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1 The healthy human virome: from virus-host symbiosis to disease

2

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29 **Abstract**

30 Viruses are ubiquitous, essential components of any ecosystem, and of multicellular organism
31 holobionts. Numerous viruses cause acute infection, killing the host or being cleared by immune
32 system. In many other cases, viruses coexist with the host as symbionts, either temporarily or for
33 the duration of the host's life. Apparently, virus-host relationships span the entire range from
34 aggressive parasitism to mutualism. Here we attempt to delineate the healthy human virome, that
35 is, the entirety of viruses that are present in a healthy human body. The bulk of the healthy virome
36 consists of bacteriophages infecting bacteria in the intestine and other locations. However, a
37 variety of viruses, such as anelloviruses and herpesviruses, and the numerous endogenous
38 retroviruses, persist by replicating in human cells, and these are our primary focus. Crucially, the
39 boundary between symbiotic and pathogenic viruses is fluid such that members of the healthy
40 virome can become pathogens under changing conditions.

41

42

43

44 **Introduction**

45 Billions of years of perennial and ubiquitous co-evolution between viruses and cells have produced
46 a broad spectrum of virus-host interaction regimes, ranging from aggressive antagonism to
47 commensalism, whereby viruses coexist with their hosts without harming them, at least, in the
48 short term, and even to mutualism when a virus is beneficial and can be essential to the host [1-4].
49 The relationship between a particular virus and its host can be rarely, if ever, defined by a single
50 regime. Rather, the mode of virus-host interaction is a function of multiple factors, including the
51 environmental conditions, host and virus population structure, the immunological status of the host
52 and many more.

53
54 Virus-host relationships that do not result in the demise of the host cell have been described across
55 the virosphere [3,4]. Hence the concept of the ‘normal’ or ‘healthy’ virome, in principle, is
56 applicable to any organism, including humans. Indeed, although most of the best characterized
57 human viruses cause acute infections and are associated with diseases, a healthy human organism
58 is host to a much greater variety of viruses [5-7]. The substantial majority of these infect bacteria
59 that inhabit the human intestine, but a number of viruses actually reproduce in human cells without
60 causing disease, at least, in the short term.

61
62 In this brief review, we systematically discuss the healthy human virome and emphasize that the
63 boundary between “normal” and pathogenic (that is, causally associated with clinically manifested
64 disease) viromes is blurred. Indeed, the same virus can be either a symbiont (with either no
65 perceptible fitness effect on the host, that is, effectively, a commensal, or with a beneficial effect)
66 or a pathogen depending on the conditions such as the health status and developmental stage of
67 the host. We further stress that the current knowledge of symbiotic viruses lags far behind that of
68 the pathogenic viruses.

69

70 **The healthy human phageome**

71 The human intestine, by far the richest microbial habitat in the body, contains about 10^{14} bacterial
72 and archaeal cells at any given moment [8]. As many microbial communities, the human
73 microbiome hosts a broad variety of viruses, in which tailed bacteriophages (class *Caudoviricetes*
74 within the realm *Duplodnaviria*) comprise the overwhelming majority [8,9], albeit with a
75 considerable contribution by ssDNA phages of the families *Microviridae* [10-12] and *Inoviridae*
76 [13] (realm *Monodnaviria*). Systematic metagenomics surveys of the human phageome identify

77 thousands of phages but show that relatively few are common components of the healthy gut
78 phageome. Thus, one of the most detailed metagenomics analyses resulted in the identification of
79 only 23 phages that were shared by >50% of the tested individuals [9]. Strikingly, the most
80 prevalent human-associated phage (and most prominent component of the healthy human virome
81 altogether), the crAssphage, has been discovered only through metagenomics [14]. This initial
82 finding has been followed by the characterization of an expansive group of crAss-like phages, also
83 by metagenome analysis [15,16]. Subsequently, some crAss-like phages have been grown in
84 cultures of the respective host bacteria, members of the phylum Bacteroidetes [17,18]. Given the
85 difficulty of growing the human intestine-associated bacteria-phage systems in the laboratory, the
86 actual size and diversity of the healthy human phageome remains to be discovered. Importantly,
87 substantial changes in the human phageome have been associated with various diseases conditions,
88 including infection with human and simian immunodeficiency viruses, and in some cases, the
89 phageome perturbation was, apparently, decoupled from the changes in the microbiome [19-21].

90

91 **Symbiotic viruses replicating in human cells**

92 Over many decades, diverse viruses have been isolated from healthy humans more or less by
93 chance. In the last few years, systematic surveys of the healthy human virome became possible
94 thanks to the advances of metagenomics [6,7]. Below we briefly discuss the viruses that have been
95 shown, either by traditional virology approaches or by metagenomics (Figure 1a), to be commonly
96 present in healthy humans without causing apparent disease, following the main divisions of the
97 current virus taxonomy [22,23]. The key aspects of the association of these viruses with the human
98 organism are summarized in Figure 1.

99

100 **Realm *Riboviria***

101 Kingdom *Orthornavira*

102 The realm *Riboviria* consists of viruses with RNA genomes as well as viruses with DNA genomes
103 that employ reverse transcription in their replication cycles. The kingdom *Orthornavira*
104 encompasses RNA viruses that share homologous RNA-dependent RNA polymerases. Many RNA
105 viruses have been isolated or detected by metatranscriptomics in healthy humans but few can be
106 confidently identified as symbionts replicating in human cells (Figure 1a).

107

108 Perhaps, the most notable apparent human symbionts among the orthornaviruses are pegiviruses
109 (family *Flaviviridae*) [24,25]. The prototypical pegivirus has been initially tentatively identified

110 as hepatitis G virus [26], but no association with hepatitis has been subsequently confirmed [27].
111 In the family tree of flavivirids, pegiviruses tightly cluster with hepaciviruses which include
112 hepatitis C virus (HCV), a major human pathogen [24,25]. However, unlike HCV, pegiviruses
113 have not been linked to any pathology. Pegivirus infection in humans is common, with the
114 incidence of about 5%, and pegiviruses readily grow in human cell cultures, leaving no doubt that
115 these are bona fide human viruses [25]. Notably, pegivirus infection appears to be associated with
116 benign clinical outcome in AIDS patients [28,29] indicating that these apparent viral symbionts of
117 humans could benefit the host via protection from other viruses.

118
119 A recent, intriguing addition to the human virome are statoviruses (for STool-Associated TOmbus-
120 like viruses) that were originally identified in multiple metagenomes from humans, macaques,
121 cows and mice [30], followed by detection in nasal-throat swabs of humans with acute respiratory
122 disease [31]. Although the actual hosts of statoviruses remain unknown, RdRP phylogeny, where
123 statovirus RdRPs cluster with a variety of unclassified tombus-like viruses from invertebrate
124 holobionts (that is, a host together with the entirety of associated symbionts and parasites) [32],
125 suggests that statoviruses are associated with either mammalian diet (e.g., plants) or, more likely,
126 some protist symbionts or parasites.

127
128 Another widespread group of putative members of the healthy human virome are members of
129 *Picobirnaviridae*. Picobirnaviruses are commonly detected in mammalian, including human,
130 intestines and have not been convincingly linked to any diseases although are suspected to be
131 associated with diarrhea [33,34]. Picobirnaviruses have never been grown in cell cultures, and
132 their true hosts remain unknown. The presence of highly conserved ribosome-binding sites (Shine-
133 Dalgarno sequences), which are a hallmark of prokaryotic mRNAs, has led to the suggestion that
134 picobirnaviruses infect bacteria in mammalian microbiomes [35].

135
136 In addition, certain food-derived plant viruses are present in the human gastrointestinal tract and
137 in feces, sometimes in substantial amounts. The list of such viruses is topped by pepper mild mottle
138 virus (PMMoV), a tobamovirus commonly found in pepper, pepper-derived products and their
139 consumers all over the world [36]. Remarkably, PMMoV retains infectivity after passing through
140 the human alimentary tract. Due to its stability and wide presence in human feces, PMMoV is used
141 as a surrogate marker of fecal contamination of water [37]. However, given that there is no

142 evidence of plant virus replication in vertebrate cells, any substantial role of plant viruses in human
143 health is an extremely remote possibility.

144

145 Kingdom *Pararnavira*

146 This virus kingdom includes viruses that employ reverse transcription in their replication cycles.
147 Over 3,000 of human endogenous retroviruses (HERVs) are integrated into the host genome,
148 comprising about 8% of human DNA [38]. Accordingly, the HERVs play important and diverse
149 roles in human biology that cannot be discussed in this brief review in any detail (for recent
150 reviews, see [39-42]). Most of the HERVs appear to descend from ancient integration events so
151 that the virus genes are disrupted and rearranged. The legacy of these ancient HERVs are genes
152 encoding virus structural proteins (Gag and Env) that have been recruited for a variety of
153 physiological functions [43], the best known being syncytins, the placental trophoblast receptors
154 [39]. However, some members of the youngest group of HERVs, known as HERV-K or HML2,
155 that are thought to have invaded the human genome less than a million years ago form virus
156 particles, particularly, in early embryogenesis [44,45]. The HERV-K viruses, at least, are bona
157 fide members of the healthy human virome. Many of the other HERVs are expressed as well and
158 are implicated in a variety of functions including modulation of innate immunity, even though
159 functional virus proteins are usually not produced [46]. In particular, it has been reported that
160 expression of one of HERV-K suppresses the spread of invasive melanoma [47]. However,
161 potential associations between HERVs and various diseases have been reported as well. Thus, the
162 relationship between the HERVs and the human host is a typical symbiosis, with both beneficial
163 and potential deleterious effects on the host (Figure 1b).

164

165 Realm *Monodnaviria*

166 Realm *Monodnaviria* includes prokaryotic and eukaryotic viruses which encode homologous
167 replication initiation endonucleases of the HUH superfamily or their inactivated derivatives, as in
168 the case of polyomaviruses and papillomaviruses [22,48]. In addition to phages of the
169 *Microviridae* and *Inoviridae* families mentioned above, several other representatives of
170 *Monodnaviria* have been repeatedly identified as part of the healthy human virome. These include
171 members of the families *Parvoviridae*, *Genomoviridae*, *Smacoviridae*, *Papillomaviridae* and
172 *Polyomaviridae* (Figure 1a). The actual hosts for human-associated genomoviruses [49] and
173 smacoviruses [50] remain unknown but these viruses likely infect human-associated microbes
174 rather than humans directly.

175
176 *Parvoviruses*
177 Parvoviruses from several genera have been detected in various samples from apparently healthy
178 humans, including human bocaviruses (HBoV; genus *Bocaparvovirus*), adeno-associated viruses
179 (AAVs; genus *Dependoparvovirus*), human parvovirus 4 (PARV4; genus *Tetraparvovirus*),
180 parvovirus B19 (B19V; genus *Erythroparvovirus*) and several protoparvoviruses (genus
181 *Protoparvovirus*) [51-54]. These viruses display highly variable cell tropism and pathogenicity.
182 For instance, AAVs and PARV4 can infect cells from multiple tissue types and are not known to
183 cause any disease. By contrast, HBoV is most commonly found in the respiratory and
184 gastrointestinal tracts as well as in blood [55,56], and is associated with acute respiratory
185 symptoms, especially in children [57]. However, the direct role of HBoV as a pathogen remains
186 unclear. B19V invades red blood cell precursors in the bone marrow and is commonly considered
187 as a human pathogen causing a wide range of pathological conditions, including the fifth disease
188 in children, persistent anemia in immunocompromised patients, transient aplastic crises, hydrops
189 fetalis in pregnant women, and arthropathy [52]. Yet, in healthy adults, B19V infections are largely
190 asymptomatic [58], with the prevalence of up to 25% in healthy human skin biopsies [59]. Thus,
191 B19V is a conditional component of the “healthy” human virome that can turn into a pathogen in
192 response to various factors (Figure 1b).

193
194 *Polyomaviruses and Papillomaviruses*
195 *Monodnaviria* includes class *Papovaviricetes* that consists of *Polyomaviridae* and
196 *Papillomaviridae*, two families of viruses with small (5-8 Kbps), circular dsDNA genomes
197 [60,61]. Papovaviruses are thought to have evolved from parvoviruses [48], with polyomaviruses
198 emerging in invertebrates and co-evolving with animals for at least half a billion years [62]. In
199 humans, polyomaviruses lead a low-profile life styles characterized by low propagation levels,
200 evasion of clearance by the immune system and asymptomatic infections in immunocompetent
201 individuals [60]. Apparently, human polyomaviruses have evolved mechanisms to limit their own
202 reproduction levels in order to establish persistent infections [63]. A poster child human
203 polyomavirus is John Cunningham virus (JCV) that establishes life-long latent infections [64]. The
204 seroprevalence of JCV and other human polyomaviruses in adults can reach 90% or higher, with
205 common coinfection by several polyomaviruses that are transmitted through direct contacts
206 between humans or through contaminated objects. Contrary to their name and the oncogenic
207 potential of the large T (tumor) antigen (the early virus protein involved in genome replication) in

208 experimental settings, most of the human polyomaviruses are not oncogenic. The Merkel cell
209 polyomavirus is the only one that has been convincingly identified as the etiological agent of the
210 eponymous carcinoma, a skin cancer caused by malignant transformation of the skin
211 neuroendocrine cells apparently facilitated by virus genome integration into the host chromosomes
212 [\[60,65\]](#).

213
214 Papillomaviruses are the closest, albeit apparently somewhat ‘younger’ relatives of
215 polyomaviruses that likely emerged in vertebrates ~350 mya, but their life style is distinct. The
216 majority of the ~200 known human papillomaviruses (HPVs) belong to Beta and Gamma types
217 (*Betapapillomavirus* and *Gammapapillomavirus* genera, respectively), and cause unapparent
218 productive infections or low-grade disease of the skin or mucosal epithelium (e.g., warts and
219 condylomas) that are normally cleared by the immune system [\[66,67\]](#). The virus replication cycle
220 is tightly linked to epithelial differentiation and is orchestrated by a regulatory network that
221 involves coordination between the cell cycle, virus DNA replication and transcription, and RNA
222 splicing [\[67,68\]](#). Most of the infections by the ‘high-risk’, Alpha HPV types (HPV16 and HPV18
223 being most prevalent; genus *Alphapapillomavirus*) in women result in more prolonged cervical
224 infections, 80-90% of which are asymptomatic and are eventually cleared by the immune system
225 [\[66,67\]](#). However, a small fraction of such infections, primarily due to defects in the immune
226 response, progress to the formation of persistent papillomas and, in a minority of cases, to cervical
227 cancer. This small fraction of HPV infections, nevertheless, accounts for close to 100% of cervical
228 cancers that affect over 500,000 women annually [\[69\]](#). On much rarer occasions, the high-risk
229 HPV also cause other types of carcinomas [\[70\]](#). Carcinogenesis is a dead end for HPV because
230 transformed cells produce no infectious virus. Therefore, despite the carcinogenic potential of
231 high-risk HPVs, by and large, these common components of human virome should be considered
232 symbionts, as demonstrated by the protection from skin cancer caused by immunity to ubiquitous
233 skin-infecting HPVs [\[71\]](#) (Figure 1b).

234
235 **Anelloviruses**
236 Members of the family *Anelloviridae* are among the most enigmatic components of the healthy
237 human virome, both in terms of their evolutionary origin and the impact on human health.
238 Anelloviruses have small icosahedral virions that encapsidate tiny (3 to 3,5 kb) circular ssDNA
239 genomes [\[72\]](#), but unlike the ssDNA viruses in the realm *Monodnaviria*, do not encode
240 recognizable homologs of the rolling circle replication endonuclease. Moreover, no homologs

241 outside the family have been detected for any of the anellovirus proteins. Hence, anelloviruses are
242 currently not included in the realm *Monodnaviria* and their provenance remains unclear [22,48].
243 The entire human population is believed to be infected with anelloviruses, and there is no
244 convincing evidence of viral clearance from infected individuals [72,73]. The infections occur at
245 an early age and so far have not been convincingly associated with any disease. The virus load
246 appears to be controlled by the immune system because virus levels increase with the level of host
247 immunosuppression [74,75]. Asymptomatic anellovirus infections are also common in other
248 mammals [73,76-78], suggesting extensive coevolution of anelloviruses with mammalian hosts.
249 Although the potential impact of anelloviruses on human health remains a matter of debate, it has
250 been suggested that they positively influence human physiology by shaping the immunity during
251 early development [72]. Thus, anelloviruses might be the most ‘friendly’, genuinely symbiotic
252 component of the human virome.

253

254 **Realm Duplodnaviria**

255 The realm *Duplodnaviria* includes viruses with dsDNA genomes that are encapsidated in
256 icosahedral capsids consisting of a distinct type of capsid protein, displaying the HK97 fold (after
257 the first phage for which the capsid protein structure was solved), with the help of the
258 corresponding variety of packaging ATPase, known as the terminase [22]. This realm includes the
259 bulk of the viruses associated with the human microbiome, namely, the numerous tailed
260 bacteriophages, as well as a major component of the virome associated with human cells, the
261 herpesviruses. Some of the human herpesviruses (*Herpesviridae*) infect a variety of cell types and
262 cause life-long latent infections [79]. Of the 9 human herpesviruses identified so far, herpes
263 simplex virus 1 (HSV1), human cytomegalovirus (HCMV), Epstein-Barr virus (EBV) and
264 varicella zoster virus (VZV) are highly prevalent in the human population. Depending on the
265 geographic location, socioeconomic status and, in the case of VZV, vaccination levels, the
266 incidence of these viruses reaches up to 96% [80-82]. The health impact of these viruses (if any)
267 depends on the age and immune system status of the infected person, with ethnicity, gender and
268 genotype being additional significant contributors.

269

270 The most stealthy of the human herpes viruses are apparently EBV and HCMV. If acquired in
271 childhood, both of these viruses typically cause asymptomatic infections, mainly, in B-
272 lymphocytes in the case of EBV [83] or in several cell types in the case of HCMV [79]. Such silent
273 infections, however, even if not manifested in disease, cause a range of effects at the molecular,

274 cellular, tissue and organism levels. In the case of EBV, the gene expression pattern of infected B-
275 cells is reprogrammed [84] and the proportion of plasma cells in blood appears to be increased [7].
276 Major immunity stimulation effects, a likely result of a balance reached over long virus-host co-
277 evolution process, are well established for HCMV. In particular, ~10% of the CD4⁺ and CD8⁺ T
278 cells in latently infected, otherwise healthy adults are HCMV-specific. Likewise, HCMV causes
279 expansion of adaptive CD57⁺ natural killer (NK) cells targeting virus-infected cells [85]. These
280 powerful arms of the immune system, however, fail to clear the virus due to its armament of
281 immunoevasins, HCMV-encoded proteins involved in modulation of host immunity [86].
282 Extensive immunity stimulation in HCMV-seropositive individuals appears to enhance
283 responsiveness and protection against heterologous viruses rather than compromise host immunity
284 [86]. These potentially positive effects notwithstanding, damaging consequences of herpesvirus
285 infections appear to be fairly common and vary from mild illness to a variety of life-threatening
286 conditions. Thus, HCMV congenital (*in utero*) infections that occur at up to 2% of childbirths
287 frequently cause neurodevelopmental defects or leukemia [85]. At the other life extremity, in
288 seniors, HCMV seropositivity is associated with increased risks of cancer, cardiovascular disease,
289 and ultimately, mortality.

290
291 The delicate, life-long EBV-host balance arising from most childhood infections is also fragile: if
292 infection occurs in even non-immunocompromised young adults, it results in infectious
293 mononucleosis ('kissing disease') [87]. Similarly, EBV is etiologically linked to Hodgkin's and
294 Burkitt's lymphomas and nasopharyngeal carcinoma which are common in Southern Chinese and
295 Eskimo people, as well as to a host of other diseases in immunocompromised individuals [83]. A
296 different pathology pattern is characteristic of VZV infections that cause varicella (chickenpox) in
297 children followed by prolonged latency that, in about 15% cases, leads to virus reactivation in
298 elderly people with weakened immune control, causing zoster (postherpetic neuralgia) [88].

299
300 The HSV1 infections exhibit another distinct pattern of virus-host interactions. This virus is
301 normally acquired in childhood causing mainly oral infections; its seroprevalence varies from 70%
302 in developed nations to 100% in developing nations [81,89]. Upon infecting epithelial cells, HSV1
303 is transmitted to axons and establishes life-long latency in dorsal root ganglia that is periodically
304 manifested in reactivation leading to recurrent acute infections or asymptomatic virus shedding.
305 Similar to other human herpesviruses, HSV1 efficiently evades antiviral innate immune responses
306 mediated by Toll-like and other pathogen recognition receptors. The underlying mechanisms of

307 HSV1 immunoevasion involve multiple virus proteins targeting diverse innate immunity signaling
308 pathways [90].

309
310 Thus, human herpesviruses display a striking variety of cell tropisms and infection patterns that
311 emerged over long-term virus-human co-evolution and co-adaptation. Some herpesviruses, in
312 particular HCMV and EBV, can reach a perfect balance with the human host and often persist for
313 the host's lifetime without causing any pathology. However, because of the complexity of virus-
314 host interactions that involve a variety of genetic, environmental and socioeconomic factors, this
315 balance is fragile and can be broken in many situations resulting in morbidity or even mortality
316 (Figure 1b). Therefore, herpesvirus-host co-existence that involves the majority of the human
317 population blurs the very concept of a 'healthy human virome'.

318
319 **Realm Varidnaviria**

320 This realm includes a broad variety of viruses with dsDNA genomes and icosahedral capsids built
321 of protein unrelated to the capsid proteins of duplodnaviruses [22]. Unlike the members of
322 *Duplodnaviria*, varidnaviruses are minor components of the healthy human virome, at best.
323 Several intriguing reports have appeared on the detection of large and giant viruses of the class
324 *Nucleocytoviricota* in healthy humans [91]. Perhaps, the most notable of these findings is the
325 detection in human blood of several members of *Marseilleviridae* one of which has been reported
326 to grow in T lymphocytes [92]. Additionally, several viruses from both *Marseilleviridae* and
327 *Mimiviridae* have been isolated from human stools or detected in human-associated metagenomes
328 [93]. Furthermore, the presence of mimiviruses in peripheral blood mononuclear cells of patients
329 with atypical pneumonia has been reported, and a role for these viruses in the pneumonia
330 pathogenesis has been suggested [94]. Unexpectedly, DNA of *Acanthocystis turfacea* chlorella
331 virus 1, a member of *Phycodnaviridae*, has been detected in nearly half of the tested oropharyngeal
332 samples from healthy humans, and also has been reported to persist in mouse macrophages [95].
333 However, so far, many of the reports on the presence of members of *Nucleocytoviricota* in human
334 samples and, especially, their ability to replicate in human cells have been disavowed in follow-
335 up studies [96]. Thus, the status of these viruses as components of the healthy human virome
336 except, perhaps, as occasional contaminants, remains dubious.

337
338 **Conclusions**

339 The healthy virome of any organism, and especially humans, clearly, is an important component

340 of the holobiont that makes a major contribution to the health status of the host. However, the very
341 concept of a healthy virome is nebulous and fluid because it is virtually impossible to ascertain
342 that any virus would not cause disease under any conditions. A strong case in point are the
343 herpesviruses that are nearly ubiquitous in the human population, remaining symbionts in most
344 individuals most of the time, but consistently cause disease, in some cases, devastating, in
345 immunocompromised individuals. Conversely, it appears plausible that any virus can become
346 beneficial to the host through protection from other viruses, general stimulation of immunity as in
347 the striking case of β -HPV protecting human hosts from skin cancer, or recruitment of virus genes
348 for host functions. The numerous HERVs integrated in the human genome can be considered the
349 paradigm of virus-host symbiosis. Generally, there is no doubt that many viruses evolved multiple
350 mechanisms to manipulate the host innate and adaptive immunity pathways, ensuring virus
351 persistence and controlling the damage to the host, as most conspicuously exemplified by the latent
352 herpesviruses that are virtually ubiquitous in the human population.

353
354 The healthy virome is obviously heterogeneous and consists of 3 distinct components (Figure 1a):
355 i) viruses that systematically enter the human organism, primarily, with food, but do not replicate
356 in humans, ii) viruses infecting prokaryotes and, possibly, unicellular eukaryotes that comprise the
357 healthy human microbiome, and iii) viruses that actually replicate and persist in human cells. With
358 the advances of metagenomics, the human “microbiovirome” has become a subject of intense
359 studies that continue bringing discoveries of new bacteriophage groups. In contrast, the “true”
360 healthy human virome is poorly understood, with many questionable sightings of diverse viruses
361 but little solid evidence on persistence mechanisms. On the whole, and in contrast to the disease-
362 associated virome, the healthy human virome appears to be dominated by DNA viruses, in
363 particular, anelloviruses and herpesviruses, that are substantially more common than RNA viruses
364 in healthy humans. A thorough investigation of this component of the healthy virome can be
365 expected to enhance our understanding of virus-host interactions and have major implications for
366 human health.

367
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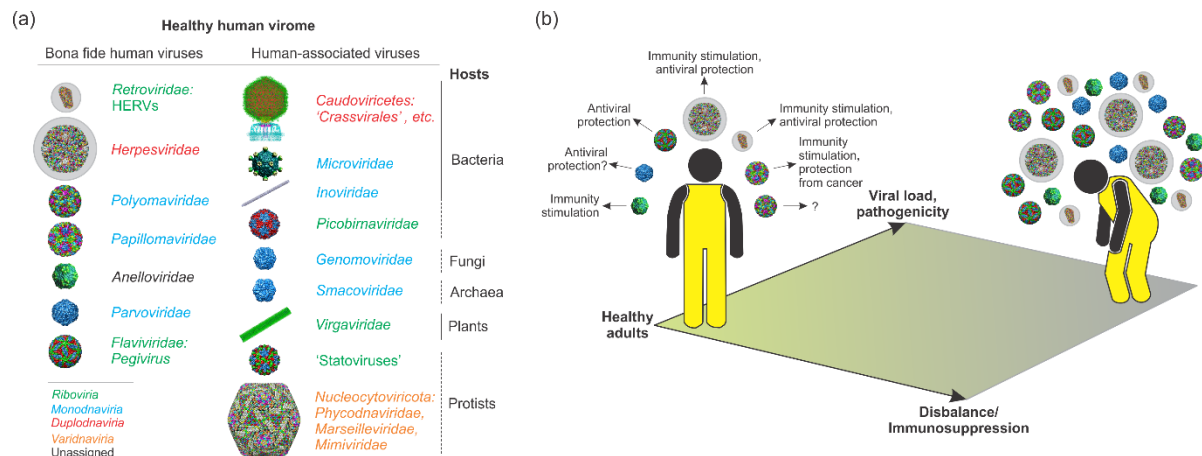
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629 **Figure 1. The healthy human virome.**

630 **(a)** Taxa of viruses found in healthy humans. Taxa of viruses replicating in human cells are shown
 631 on the left, whereas those of viruses infecting human-associated microbes or associated with food
 632 sources are shown on the right (the actual or suspected hosts are listed next to the corresponding
 633 taxa, with the uncertain assignments indicated with broken lines). Depicted virus taxa are
 634 represented with virion structures which were retrieved from VIPERdb (viperdbscripps.edu) or
 635 the Electron Microscopy Data Bank (<https://www.ebi.ac.uk/pdbe/emdb/>). When the structure of a
 636 virus representing a particular taxon was not available, a structurally related member was chosen
 637 instead. Virus taxa are colored according to their realm affiliation (the key is provided at the
 638 bottom).

639 **(b)** Fluidity of the healthy human virome. The (potential) beneficial effects of the healthy human
 640 virome are indicated next to the corresponding virus structures. Question marks denote
 641 uncertainty. Upon changes in the health status/immunosuppression, viruses that cause
 642 asymptomatic infections or are beneficial in healthy individuals proliferate and can cause diseases
 643 including severe ones. The figure illustrates the general tendency of increased virus load under
 644 immunosuppression/disease conditions and should not be interpreted as a quantitative
 645 representation of the changes for any depicted group of viruses.