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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<sup>+</sup> and CD8<sup>+</sup> T  
278 cells in latently infected, otherwise healthy adults are HCMV-specific. Likewise, HCMV causes  
279 expansion of adaptive CD57<sup>+</sup> 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  $\beta$ -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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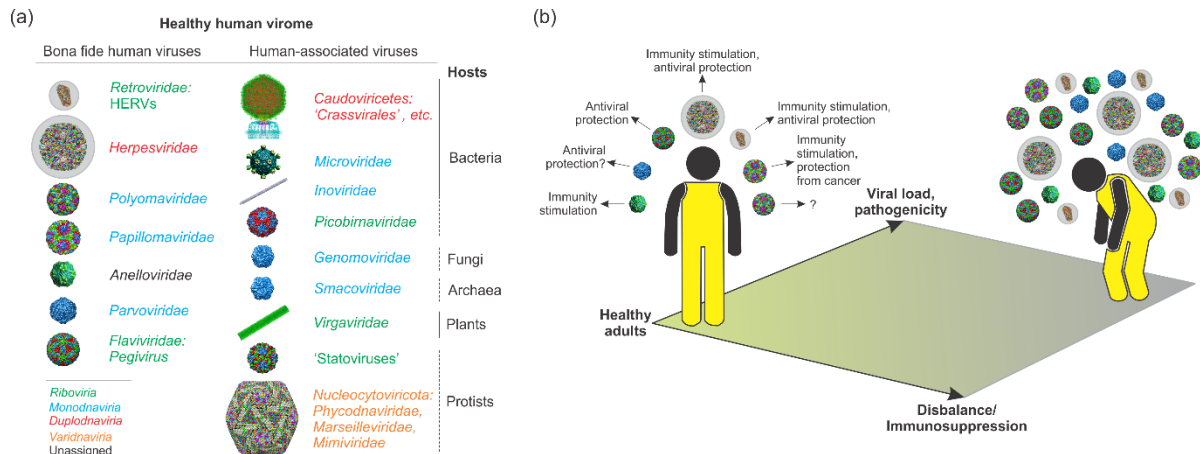
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629 **Figure 1. The healthy human virome.**

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](http://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.