195–207.
- 39 Miki T, Holst O, Hardt W-D. The bactericidal activity of the C-type lectin RegIII β against Gram-negative bacteria
40 involves binding to lipid A. *J Biol Chem* 2012;**287**:34844–55.

- 41 MILLER CP, BOHNHOFF M, DRAKE BL. The effect of antibiotic therapy on susceptibility to an experimental
42 enteric infection. *Trans Assoc Am Physicians* 1954;**67**:156–61.
- 43 Modi SR, Collins JJ, Relman DA. Antibiotics and the gut microbiota. *J Clin Invest* 2014;**124**:4212–8.
- 44 Moor K, Diard M, Sellin ME *et al.* High-avidity IgA protects the intestine by enchainning growing bacteria. *Nature*
45 2017;**544**:498–502.
- 46 Moran NA, Sloan DB. The Hologenome Concept: Helpful or Hollow? *PLoS Biol* 2015;**13**:e1002311.
- 47 Moreira CG, Russell R, Mishra AA *et al.* Bacterial Adrenergic Sensors Regulate Virulence of Enteric Pathogens in
48 the Gut. *MBio* 2016;**7**:e00826–16.
- 49 Mougous JD, Cuff ME, Raunser S *et al.* A virulence locus of *Pseudomonas aeruginosa* encodes a protein secretion
50 apparatus. *Science* 2006;**312**:1526–30.
- 51 Muegge BD, Kuczynski J, Knights D *et al.* Diet drives convergence in gut microbiome functions across mammalian
52 phylogeny and within humans. *Science* 2011;**332**:970–4.
- 53 Namasivayam S, Maiga M, Yuan W *et al.* Longitudinal profiling reveals a persistent intestinal dysbiosis triggered by
54 conventional anti-tuberculosis therapy. *Microbiome* 2017;**5**:71.
- 55 Nedialkova LP, Denzler R, Koeppel MB *et al.* Inflammation fuels colicin Ib-dependent competition of *Salmonella*
56 serovar Typhimurium and *E. coli* in enterobacterial blooms. Galán JE (ed.). *PLoS Pathog* 2014;**10**:e1003844.
- 57 Neville BA, Forster SC, Lawley TD. Commensal Koch's postulates: establishing causation in human microbiota
58 research. *Curr Opin Microbiol* 2017;**42**:47–52.
- 59 Ng KM, Ferreyra JA, Higginbottom SK *et al.* Microbiota-liberated host sugars facilitate post-antibiotic expansion of
60 enteric pathogens. *Nature* 2013;**502**:96–9.
- 61 Niehus R, Picot A, Oliveira NM *et al.* The evolution of siderophore production as a competitive trait. *Evolution*
62 2017;**71**:1443–55.
- 63 Nunn KL, Wang Y-Y, Harit D *et al.* Enhanced Trapping of HIV-1 by Human Cervicovaginal Mucus Is Associated
64 with *Lactobacillus crispatus*-Dominant Microbiota. *MBio* 2015;**6**:e01084–15.
- 65 O'Malley MA. The nineteenth century roots of “everything is everywhere.” *Nat Rev Microbiol* 2007;**5**:647–51.
- 66 Osborne LC, Monticelli LA, Nice TJ *et al.* Coinfection. Virus-helminth coinfection reveals a microbiota-independent
67 mechanism of immunomodulation. *Science* 2014;**345**:578–82.
- 68 Pabst O, Cerovic V, Hornef M. Secretory IgA in the Coordination of Establishment and Maintenance of the
69 Microbiota. *Trends Immunol* 2016;**37**:287–96.
- 70 Parfrey LW, Walters WA, Knight R. Microbial eukaryotes in the human microbiome: ecology, evolution, and future
71 directions. *Front Microbiol* 2011;**2**:153.
- 72 Parfrey LW, Walters WA, Lauber CL *et al.* Communities of microbial eukaryotes in the mammalian gut within the
73 context of environmental eukaryotic diversity. *Front Microbiol* 2014;**5**:298.
- 74 Parsons DA, Heffron F. *sciS*, an *icmF* homolog in *Salmonella enterica* serovar Typhimurium, limits intracellular
75 replication and decreases virulence. *Infect Immun* 2005;**73**:4338–45.
- 76 Pelaseyed T, Bergström JH, Gustafsson JK *et al.* The mucus and mucins of the goblet cells and enterocytes
77 provide the first defense line of the gastrointestinal tract and interact with the immune system. *Immunol Rev*
78 2014;**260**:8–20.
- 79 Pereira FC, Berry D. Microbial nutrient niches in the gut. *Environ Microbiol* 2017;**19**:1366–78.
- 80 Peterson DA, McNulty NP, Guruge JL *et al.* IgA response to symbiotic bacteria as a mediator of gut homeostasis.
81 *Cell Host Microbe* 2007;**2**:328–39.
- 82 Petersson J, Schreiber O, Hansson GC *et al.* Importance and regulation of the colonic mucus barrier in a mouse

- 83 model of colitis. *Am J Physiol Gastrointest Liver Physiol* 2011;**300**:G327–33.
- 84 Platts-Mills JA, Taniuchi M, Uddin MJ *et al.* Association between enteropathogens and malnutrition in children aged
85 6-23 mo in Bangladesh: a case-control study. *Am J Clin Nutr* 2017;**105**:1132–8.
- 86 Plichta DR, Juncker AS, Bertalan M *et al.* Transcriptional interactions suggest niche segregation among
87 microorganisms in the human gut. *Nat Microbiol* 2016;**1**:16152.
- 88 Png CW, Lindén SK, Gilshenan KS *et al.* Mucolytic bacteria with increased prevalence in IBD mucosa augment in
89 vitro utilization of mucin by other bacteria. *Am J Gastroenterol* 2010;**105**:2420–8.
- 90 Pourabedin M, Chen Q, Yang M *et al.* Mannan- and xylooligosaccharides modulate caecal microbiota and
91 expression of inflammatory-related cytokines and reduce caecal *Salmonella* Enteritidis colonisation in young
92 chickens. Nakatsu C (ed.). *FEMS Microbiol Ecol* 2017;**93**:fiw226.
- 93 Puhar A, Sansonetti PJ. Type III secretion system. *Curr Biol* 2014;**24**:R784–91.
- 94 Pukatzki S, Ma AT, Sturtevant D *et al.* Identification of a conserved bacterial protein secretion system in *Vibrio*
95 *cholerae* using the *Dictyostelium* host model system. *Proc Natl Acad Sci USA* 2006;**103**:1528–33.
- 96 Qin J, Li R, Raes J *et al.* A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*
97 2010;**464**:59–65.
- 98 Qiu J, Luo Z-Q. *Legionella* and *Coxiella* effectors: strength in diversity and activity. *Nat Rev Microbiol* 2017;**23**:274.
- 99 Raffatellu M, George MD, Akiyama Y *et al.* Lipocalin-2 resistance confers an advantage to *Salmonella enterica*
00 serotype Typhimurium for growth and survival in the inflamed intestine. *Cell Host Microbe* 2009;**5**:476–86.
- 01 Rakoff-Nahoum S, Foster KR, Comstock LE. The evolution of cooperation within the gut microbiota. *Nature*
02 2016;**533**:255–9.
- 03 Ramanan D, Bowcutt R, Lee SC *et al.* Helminth infection promotes colonization resistance via type 2 immunity.
04 *Science* 2016;**352**:608–12.
- 05 Ramirez-Farias C, Slezak K, Fuller Z *et al.* Effect of inulin on the human gut microbiota: stimulation of
06 *Bifidobacterium adolescentis* and *Faecalibacterium prausnitzii*. *Br J Nutr* 2009;**101**:541–50.
- 07 Randremanana RV, Razafindratsimandresy R, Andriatahina T *et al.* Etiologies, Risk Factors and Impact of Severe
08 Diarrhea in the Under-Fives in Moramanga and Antananarivo, Madagascar. Huang Y-C (ed.). *PLoS ONE*
09 2016;**11**:e0158862.
- 10 Rescigno M. Intestinal microbiota and its effects on the immune system. *Cell Microbiol* 2014;**16**:1004–13.
- 11 Rey FE, Gonzalez MD, Cheng J *et al.* Metabolic niche of a prominent sulfate-reducing human gut bacterium. *Proc*
12 *Natl Acad Sci USA* 2013;**110**:13582–7.
- 13 Reynolds LA, Redpath SA, Yurist-Doutsch S *et al.* Enteric Helminths Promote *Salmonella* Coinfection by Altering
14 the Intestinal Metabolome. *J INFECT DIS* 2017;**215**:1245–54.
- 15 Ridaura VK, Faith JJ, Rey FE *et al.* Gut microbiota from twins discordant for obesity modulate metabolism in mice.
16 *Science* 2013;**341**:1241214–4.
- 17 Ridlon JM, Kang DJ, Hylemon PB *et al.* Bile acids and the gut microbiome. *Curr Opin Gastroenterol* 2014;**30**:332–
18 8.
- 19 Riley MA, Wertz JE. Bacteriocins: evolution, ecology, and application. *Annu Rev Microbiol* 2002;**56**:117–37.
- 20 Rivera-Chávez F, Lopez CA, Bäumlér AJ. Oxygen as a driver of gut dysbiosis. *Free Radic Biol Med* 2017;**105**:93–
21 101.
- 22 Rivera-Chávez F, Lopez CA, Zhang LF *et al.* Energy Taxits toward Host-Derived Nitrate Supports a *Salmonella*
23 Pathogenicity Island 1-Independent Mechanism of Invasion. *MBio* 2016a;**7**:e00960–16.
- 24 Rivera-Chávez F, Zhang LF, Faber F *et al.* Depletion of Butyrate-Producing Clostridia from the Gut Microbiota

- 25 Drives an Aerobic Luminal Expansion of Salmonella. *Cell Host Microbe* 2016b;**19**:443–54.
- 26 Rivière A, Selak M, Lantin D *et al.* Bifidobacteria and Butyrate-Producing Colon Bacteria: Importance and
27 Strategies for Their Stimulation in the Human Gut. *Front Microbiol* 2016;**7**:979.
- 28 Rodríguez-Díaz J, García-Mantrana I, Vila-Vicent S *et al.* Relevance of secretor status genotype and microbiota
29 composition in susceptibility to rotavirus and norovirus infections in humans. *Sci Rep* 2017;**7**:45559.
- 30 Rossi O, van Berkel LA, Chain F *et al.* Faecalibacterium prausnitzii A2-165 has a high capacity to induce IL-10 in
31 human and murine dendritic cells and modulates T cell responses. *Sci Rep* 2016;**6**:18507.
- 32 Round JL, Mazmanian SK. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the
33 intestinal microbiota. *Proc Natl Acad Sci USA* 2010;**107**:12204–9.
- 34 Russell AB, Wexler AG, Harding BN *et al.* A type VI secretion-related pathway in Bacteroidetes mediates
35 interbacterial antagonism. *Cell Host Microbe* 2014;**16**:227–36.
- 36 Rutayisire E, Huang K, Liu Y *et al.* The mode of delivery affects the diversity and colonization pattern of the gut
37 microbiota during the first year of infants' life: a systematic review. *BMC Gastroenterol* 2016;**16**:86.
- 38 Salomon D, Klimko JA, Trudgian DC *et al.* Type VI Secretion System Toxins Horizontally Shared between Marine
39 Bacteria. Mougous JD (ed.). *PLoS Pathog* 2015;**11**:e1005128.
- 40 Salzman NH, Hung K, Haribhai D *et al.* Enteric defensins are essential regulators of intestinal microbial ecology.
41 *Nat Immunol* 2010;**11**:76–83.
- 42 Sana TG, Flaugnatti N, Lugo KA *et al.* Salmonella Typhimurium utilizes a T6SS-mediated antibacterial weapon to
43 establish in the host gut. *Proc Natl Acad Sci USA* 2016;**113**:E5044–51.
- 44 Sana TG, Lugo KA, Monack DM. T6SS: The bacterial “fight club” in the host gut. Hogan DA (ed.). *PLoS Pathog*
45 2017;**13**:e1006325.
- 46 Sansonetti PJ. War and peace at mucosal surfaces. *Nature Reviews Immunology* 2004;**4**:953–64.
- 47 Sassone-Corsi M, Chairatana P, Zheng T *et al.* Siderophore-based immunization strategy to inhibit growth of
48 enteric pathogens. *Proc Natl Acad Sci USA* 2016a;**113**:13462–7.
- 49 Sassone-Corsi M, Nuccio S-P, Liu H *et al.* Microcins mediate competition among Enterobacteriaceae in the
50 inflamed gut. *Nature* 2016b;**540**:280–3.
- 51 Schnupf P, Gaboriau-Routhiau V, Cerf-Bensussan N. Host interactions with Segmented Filamentous Bacteria: an
52 unusual trade-off that drives the post-natal maturation of the gut immune system. *Semin Immunol*
53 2013;**25**:342–51.
- 54 Schnupf P, Gaboriau-Routhiau V, Sansonetti PJ *et al.* Segmented filamentous bacteria, Th17 inducers and helpers
55 in a hostile world. *Curr Opin Microbiol* 2017;**35**:100–9.
- 56 Schütte A, Ermund A, Becker-Pauly C *et al.* Microbial-induced meprin β cleavage in MUC2 mucin and a functional
57 CFTR channel are required to release anchored small intestinal mucus. *Proc Natl Acad Sci USA*
58 2014;**111**:12396–401.
- 59 Sekirov I, Tam NM, Jogova M *et al.* Antibiotic-induced perturbations of the intestinal microbiota alter host
60 susceptibility to enteric infection. *Infect Immun* 2008;**76**:4726–36.
- 61 Shannon B, Gajer P, Yi TJ *et al.* Distinct Effects of the Cervicovaginal Microbiota and Herpes Simplex Type 2
62 Infection on Female Genital Tract Immunology. *J INFECT DIS* 2017a;**215**:1366–75.
- 63 Shannon B, Yi TJ, Perusini S *et al.* Association of HPV infection and clearance with cervicovaginal immunology
64 and the vaginal microbiota. *Mucosal Immunol* 2017b;**6**:751.
- 65 Shimotoyodome A, Meguro S, Hase T *et al.* Short chain fatty acids but not lactate or succinate stimulate mucus
66 release in the rat colon. *Comp Biochem Physiol, Part A Mol Integr Physiol* 2000;**125**:525–31.
- 67 Si M, Zhao C, Burkinshaw B *et al.* Manganese scavenging and oxidative stress response mediated by type VI

- 68 secretion system in *Burkholderia thailandensis*. *Proc Natl Acad Sci USA* 2017;**114**:E2233–42.
- 69 Siegwald L, Audebert C, Even G *et al*. Targeted metagenomic sequencing data of human gut microbiota
70 associated with *Blastocystis* colonization. *Sci Data* 2017;**4**:170081.
- 71 Slack E, Balmer ML, Fritz JH *et al*. Functional flexibility of intestinal IgA - broadening the fine line. *Front Immunol*
72 2012;**3**:100.
- 73 Slack E, Hapfelmeier S, Stecher B *et al*. Innate and adaptive immunity cooperate flexibly to maintain host-
74 microbiota mutualism. *Science* 2009;**325**:617–20.
- 75 Smith MI, Yatsunenkov T, Manary MJ *et al*. Gut microbiomes of Malawian twin pairs discordant for kwashiorkor.
76 *Science* 2013;**339**:548–54.
- 77 Sommer F, Adam N, Johansson MEV *et al*. Altered mucus glycosylation in core 1 O-glycan-deficient mice affects
78 microbiota composition and intestinal architecture. Sanz Y (ed.). *PLoS ONE* 2014;**9**:e85254.
- 79 Spasova DS, Surh CD. Blowing on embers: commensal microbiota and our immune system. *Front Immunol*
80 2014;**5**:318.
- 81 Spees AM, Wangdi T, Lopez CA *et al*. Streptomycin-Induced Inflammation Enhances *Escherichia coli* Gut
82 Colonization Through Nitrate Respiration. *MBio* 2013;**4**:e00430–13–e00430–13.
- 83 Spiga L, Winter MG, Furtado de Carvalho T *et al*. An Oxidative Central Metabolism Enables *Salmonella* to Utilize
84 Microbiota-Derived Succinate. *Cell Host Microbe* 2017;**22**:291–6.
- 85 Stecher B, Chaffron S, Käppli R *et al*. Like will to like: abundances of closely related species can predict
86 susceptibility to intestinal colonization by pathogenic and commensal bacteria. Ochman H (ed.). *PLoS Pathog*
87 2010;**6**:e1000711.
- 88 Stecher B, Denzler R, Maier L *et al*. Gut inflammation can boost horizontal gene transfer between pathogenic and
89 commensal Enterobacteriaceae. *Proc Natl Acad Sci USA* 2012;**109**:1269–74.
- 90 Stecher B, Hardt W-D. Mechanisms controlling pathogen colonization of the gut. *Curr Opin Microbiol* 2011;**14**:82–
91 91.
- 92 Stelter C, Käppli R, König C *et al*. *Salmonella*-induced mucosal lectin RegIII β kills competing gut microbiota. May
93 RC (ed.). *PLoS ONE* 2011;**6**:e20749.
- 94 Stokholm J, Thorsen J, Chawes BL *et al*. Cesarean section changes neonatal gut colonization. *J Allergy Clin*
95 *Immunol* 2016;**138**:881–2.
- 96 Studer N, Desharnais L, Beutler M *et al*. Functional Intestinal Bile Acid 7 α -Dehydroxylation by *Clostridium scindens*
97 Associated with Protection from *Clostridium difficile* Infection in a Gnotobiotic Mouse Model. *Front Cell Infect*
98 *Microbiol* 2016;**6**:191.
- 99 Subramanian S, Huq S, Yatsunenkov T *et al*. Persistent gut microbiota immaturity in malnourished Bangladeshi
00 children. *Nature* 2014;**510**:417–21.
- 01 Suzuki K, Meek B, Doi Y *et al*. Aberrant expansion of segmented filamentous bacteria in IgA-deficient gut. *Proc*
02 *Natl Acad Sci USA* 2004;**101**:1981–6.
- 03 Tailford LE, Crost EH, Kavanaugh D *et al*. Mucin glycan foraging in the human gut microbiome. *Front Genet*
04 2015a;**6**:81.
- 05 Tailford LE, Owen CD, Walshaw J *et al*. Discovery of intramolecular trans-sialidases in human gut microbiota
06 suggests novel mechanisms of mucosal adaptation. *Nat Commun* 2015b;**6**:7624.
- 07 Thiennimitr P, Winter SE, Winter MG *et al*. Intestinal inflammation allows *Salmonella* to use ethanolamine to
08 compete with the microbiota. *Proc Natl Acad Sci USA* 2011;**108**:17480–5.
- 09 Tian Y, Zhao Y, Shi L *et al*. Type VI Secretion Systems of *Erwinia amylovora* Contribute to Bacterial Competition,
10 Virulence, and Exopolysaccharide Production. *Phytopathology* 2017;**107**:654–61.

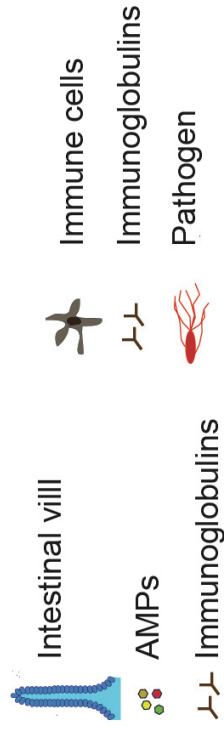
- 11 Tomas J, Mulet C, Saffarian A *et al.* High-fat diet modifies the PPAR- γ pathway leading to disruption of microbial
12 and physiological ecosystem in murine small intestine. *Proc Natl Acad Sci USA* 2016;**113**:E5934–43.
- 13 Torow N, Hornef MW. The Neonatal Window of Opportunity: Setting the Stage for Life-Long Host-Microbial
14 Interaction and Immune Homeostasis. *J Immunol* 2017;**198**:557–63.
- 15 Turfkruyer M, Verhasselt V. Breast milk and its impact on maturation of the neonatal immune system. *Curr Opin*
16 *Infect Dis* 2015;**28**:199–206.
- 17 Turnbaugh PJ, Ley RE, Mahowald MA *et al.* An obesity-associated gut microbiome with increased capacity for
18 energy harvest. *Nature* 2006;**444**:1027–31.
- 19 Uebanso T, Ohnishi A, Kitayama R *et al.* Effects of Low-Dose Non-Caloric Sweetener Consumption on Gut
20 Microbiota in Mice. *Nutrients* 2017;**9**:560.
- 21 Unterweger D, Miyata ST, Bachmann V *et al.* The *Vibrio cholerae* type VI secretion system employs diverse
22 effector modules for intraspecific competition. *Nat Commun* 2014;**5**:3549.
- 23 Ursell LK, Metcalf JL, Parfrey LW *et al.* Defining the human microbiome. *Nutrition Reviews* 2012;**70 Suppl 1**:S38–
24 44.
- 25 Vaishnava S, Yamamoto M, Severson KM *et al.* The antibacterial lectin RegIII γ promotes the spatial
26 segregation of microbiota and host in the intestine. *Science* 2011;**334**:255–8.
- 27 Valeri M, Rossi Paccani S, Kasendra M *et al.* Pathogenic *E. coli* exploits SslE mucinase activity to translocate
28 through the mucosal barrier and get access to host cells. Chakravorty D (ed.). *PLoS ONE* 2015;**10**:e0117486.
- 29 Van den Bossche L, Hindryckx P, Devisscher L *et al.* Ursodeoxycholic Acid and Its Taurine- or Glycine-Conjugated
30 Species Reduce Colitogenic Dysbiosis and Equally Suppress Experimental Colitis in Mice. Elkins CA (ed.).
31 *Appl Environ Microbiol* 2017;**83**:e02766–16.
- 32 van der Post S, Subramani DB, Bäckström M *et al.* Site-specific O-glycosylation on the MUC2 mucin protein
33 inhibits cleavage by the *Porphyromonas gingivalis* secreted cysteine protease (RgpB). *J Biol Chem*
34 2013;**288**:14636–46.
- 35 Van der Waaij D, Berghuis-de Vries JM, Lekkerkerk-van der Wees JEC. Colonization resistance of the digestive
36 tract in conventional and antibiotic-treated mice. *Journal of Hygiene* 2009;**69**:405–11.
- 37 Vazquez-Gutierrez P, de Wouters T, Werder J *et al.* High Iron-Sequestering Bifidobacteria Inhibit Enteropathogen
38 Growth and Adhesion to Intestinal Epithelial Cells In vitro. *Front Microbiol* 2016;**7**:1480.
- 39 Velasquez-Manoff M. Gut microbiome: the peacekeepers. *Nature* 2015;**518**:S3–11.
- 40 Wagner VE, Dey N, Guruge J *et al.* Effects of a gut pathobiont in a gnotobiotic mouse model of childhood
41 undernutrition. *Sci Transl Med* 2016;**8**:366ra164–4.
- 42 Wahlström A, Sayin SI, Marschall H-U *et al.* Intestinal Crosstalk between Bile Acids and Microbiota and Its Impact
43 on Host Metabolism. *Cell Metab* 2016;**24**:41–50.
- 44 Walk ST, Blum AM, Ewing SA-S *et al.* Alteration of the murine gut microbiota during infection with the parasitic
45 helminth *Heligmosomoides polygyrus*. *Inflamm Bowel Dis* 2010;**16**:1841–9.
- 46 Walsh KP, Brady MT, Finlay CM *et al.* Infection with a helminth parasite attenuates autoimmunity through TGF-
47 beta-mediated suppression of Th17 and Th1 responses. *J Immunol* 2009;**183**:1577–86.
- 48 Wan B, Zhang Q, Ni J *et al.* Type VI secretion system contributes to Enterohemorrhagic *Escherichia coli* virulence
49 by secreting catalase against host reactive oxygen species (ROS). Zamboni DS (ed.). *PLoS Pathog*
50 2017;**13**:e1006246.
- 51 Wang T, Si M, Song Y *et al.* Type VI Secretion System Transports Zn²⁺ to Combat Multiple Stresses and Host
52 Immunity. Skaar EP (ed.). *PLoS Pathog* 2015;**11**:e1005020.
- 53 Willemsen LEM, Koetsier MA, van Deventer SJH *et al.* Short chain fatty acids stimulate epithelial mucin 2
54 expression through differential effects on prostaglandin E(1) and E(2) production by intestinal myofibroblasts.

- 55 *Gut* 2003;**52**:1442–7.
- 56 Winston JA, Theriot CM. Impact of microbial derived secondary bile acids on colonization resistance against
57 *Clostridium difficile* in the gastrointestinal tract. *Anaerobe* 2016;**41**:44–50.
- 58 Winter SE, Bäumlér AJ. Why related bacterial species bloom simultaneously in the gut: principles underlying the
59 “Like will to like” concept. *Cell Microbiol* 2014a;**16**:179–84.
- 60 Winter SE, Bäumlér AJ. Dysbiosis in the inflamed intestine: chance favors the prepared microbe. *Gut Microbes*
61 2014b;**5**:71–3.
- 62 Winter SE, Keestra AM, Tsolis RM *et al.* The Blessings and Curses of Intestinal Inflammation. *Cell Host Microbe*
63 2010a;**8**:36–43.
- 64 Winter SE, Lopez CA, Bäumlér AJ. The dynamics of gut-associated microbial communities during inflammation.
65 *EMBO Rep* 2013;**14**:319–27.
- 66 Winter SE, Thiennimitr P, Winter MG *et al.* Gut inflammation provides a respiratory electron acceptor for
67 *Salmonella*. *Nature* 2010b;**467**:426–9.
- 68 Winter SE, Winter MG, Xavier MN *et al.* Host-derived nitrate boosts growth of *E. coli* in the inflamed gut. *Science*
69 2013;**339**:708–11.
- 70 Wrzosek L, Miquel S, Noordine M-L *et al.* *Bacteroides thetaiotaomicron* and *Faecalibacterium prausnitzii* influence
71 the production of mucus glycans and the development of goblet cells in the colonic epithelium of a gnotobiotic
72 model rodent. *BMC Biol* 2013;**11**:61.
- 73 Yang M, Liu Z, Hughes C *et al.* Bile salt-induced intermolecular disulfide bond formation activates *Vibrio cholerae*
74 virulence. *Proc Natl Acad Sci USA* 2013;**110**:2348–53.
- 75 Yatsunencko T, Rey FE, Manary MJ *et al.* Human gut microbiome viewed across age and geography. *Nature*
76 2012;**486**:222–7.
- 77 Zaiss MM, Rapin A, Lebon L *et al.* The Intestinal Microbiota Contributes to the Ability of Helminths to Modulate
78 Allergic Inflammation. *Immunity* 2015;**43**:998–1010.
- 79

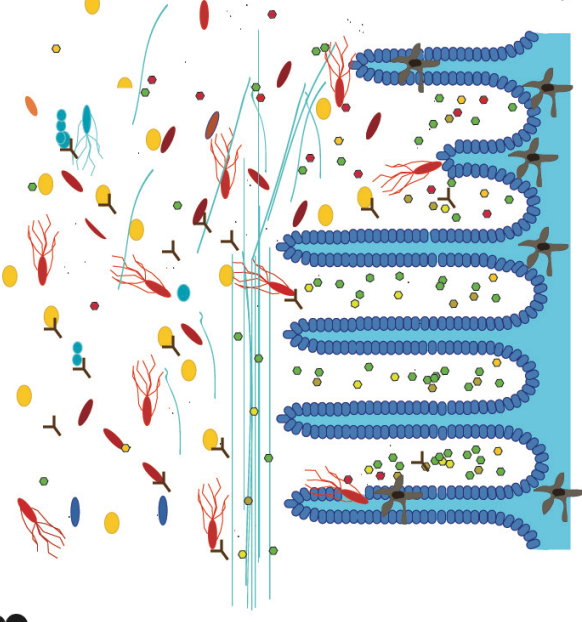
A



Homeostasis



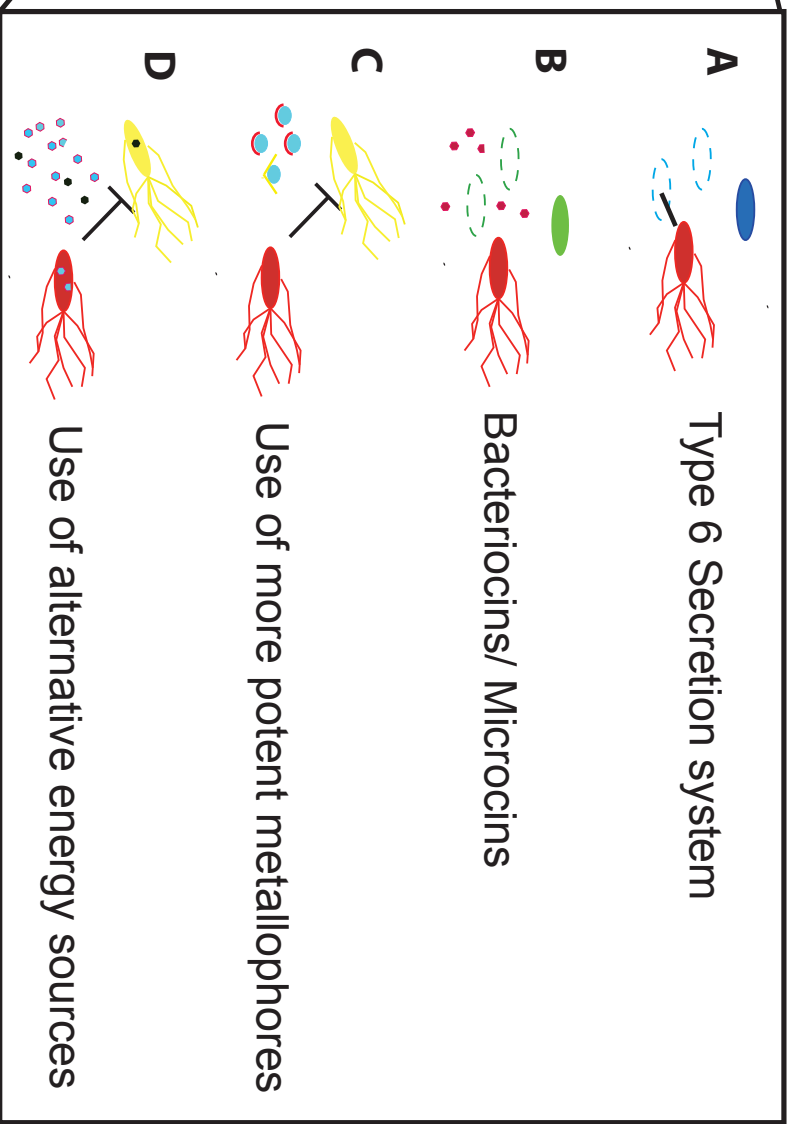
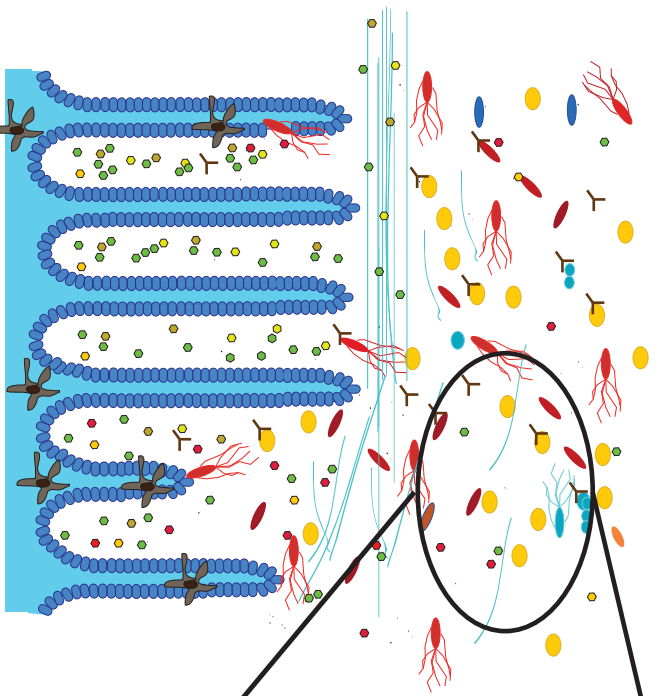
B



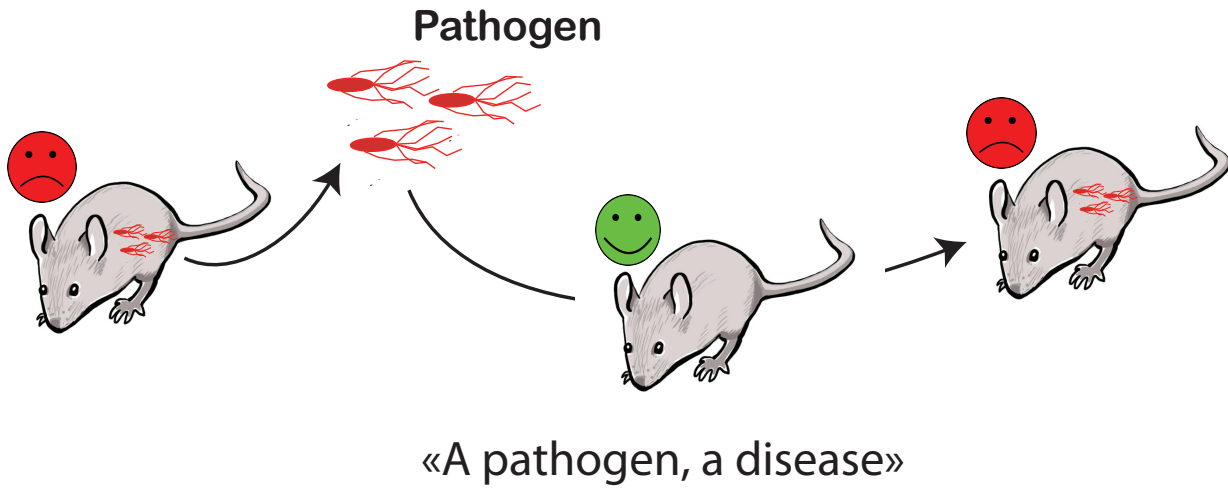
Dysbiosis



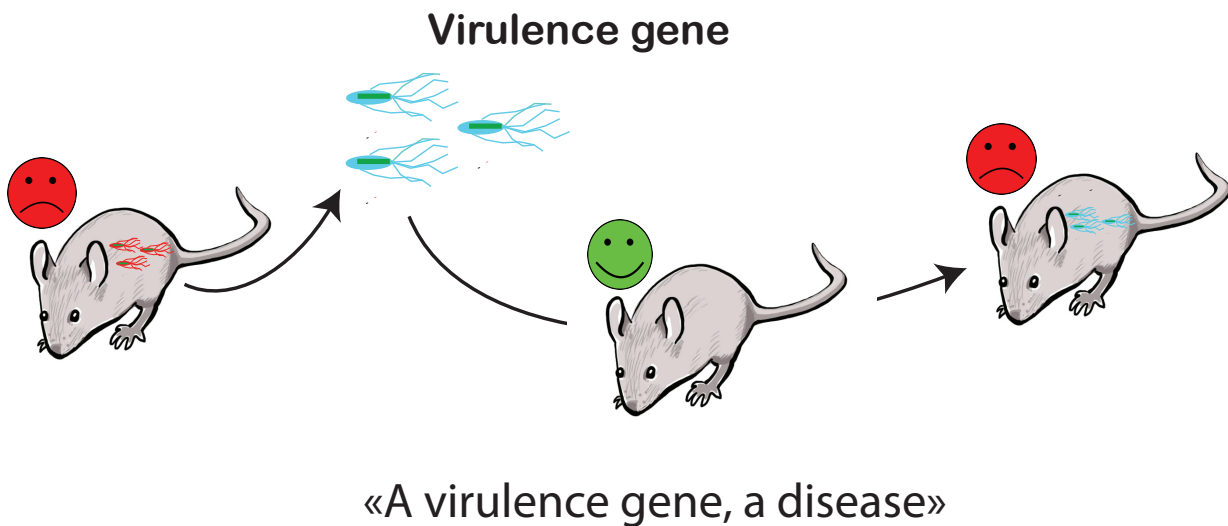
Decrease in microbiota diversity
 Thinning of mucus layer
 Microbiota in intravillous space
 Epithelial damage
 Villi blunting
 Influx of immune cells
 Increased production of AMPs
 Production/ secretion of targeted Igs



Koch's postulate



Molecular Koch's postulate



Ecological Koch's postulate

