Interactomics: Dozens of Viruses, Co-evolving With Humans, Including the Influenza A Virus, may Actively Distort Human Aging

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Associate editor: Thomas Leitner

Abstract

Some viruses (e.g., human immunodeficiency virus 1 and severe acute respiratory syndrome coronavirus 2) have been experimentally proposed to accelerate features of human aging and of cellular senescence. These observations, along with evolutionary considerations on viral fitness, raised the more general puzzling hypothesis that, beyond documented sources in human genetics, aging in our species may also depend on virally encoded interactions distorting our aging to the benefits of diverse viruses. Accordingly, we designed systematic network–based analyses of the human and viral protein interactomes, which unraveled dozens of viruses encoding proteins experimentally demonstrated to interact with proteins from pathways associated with human aging, including cellular senescence. We further corroborated our predictions that specific viruses interfere with human aging using published experimental evidence and transcriptomic data; identifying influenza A virus (subtype H1N1) as a major candidate age distorter, notably through manipulation of cellular senescence. By providing original evidence that viruses may convergently contribute to the evolution of numerous age-associated pathways through co-evolution, our network-based and bipartite network–based methodologies support an ecosystemic study of aging, also searching for genetic causes of aging outside a focal aging species. Our findings, predicting age distorters and targets for anti-aging therapies among human viruses, could have fundamental and practical implications for evolutionary biology, aging study, virology, medicine, and demography.

Key words: **protein–protein interaction, viruses, age-distorters, cellular senescence, co-evolution, evolutionary theories of aging.**

Article

Introduction

Some viruses, such as the human immunodeficiency virus (HIV-1; Reynoso et al. 2012; Pfefferbaum et al. 2014; Horvath and Levine 2015; Cohen and Torres 2017; Humphreys et al. 2020; Seoane et al. 2020; Schank et al. 2021; Horvath et al. 2022) and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; Mongelli et al. 2021; Tripathi et al. 2021; Cao et al. 2022; Tsuji et al. 2022), have been recently proposed to accelerate features of human aging and of human cellular senescence based on experimental evidence. Similar claims have been made for several other viruses, such as the dengue virus serotype 2 (Seoane et al. 2020). Moreover, some works suggested that latent cytomegalovirus (CMV) infection impairs immunity in old age and might propagate immune senescence (Mekker et al. 2012), contributing to a decade of debates on the potential impact, or as it presently seems, limited, impact, of latent infections of the human CMV (HCMV) on human aging (Redeker et al. 2018; Nikolich-Žugich et al. 2020). Together, these observations, centered on specific human viruses, show that considering viruses as potentially relevant agents to understand our aging is a raising concern (Humphreys et al. 2020; Seoane et al. 2020; Teulière et al. 2021). Additional works stressed that, in a context of evolutionary arms race and co-evolution, a diversity of interference, for example, on host apoptosis, host growth and host immunity, can be mediated by viral genes (Gillet and Brun 1996; Iranzo et al. 2014; Frasca and Blomberg 2016; Aiello et al. 2017; Connolly and Fearnhead 2017; Kuss-Duerkop et al. 2017; Schönrich et al. 2017; Mlih et al. 2018; Zamaraev et al. 2020; Teulière et al. 2021). Moreover, evolutionary considerations on viral fitness (Gillet and Brun 1996; Humphreys et al. 2020; Kelley et al. 2020; Zamaraev et al. 2020; Teulière et al. 2021) brought forward the more general hypothesis that human aging might depend on interactions with a

broad phylogenetic diversity of viral lineages. Namely, many viruses could act as agedistorters (Teulière et al. 2021), meaning that their reproduction benefits from interferences with their host aging processes. More precisely, two major kinds of age-distorting viruses were recently theorized: (1) agedistorters of type 2 that alter aging as their infection generates damages and dysbalance in their hosts, yet without interfering with specific host aging-associated pathways, and (2) agedistorters of type 1, that is, viruses whose gene products directly interfere with components of their host aging-assoc-iated pathways. Furthermore, when characterized, the specific mode of age distorsion could support more detailed classifications of these two kinds of age distorters, depending on which hallmarks of aging (López-Otín et al. 2013) are impacted by the age-distorting virus (e.g., within agedistorters of type 2, one could imagine "resource-depleting viruses," and within agedistorters of type 1, one could imagine distinguishing "cellular senescence-inducing viruses" or "mitochondrial dysfunction-inducing viruses" or "generalist agedistorters" that impact multiple hallmarks of aging). In principle, such virus-host interaction could accelerate aging, but it could also delay aging.

Owing to the considerable number of human viruses, this evolutionary-minded view encourages a reconceptualization of the locus of aging, no longer exclusively focused on our own genetic material but expanded toward a larger set of genetic entities interacting with our species, such as viruses (Johnson et al. 2019; Teulière et al. 2021). Although this reconceptualization suggests a worrying diversity of possible sources of threats to our healthy aging, the hypothesis that some viruses distort human aging also appreciably comes with a unique potential to offer novel anti-aging treatments concentrated on specific viral agedistorters, their age-distorting genes and proteins, as well as their human proteic interactors. Adopting an eco-evolutionary perspective can thus drive new findings of molecular evolution and enrich the understanding of both the ultimate and proximal causes of critical organismal phenotypes.

Problematically, even though compelling cases have been reported for viral age distortion (Teulière et al. 2021), type 1 viral distorters of human aging have not yet been systematically identified. The extent and diversity of viruses able to directly interfere with pathways associated with human aging, as well as their genes and mechanisms of action, remain therefore to be characterized. Fortunately, these important questions can now be effectively addressed by connecting several available -omics resources. Precisely, knowledge from interactome databases, reporting interactions between functionally annotated human proteins, in particular proteins associated with various aspects of human aging, for example, cellular senescence (Tacutu et al. 2018; Avelar et al. 2020) can be integrated with knowledge on experimentally supported protein–protein interspecific interactions, such as interactions between human and viral proteins (Szklarczyk et al. 2019; Yang et al. 2021). Experimental support for these interactions is provided by assays detecting molecular interactions using affinity (e.g., coimmunoprecipitation, pull down, or tandem-affinity purification assays), protein complementation (e.g., yeast two-hybrid assays), biophysical (e.g., mass spectrometry, X-ray crystallography) and other biochemical (e.g., electrophoretic mobility shift assays) assays. Moreover, proteic interactomes are routinely analyzed using the framework of protein–protein interaction (PPI) networks. For instance, so-called "human longevity networks" (Budovsky et al. 2007; Bell et al. 2009; Fernandes et al. 2016) feature proteins associated with human aging as their nodes and represent interactions between these human proteins by direct edges. Experimentally supported interactions between human proteins can be recovered from all PPIs listed in the STRING database, by filtering them based on their "experiments" subscore (Szklarczyk et al. 2019). This score reflects the amount of experimental support, that is, provided by biochemical/biophysical assays, for each interaction. Importantly, this network formalism can then be exploited through network science approaches, allowing one to identify highly central human proteins in the human longevity network, and in interspecific PPI bipartite networks to define which of these critical human proteins are targeted by viral proteins from diverse phylogenetic sources.

Precisely, we took advantage of such data and designed a systematic network–based analysis of the human and viral protein interactomes to identify viral proteins experimentally demonstrated (on the basis of published supporting biochemical/biophysical assays that detect molecular interactions, as indicated by STRING and Human–Virus protein Interaction DataBase [HVIDB] databases) to interact with human proteins associated with human aging and with human cellular senescence. Our working hypothesis was that when a viral protein was demonstrated to interact with some human proteins in carefully controlled experimental set-ups, then this viral protein has the potential to interfere with the same human proteins during the course of its infection. Remarkably, our work unraveled such interactions for viral proteins from dozens of human viruses and identified their human targets. From these findings, we derived a list of top viral candidates predicted to interfere with human aging through proteic interactions with aging-associated pathways, computed possible additive effects of coinfections by multiple candidate agedistorters on human aging-associated pathways, and, when possible, we further corroborated our predictions and characterized the modes of action of these viruses by providing independent published experimental evidence from molecular and cellular biology, from transcriptomic data and using functional inferences. Unexpectedly, the influenza A virus (subtype H1N1), emerged as a major candidate age distorter of type 1, in particular through its encoded genetic potential to interact with human cellular senescence. Overall, our evolutionary-minded work provided new multi-faceted evidence to support the hypothesis that many viruses interfere with many aspects of human aging and predicted targets for anti-aging therapies among human viruses.

Results

Hundreds of Viruses Connect to Human Aging-Associated Pathways via Viral Proteins

Experimentally demonstrated interactions described in the STRING human PPI network were selected on the basis of published experimental support using biochemical/biophysical molecular interaction detection assays (see Materials and Methods; Szklarczyk et al. 2019). The selected PPIs were used to define an updated "human longevity network," comprised of interacting proteins associated with human cellular senescence (Avelar et al. 2020) and human longevity/aging (Tacutu et al. 2018), as well as aging-associated proteins for which proteic interactions with other aging-associated proteins are currently unknown and which therefore form isolated nodes in the PPI longevity network. We then determined the set of viral proteins experimentally demonstrated (in majority using affinity-based assays, see Materials and Methods) to interact with this human longevity network using the HVIDB (fig. 1) and clustered the viral proteins interacting with human age-associated proteins into homologous families. This protocol returned a list of viral proteins, of homologous families of viral proteins, and of viral strains with experimentally characterized potential to interfere with proteins associated with several aspects of human aging. More precisely, 1,031 viral proteins, distributed across 148 viral strains, displayed experimentally supported interactions with 429 human proteins associated with aging (fig. 1, supplementary table S1, Supplementary Material online).

A broad phylogenetic diversity of viruses (dsDNA viruses, such as Herpesviridae, like HHV-4; ssRNA positive viruses, such as Retroviridae, like HIV-1; ssRNA negative viruses, such as Arenaviridae, like lymphocytic choriomeningitis virus [LCMV], and one ssDNA virus, the Parvoviridae AAV-2) encodes proteins reported to interact with three or more distinct human age-associated proteins (fig. 2). Some viruses even connect to a high number of human proteins (e.g., >100), which are generally central in the human longevity network as well as in the entire human PPI networks, as assessed by closeness value analyses (supplementary fig. S2, Supplementary Material online). Logically, viruses with larger genome sizes generally connect to more human proteins, but there are remarkable exceptions (figs. 3 and 4 and see below for a deeper discussion). This variation in the number of human proteins potentially targeted by viruses with similarly sized-genomes may reflect genuinely contrasted evolutionary strategies (e.g., with some viruses being more prone to hijack host aging-associated pathways) and/or a bias in the intensity by which different viral interactomes have been studied (i.e., a higher number of proteic partners being described for more extensively investigated viruses). In the context of an evolutionary arms race between viruses and host however, it makes sense that viruses would preferentially interact with highly central host proteins, not only because interacting with such proteins might allow the hijacking of important host processes, but also because such host proteins are under strong evolutionary constraints and display limited potential to evade viral pressure, precisely due to their high centrality.

We observed that some human proteins were connected to multiple viruses in HVIDB. We tested the statistical significance of this pattern of convergent connection between viral and human proteins. For this, we generated a distribution of 1,000 random bipartite virus–human protein networks, under the null hypothesis that viruses with the same genome sizes than in our data set would connect to the same number of randomly chosen human proteic interactors as in our data set. We compared the properties of these random bipartite networks with those of HVIDB (see Materials and Methods). By determining which human proteins have a significantly high in-degree in the bipartite virus–human protein network, defined as the number of viral proteins able to interact with these human proteins in the HVIDB interspecific PPI network, we identified which human proteins were significantly enriched among the possible targets of real viruses. 10% of the human proteins with multiple reported interactions with viral proteins were connected by significantly more viruses than expected by chance (using random bipartite networks to determine an empirical *P*-value with a significance threshold set at 0.05, after Bonferroni correction, see Materials and Methods), indicating that some human proteins are indeed preferentially connected by viruses. Moreover, we tested whether specific human proteins, in our case aging-associated proteins, were significantly connected by more viruses than expected by chance, a pattern suggestive of convergent targeting of those aging-associated human proteins by viruses. Among 347 aging-associated human proteins, we found that 20% were connected by significantly more viruses than expected by chance ($P < 0.05$ adjusted with Bonferroni correction, supplementary fig. S3, Supplementary Material online), indicating that viruses preferentially target aging-associated human proteins with respect to other human proteins. Next, we tested whether these aging-associated proteins significantly connected to viruses were also among the most central in the human PPI network. To find the most central proteins in the human PPI network, we ranked human proteins by decreasing values of degree (number of direct neighbors) and observed that the 20% of aging-associated human proteins significantly connected to viruses were indeed more central than the other aging-associated proteins ($P = 9.165e\text{-}12$, Wilcoxon rank sum test). Overall, our analysis shows that viruses significantly and convergently interact with 69 significantly central human proteins associated with aging (supplementary fig. S3, Supplementary Material online).

We arbitrarily ranked the viruses connected to human aging proteins into ranked lists of candidate viral agedistorters and of candidate viral age-distorting proteins in order to highlight the viral proteins connected to the highest number of human protein associated with aging (top candidate age-distorting proteins). Accordingly, the top 100

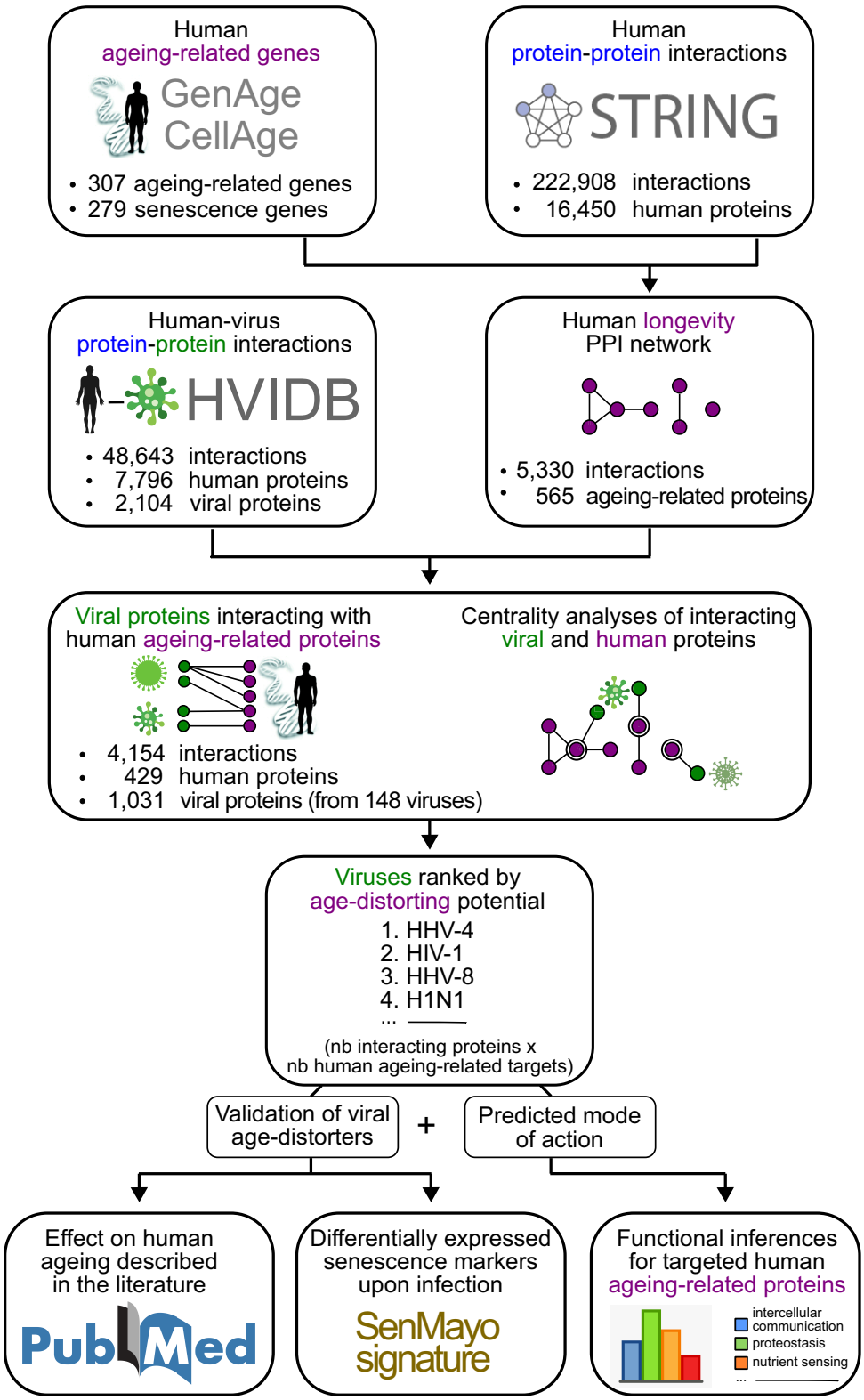

Fig. 1. Overview of the research protocol implemented in our analysis.

viral age-distorting proteins describe which viral proteins are suspected to strongly interact with host aging, defining future possible targets of choice for anti-aging treatments (supplementary table S4, Supplementary Material online). Logically, these viral proteins comprise the "usual proteic suspects", for example, the HIV-1 Tat protein (Cohen and Torres 2017; Seoane et al. 2020; Schank et al. 2021), the E7 protein from human papillomavirus 16 (HPV16; Zamaraev et al. 2020), etc., often mentioned in the literature in a context of viral hijacking (Forterre 2013) of host pathways. Next, in order to identify the viral protein families that may interfere with human aging and be evolutionarily conserved across viruses (supplementary table S5, Supplementary Material online), we determined

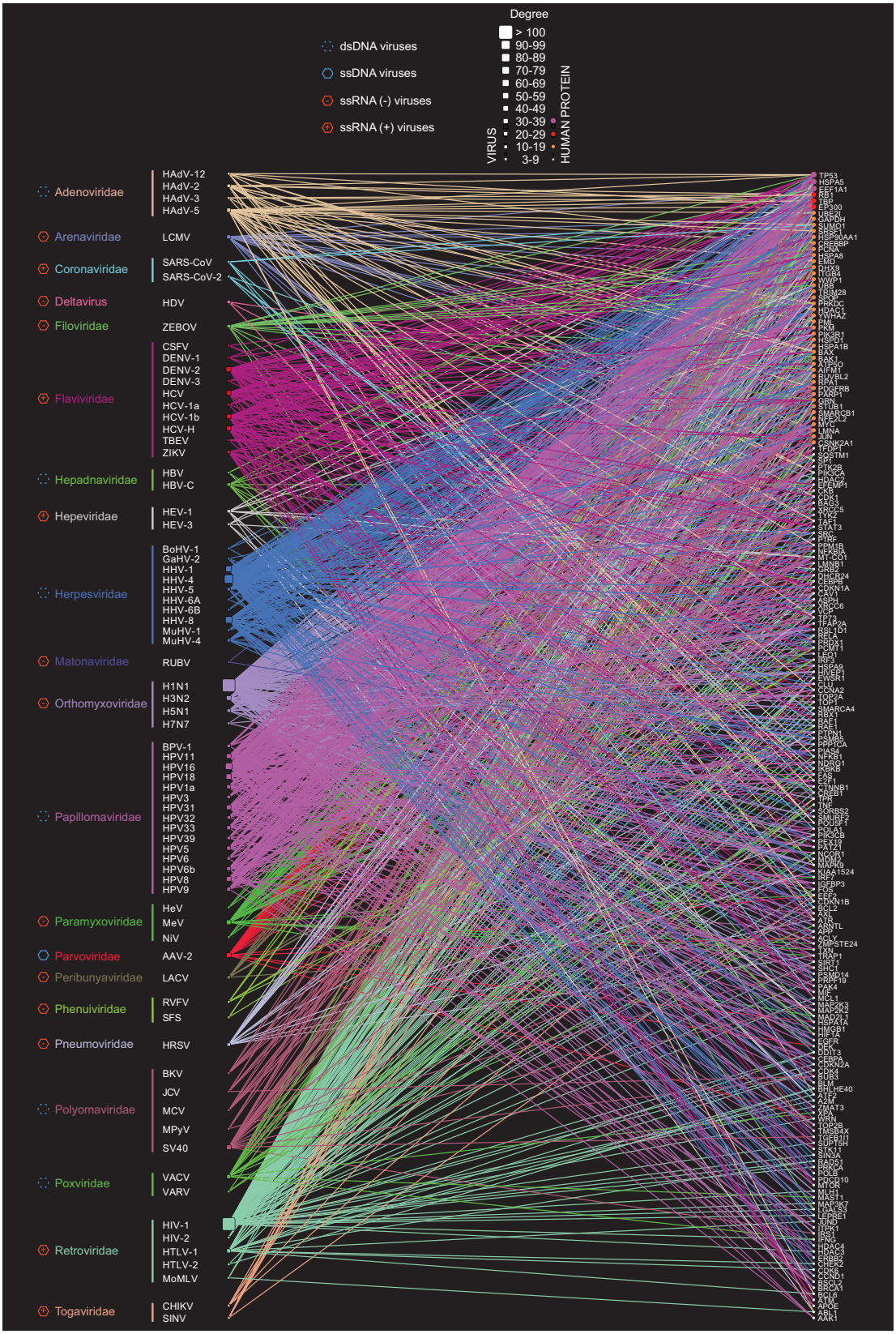

Fig. 2. Virus–human proteins bipartite network. In the bipartite network extracted from the human–virus PPI database HVIDB, 190 human proteins associated to longevity, aging, and/or cellular senescence connected to three or more virus strains (degree ≥ 3) are displayed as circular nodes on the right. 75 viruses connected to three or more human proteins are displayed as square nodes on the left, and grouped by viral family in alphabetical order from top to bottom. The type of viruses is indicated by a hexagonal symbol next to each viral family. For each type of nodes, the degree is indicated by node size and color as indicated. A total of 1,350 virus–human protein interactions are represented as colored edges connecting nodes. Edges color correspond to the arbitrary color used for the viral family corresponding to the virus involved in the interaction.

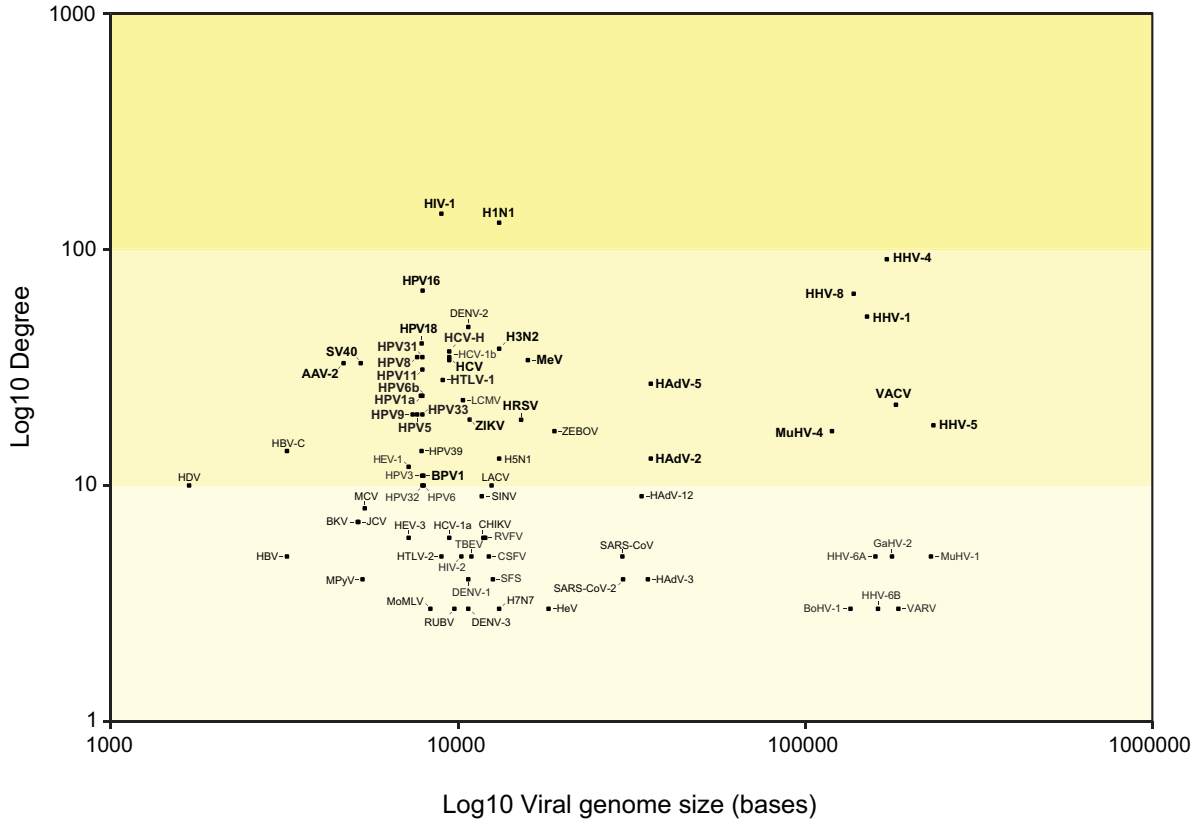

FIG. 3. Relationship between viral genome size and number of human interactors. For each virus connected to three or more human proteins, the reference Log10-transformed genome size was plotted against the Log10-transformed degree (number of documented interacting human proteins) of the virus in the bipartite network from figure 2. Virus names are indicated for each data point and names in bold indicate viruses from the top25 candidate agedistorters in tables 1 and 2. For influenza A (subtype H1N1), the number of human interactors is determined by the aggregation of the interactions associated with the 20 H1N1 strains present in HVIDB.

whether these top candidate age-distorting viral proteins belonged to common protein families shared across viral lineages or instead formed distinct lineage-specific protein families. Interestingly, there were very few candidate age-distorting protein families shared above the level of viral phyla. Specifically, 122 viruses from 28 different phyla independently evolved 231 different sets of gene families that were demonstrated to convergently interact, based on network shuffling tests, with 69 human proteins associated with aging.

Interestingly, our finding that phylogenetically distant and even unrelated candidate agedistorters convergently connect to the same human proteins is consistent with past experimental discoveries focusing on the human PI3K-AKT-mTOR pathway, suggested to be an important molecular target for both DNA and RNA viruses. Namely, the successful replication of different phylogenetic lineages of viruses depends upon the activation of proteins from the PI3K-AKT-mTOR pathway (Cooray 2004; Shin et al. 2007; Buchkovich et al. 2008; Murray et al. 2012) likely because this pathway, associated with host aging, achieves many functions in hosts. In brief, the PI3K-AKT-mTOR pathway can regulate cellular macromolecular synthesis, metabolism, growth, and survival and thus its hijacking can contribute to establishing an environment accommodated to the increased demand for nutrients, energy, and macromolecular synthesis that comes with viral infection (Buchkovich et al. 2008). From an evolutionary perspective, virus fitness was proposed to benefit both from activating this pathway and from overcoming its inhibition when host cellular stress responses are activated during viral infection (Buchkovich et al. 2008; Kuss-Duerkop et al. 2017). Our analysis generalizes these observations by reporting that, among 34 human proteins directly connected to mTOR and convergently connected to a diversity of viral proteins, 10 proteins (beyond the known cases of Akt, or of the mTORC1 inhibitor REDD1 (Kuss-Duerkop et al. 2017), namely EGFR, EP300, PML, PRKDC, RUVBL2, SQSTM1, SUMO1, TP53, VCP, and YWHAZ, have a significantly higher number of interactions with viral proteins/viruses than expected by chance (as determined using random bipartite network permutations to determine an empirical *P*-value with a significance threshold set at 0.05, after Bonferroni correction, see Materials and Methods, supplementary fig. S6, Supplementary Material online). In addition, we also report that 59 additional human proteins, not directly connected to mTOR, have a higher number of interactions with viral proteins than expected by chance (supplementary fig. S3, Supplementary Material

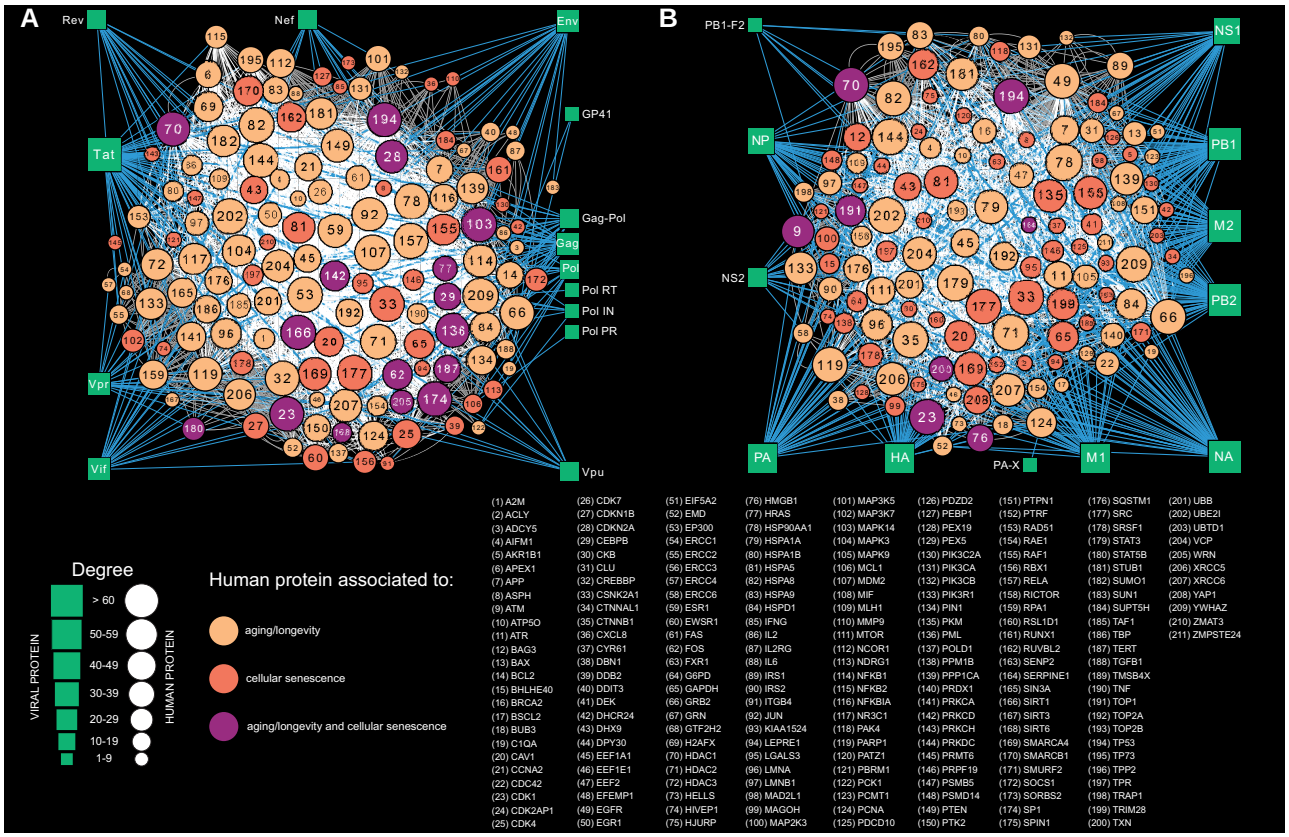

Fig. 4. Interspecific PPIs for HIV-1 and H1N1. PPI networks represent the documented intraspecific interactions between human proteins associated to longevity, aging, and/or cellular senescence (white edges), and interspecific interactions between these human proteins and viral proteins from (*A*) HIV-1 and (*B*) influenza A (subtype H1N1) (blue edges). Interactions for H1N1 correspond to the aggregation of the interactions associated with the 20 H1N1 strains present in HVIDB, with the most frequently used strains being A/Wilson-Smith/1933 H1N1 (63% of interactions) and A/Puerto Rico/8/1934 H1N1 (27, 5% of interactions). Node shapes and colors represent human (circles, light orange: association to aging/longevity only; dark orange: association to cellular senescence only; purple: association to aging/longevity and cellular senescence) and viral proteins (squares, green). For each type of nodes, the degree is reflected by the node size as indicated. Viral protein names are indicated next to their node, human protein names are coded by numbers as indicated.

online). Thus, our findings strongly suggest that, in addition to the evolution of mTOR signaling, which was speculated in the past to be convergently affected by some pathogens through arms race (Martin et al. 2012), viruses may have also contributed to the evolution of other age-associated pathways through coevolution.

Dozens of Viruses are Strongly Connected to Human Aging-Associated Pathways

As we also computed the average centrality of the human proteins targeted by each virus in the human longevity network, we could sort human viruses based on their genetic potential to interact with central human proteins associated with human cellular senescence (table 1) and with human aging in general (table 2). From this, we identified 2 lists of top 25 candidate agedistorters that we selected based on the large absolute number of candidate age-distorting proteins they harbored and could use to interact with a large number of human proteins associated with human aging. As expected, these 2 lists of top 25 candidate agedistorters strongly overlap, because the contents of the GenAge and CellAge databases are not independent, featuring a total of 30 viruses. In order to highlight the most trustable of these predictions, we focused on the nature of the experimental support for the interspecific PPIs associated with these 30 viruses (supplementary fig. S7, Supplementary Material online). Interactions were classified to reflect their level of support, from less well supported, based only on protein complementation assays which comprise yeast two hybrid assays ("protein complementation assays only"), to more stringent support based on affinity technologies ("affinity technology assays only"), and better support provided by data curation ("imported from Reactome") or a variety of other biochemical/biophysical assays (see Materials and Methods). This analysis suggests that HIV-1, HHV-8, AAV-2, and HRSV interactions have the highest quality of support, in contrast to HPV1a, HPV33, HPV9, MuHV4, HPV8, or H3N2 interactions.

Furthermore, we compared the possible human targets for all pairs of these top candidate agedistorters to evaluate their potential additive effects in case of coinfection by two such viruses. Coinfection scores were computed as indicated in the Materials and Methods. These analyses suggest that some viral coinfections (namely between influenza A virus [subtype H1N1], HHV-1, HHV-4,

Table 1. Top 25 Viruses Able to Interact With Human Cellular Senescence-associated Proteins in the HVIDB.

Virus[a]	Viral family	Viral sequences	Human interactors	Score[b]	Degree[c]
HHV-4	Herpesviridae	35	45	1575	28.8
H1N1	Orthomyxoviridae	11	64	704	24.0
HIV-1	Retroviridae	10	57	570	29.3
HHV-8	Herpesviridae	17	29	493	28.9
HHV-1	Herpesviridae	15	22	330	48.5
HPV16	Papillomaviridae	5	37	185	55.4
HPV18	Papillomaviridae	5	26	130	45.6
HPV31	Papillomaviridae	6	19	114	56.0
HPV11	Papillomaviridae	6	18	108	52.1
H3N2	Orthomyxoviridae	6	16	96	29.9
HPV8	Papillomaviridae	3	24	72	43.4
SV40	Polyomaviridae	4	18	72	61.1
HHV-5	Herpesviridae	9	8	72	53.1
HPV1a	Papillomaviridae	4	17	68	33.4
HTLV-1	Retroviridae	4	16	64	34.4
MeV	Paramyxoviridae	5	10	50	41.6
HAdV-5	Adenoviridae	6	8	48	65.2
ZIKV	Flaviviridae	4	11	44	23.2
HPV33	Papillomaviridae	3	13	39	51.3
HPV5	Papillomaviridae	3	13	39	36.9
HPV9	Papillomaviridae	3	12	36	40.1
HPV6b	Papillomaviridae	3	11	33	26.6
HCV-H	Flaviviridae	2	16	32	46.8
HAdV-2	Adenoviridae	5	6	30	116.5
HCV	Flaviviridae	2	14	28	163.7

[a]Virus names are those used in the human-virus PPI database HVIDB.
[b]Viruses were ordered by decreasing score (Score), computed for each virus by multiplying the number of viral protein sequences able to interact with human proteins (Viral sequences) by the number of human proteins connected to the virus (Human interactors).
[c]The average degree of human proteic interactors in the longevity network is indicated (Degree).

HHV-8, and HIV-1, supplementary fig. S8*A*, Supplementary Material online) may be of special concern owing to their high additive potential to interfere with human aging, assuming their sites of infection overlap. Using random bipartite network permutations, we could derive an empirical *P*-value (see Materials and Methods) pointing to statistically significant high score values ($P < 0.05$ with Bonferroni adjustment), in particular for HHV-8 in combination with HPV16, human adenovirus 2 (HAdV-2), bovine papillomavirus type 1 (BPV-1), human T-cell leukemia virus-1 (HTLV-1), or HPV1a (stars in supplementary fig. S8*A*, Supplementary Material online). We also compared the sets of human proteins connected by each pair of viruses in our list of top candidates, in order to identify coinfections with the potential to reinforce interactions with given human aging-associated proteins (supplementary fig. S8*B*, Supplementary Material online). Shared sets of human interactors were observed for a cluster of papillomaviruses (HPV8, HPV33, HPV9, HPV1a, HPV5, HPV16, HPV18, HPV11, and HPV6b) on the one hand, and another cluster containing MeV, AAV-2, HHV-1, HHV, H1N1, and HIV-1 on the other hand. For these clusters, several Jaccard index values were statistically significant when compared with Jaccard indices in random bipartite networks (stars in supplementary fig. S8*B*, Supplementary Material online, $P < 0.05$ with Bonferroni adjustment), indicating which pairs of viruses have a significant overlap in their sets of human interactors and a potentially enhanced age-distorting effect in coinfections.

Inferences of the Modes of Action of Viral Age Distorters

We sought to evaluate whether our top candidate age distorters could be further characterized based on their potential interaction with proteins associated with specific hallmarks of aging. To assess this, we used a bipartite network analysis (Corel et al. 2018) to identify sets of human proteins directly connected to each virus. Based on the functional annotations of these sets of human proteic interactors, we performed functional inferences to gain an approximate view of which host processes may be impacted during infection by each virus. For this, we associated each human protein connected by a candidate viral age-distorting gene to a hallmark of human aging, or to general human aging, based on former published evidence (Tacutu et al. 2018; Avelar et al. 2020; Holzscheck et al. 2020; Saul et al. 2022). We used that logic to approximate the type of impact on human aging that each candidate viral age distorter may produce, by distinguishing whether these human proteins were currently reported to be associated with general human aging or more specifically with some hallmarks of aging, including cellular senescence. Thus, for each candidate viral age distorter, we first contrasted the proportion of its human proteic interactors associated with human cellular senescence according to the CellAge database (Avelar et al. 2020) with the proportion of its human proteic interactors associated with general aging, by subtracting the proteins listed in the CellAge database from the more generalist GenAge

Table 2. Top 25 Viruses Able to Interact With Human Longevity and Aging-associated Proteins in the HVIDB.

Virus[a]	Viral family	Viral sequences	Human interactors	Score[b]	Degree[c]
HHV-4	Herpesviridae	41	56	2296	40.7
HHV-8	Herpesviridae	25	43	1075	58.4
HIV-1	Retroviridae	10	101	1010	41.4
H1N1	Orthomyxoviridae	12	74	888	47.3
HHV-1	Herpesviridae	19	36	684	56.4
HPV16	Papillomaviridae	7	45	315	64.0
VACV	Poxviridae	14	16	224	39.2
HPV31	Papillomaviridae	8	26	208	57.5
HAdV-5	Adenoviridae	8	23	184	66.0
MuHV-4	Herpesviridae	13	13	169	61.1
H3N2	Orthomyxoviridae	6	24	144	46.2
HHV-5	Herpesviridae	10	12	120	54.1
HPV6b	Papillomaviridae	6	17	102	33.7
HPV11	Papillomaviridae	5	19	95	63.2
SV40	Polyomaviridae	4	23	92	61.6
HPV18	Papillomaviridae	4	21	84	57.0
MeV	Paramyxoviridae	3	26	78	49.6
HCV	Flaviviridae	3	24	72	154.0
HAdV-2	Adenoviridae	6	12	72	88.2
HRSV	Pneumoviridae	5	14	70	36.8
HTLV-1	Retroviridae	4	16	64	48.5
HPV8	Papillomaviridae	3	20	60	59.0
AAV-2	Parvoviridae	2	25	50	66.9
ZIKV	Flaviviridae	4	11	44	38.1
BPV-1	Papillomaviridae	4	10	40	73.5

[a]Virus names are those used in the human-virus PPI database HVIDB.
[b]Viruses were ordered by decreasing score (Score), computed for each virus by multiplying the number of viral protein sequences able to interact with human proteins (Viral sequences) by the number of human proteins connected to the virus (Human interactors).
[c]The average degree of human proteic interactors in the longevity network is indicated (Degree).

database (Tacutu et al. 2018; supplementary fig. S9A, Supplementary Material online). We also quantified the proportion of human proteic interactors that belonged to a recently published list of biomarkers of human cellular senescence (supplementary fig. S9A, Supplementary Material online; Saul et al. 2022). Finally, we quantified the proportion of human proteic interactors associated with each hallmark of aging, according to a classification kindly provided by (Holzscheck et al. 2020; supplementary fig. S9B, Supplementary Material online). We observed that all our top candidates had genetic potential to interact with human proteins associated with several hallmarks of aging, and therefore could be considered as "general age distorters."

Moreover, we used published transcriptomic data to further investigate the potential of several top age-distorter candidates to interfere with cellular senescence. We took advantage of the recent demonstration that human cellular senescence can be empirically deduced from transcriptomes through differential expression of a set of 125 biomarker genes, known as SenMayo biomarkers (Saul et al. 2022), to search for evidence of an alteration of cellular senescence associated with various viral infection (Kaczkowski et al. 2012; Jagya et al. 2014; Peng et al. 2014; Bercovich-Kinori et al. 2016; Devadas et al. 2016; Hu et al. 2016; Tang et al. 2016; Zhang et al. 2016; Boldanova et al. 2017; Deshiere et al. 2017; Harden et al. 2017; Hojka-Osinska et al. 2017; Klymenko et al. 2017; McGrath et al. 2017; Oberstein and Shenk 2017; Oh et al. 2017; Razooky et al. 2017; Viollet et al. 2017; Zhu et al. 2017; Journo et al. 2018; Tso et al. 2018; Golumbeanu et al. 2019; Mrozek-Gorska et al. 2019; Wang et al. 2019; Blanco-Melo et al. 2020; Dissanayake et al. 2020; Li et al. 2020; Seelbinder et al. 2020; Sen et al. 2020; Sheng et al. 2020; Thompson et al. 2020; Winer et al. 2020; Zhuravlev et al. 2020; Bauby et al. 2021; Chandrashekar et al. 2021; Chow et al. 2021; Coelho et al. 2021; Dapat et al. 2021; van der Heijden et al. 2021; Hong et al. 2021; Tegtmeyer et al. 2021; Tsalik et al. 2021; Yanagi et al. 2021; Yuan et al. 2021; Alberts et al. 2022; Bell et al. 2022; Montanari et al. 2022; Park et al. 2022; van Solingen et al. 2022; Zai et al. 2022) and GSE53993, GSE78711, GSE82232, GSE84346, GSE84897, GSE87750, GSE89008, GSE92496, GSE93385, GSE97672, GSE101760, GSE102924, GSE186908, GSE192528, GSE194179). We observed that among all human transcriptomes available to us to contrast human gene expression in absence and in presence of a viral infection, differential gene expression analyses under healthy and infected conditions reported a large fraction of differentially expressed biomarkers of cellular senescence associated with the SARS-CoV-2 (fig. 5, columns 1–6), HHV-4 (fig. 5, columns 30–34), HHV8/human herpesvirus-8 (KSHV; fig. 5, columns 35–37), HCMV (fig. 5, columns 38–43), and hepatitis C virus (HCV; fig. 5, columns 51–54) infections, consistently with published reports of infection-induced senescence for those viruses (Humphreys et al. 2020; Seoane et al. 2020; Tripathi et al. 2021; Tsuji et al. 2022). Further, among viruses in the top

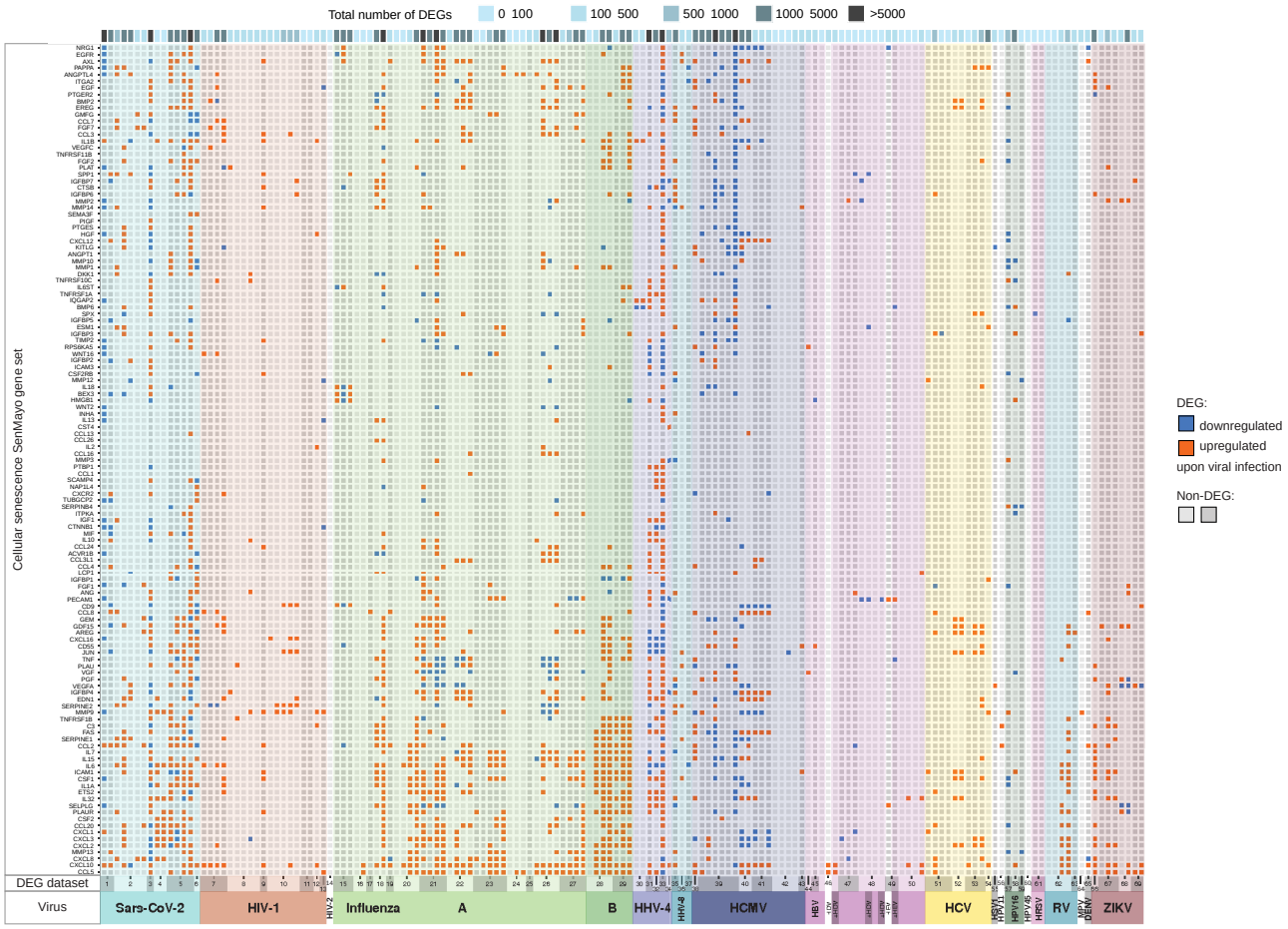

Fig. 5. SenMayo gene set expression during infection of viruses predicted to interfere with human cellular senescence. Lists of DEGs from RNAseq and microarray data have been gathered from the literature and the HVIDB for the viruses indicated at the bottom of the figure. The presence of SenMayo senescence biomarkers within these DEGs was assessed to represent potential interferences on human cellular senescence as a result of viral infection. Each line represents the expression profile of a given SenMayo biomarker. Data sources (DEG data set: articles or data set identifier) are numbered and visually delimited by an alternance of light-gray/dark-gray backgrounds, with some sources providing several samples or time points (supplementary table S10, Supplementary Material online). Samples sources are: (1) Alberts et al. (2022); (2) Park et al. (2022); (3) van Solingen et al. (2022); (4) Chandrashekar et al. (2021); (5) Chow et al. (2021); (6) Blanco-Melo et al. (2020); (7) Deshiere et al. (2017); (8) Golumbeanu et al. (2019); (9) van der Heijden et al. (2021); (10) Bauby et al. (2021); (11) GSE53993; (12) Coelho et al. (2021); (13, 14) Devadas et al. (2016); (15) Bell et al. (2022); (16) GSE186908; (17) GSE192528; (18) Thompson et al. (2020); (19, 63–65) Tsalik et al. (2021); (20, 28, 62) Dissanayake et al. (2020); .(21) Zhuravlev et al. (2020); (22) GSE97672; (23, 27) GSE89008; (24) GSE82232; (25) GSE101760; (26) GSE97672; (29) Sheng et al. (2020); (30) Hong et al. (2021); (31) Mrozek-Gorska et al. (2019); (32) Wang et al. (2019); (33) Yanagi et al. (2021); (34) GSE84897; (35) Tso et al. (2018); (36) Journo et al. (2018); (37) GSE79032; (38) Seelbinder et al. (2020); (39) Oberstein and Shenk (2017); (40–42) Sen et al. (2020); (43) Zhang et al. (2016); (44, 49) Jagya et al. (2014); (45) Yuan et al. (2021); (46) GSE194179; (47) Zai et al. (2022); (48) Winer et al. (2020); (50) Montanari et al. (2022); (51) Tegtmeyer et al. (2021); (52) Hojka-Osinska et al. (2017); (53) Li et al. (2020); (54) GSE84346; (55) Hu et al. (2016); (56, 59, 60) Kaczkowski et al. (2012); (57) Klymenko et al. (2017); (58) GSE92496; (61) Dapat et al. (2021); (66) GSE102924; (67) GSE93385; (68) GSE78711; (69) GSE87750. Each column represents a condition of infection, for example, by a given virus in a given human tissue, or successive time points obtained for a tissue during a given viral infection. In the latter case, columns following differential gene expression during an infection are ordered chronologically from left to right in the heatmap. Over- and under-expressed SenMayo biomarkers are represented by red and blue squares, respectively. The total number of DEGs associated with each sample is indicated by the shade of blue at the top of the figure.

25 candidate senescence distorters (table 1), HIV-1 (consistently with Seoane et al. 2020), HPV16, and ZIKV (fig. 5, columns 7–13, 57–59, 66–69) indeed displayed differentially expressed SenMayo biomarkers in addition to HHV-4, HHV-8/KSHV, and HCV, whereas HPV11 and HRSV, for which we analyzed one data set each (fig. 5, columns 56, 61), did not. Remarkably, this important proof of concept suggests that infection by either influenza A or influenza B can also interfere with human senescence, because our heatmap also reveals a large fraction of differentially expressed biomarkers of cellular senescence for samples from various tissues and data collections of human infected by at least six H1N1 and one H3N2 influenza A strains, as well as two influenza B strains (fig. 5, columns 15–29, supplementary table S10, Supplementary Material online). In details, observed variations between influenza transcriptomic studies may be partly explained by their experimental designs, mainly concerning time post infection

before analysis. Accordingly, most H1N1 columns showing a high number of differentially expressed biomarkers of cellular senescence relates to 12 to 48 h post infection, as is especially clear for time-course transcriptomic analyses of infection (fig. 5, columns 20, 22, 23), whereas H1N1 studies showing a low number of differentially expressed genes have been conducted for 12 h post infection or less (fig. 5, columns 15, 16, 24). Similar dynamics were observed for influenza A H3N2 strains (fig. 5, columns 26, 27) and influenza B strains (fig. 5, columns 28, 29). Moreover, studies used a variety of cell lines and viral strains, although the two main H1N1 strains used to compose the H1N1–human PPI network (63% from A/Wilson-Smith/1933 H1N1, 27.5% from A/Puerto Rico/8/1934 H1N1) were among the viral strains tested in the transcriptomic data set (fig. 5, columns 18, 21, 24, 25).

Interestingly, influenza B strains are barely represented in the PPI data with only nine PPIs recorded in the HVIDB and thus were logically not predicted as age distorters in our analysis. However, differential expression of many SenMayo biomarkers strongly suggests both influenza A and B viruses interfere with the normal process of cellular senescence. Of note, the molecular mechanisms that produce this effect on cellular senescence were not mainly due to direct interactions between influenza viral proteins and the human proteins from the SenMayo biomarker list (supplementary fig. S9A, Supplementary Material online). Rather, some mechanisms producing this transcriptomic signature suggesting altered cellular senescence associated with influenza A H1N1 infection can probably be searched for among the 45% of human proteins, listed in CellAge, with which H1N1 interacts and experimentally known to be associated with cellular senescence (supplementary fig. S9A, Supplementary Material online; Avelar et al. 2020).

In contrast, even though interference with cellular senescence has been associated with HBV-induced hepatocellular carcinoma upon chronic infection (Seoane et al. 2020; Giannakoulis et al. 2021), only few differentially expressed SenMayo biomarkers were detected in cultured cells upon HBV infection, or upon HBV co-infection with either HDV or HEV (fig. 5, columns 44–49), nor in liver biopsies from chronically infected patients (fig. 5, column 50). These observations suggest that HBV-associated cellular senescence may depend on host cell transformation rather than directly result from viral infection.

We concluded that some viruses (HHV-4/Epstein–Barr virus [EBV]; SARS-CoV-2; influenza A, subtypes H1N1 and H3N2; influenza B; HCMV; HHV-8/KSHV; RV; ZIKV; HPV16; HIV-1; HCV) affect human cellular senescence, and therefore may negatively affect their host homeostasis.

Published Experimental Evidence Corroborate Age-Distorter Predictions

Importantly, in addition to our transcriptomic analyses, our predictions of age distorters can be backed up by published compatible experimental evidence and, in some cases, by additional independent experimental support, meaning that different series of proofs of concept support our predictions. Thus, emblematically, HIV-1 figures among the 25 viruses with the highest interaction scores listed as candidate human age distorters (tables 1 and 2). The ability of HIV-1 to interfere with the cell cycle and with the aging of its hosts has long been recognized. For instance, HIV-1 can induce telomerase activity in monocyte-derived macrophages, which is expected to turn these infected host cells into resistant viral reservoirs (Reynoso et al. 2012). HIV-1 can also cause immunosenescence (Cohen and Torres 2017) and provoke stress-induced premature senescence of non-immune cells (Cohen and Torres 2017) and progressive mitochondrial damages that contribute to accelerated aging and cellular dysfunction (Schank et al. 2021). Consistently, HIV-1 infection was reported to increase epigenetic age both in brain tissue and in the blood (Horvath and Levine 2015). In addition, morphological reports identified an acceleration of the normal aging trajectory in several regions of the human brain, such as the neocortex and the thalamus of HIV-infected individuals in general good health (Pfefferbaum et al. 2014). HIV-1 infection was also causally connected to cases of osteoporosis and of osteopenia (Seoane et al. 2020).

Likewise, several other viruses from our list of candidate age distorters appear reasonable candidates based on former independent knowledge. For example, the Mink enteritis virus (MEVB) was demonstrated to significantly increase apoptosis in various mink organs as well as to induce apoptosis in human embryonic kidney 293T cells (Lin et al. 2019). This is noteworthy because viral interactions with apoptosis are recognized to affect host homeostasis, and dysregulation of apoptosis appears as a pleiotropic driving force of tissue aging (Mlih et al. 2018). Likewise, the LCMV and the vaccinia virus (VACV) were demonstrated to induce abundant senescent CD8 T cells in vivo in mice (Voehringer et al. 2001). Thus, some compelling evidence for a contribution of HHV-1 (HSV-1) to host aging also deserves mention. Although the role of this virus regarding aging is debated, some prominent works considered HSV-1 as causally involved in Alzheimer's disease when present in the brain of APOE-e4 carriers (Itzhaki 2021). Upon infection, HSV-1 was described to induce oxidative stress resulting in neuronal oxidative damages, to disrupt autophagy and to interfere with apoptosis (Itzhaki 2021).

More generally speaking, our list of viruses predicted to behave as human age distorters features many recognized human oncoviruses, such as HHV-4, also known as the EBV, several HPVs, HCV, HTLV-1, KSHV, which have all been reported to increase the transcription of their host telomere reverse transcriptase (Bellon and Nicot 2017), and all been demonstrated to interfere with human cellular aging. For instance, HPVs, in particular HPV16/18 use their viral oncoproteins E6 and E7 to manipulate host signaling pathways involved in cell proliferation, cell death, and innate immunity (Lo Cigno et al. 2020), depleting multiple innate immunity effectors. Moreover, HPV-18 protein

E2 can delay replicative senescence of human keratinocytes by downregulating antisense noncoding mitochondrial RNA-2 (Villota et al. 2018). Consistently, HPV16/18 infections have been proposed to correlate with epigenetic age acceleration of cervical squamous cell carcinoma (Lu et al. 2020). Likewise, protein E7 of HPV-8 deregulates the phosphorylation status of nuclear proteins involved in DNA damage repair and replication (Kirschberg et al. 2020), contributing to cancer formation, and HPV6b induces cell senescence into primary human cervical epithelial cells (Pecoraro et al. 1989). To our knowledge, experimental evidence independently supporting a role of HPV31 in human aging is less clear, although expressed sequence tag analyses provided evidence that HPV31 encodes genes whose products can alter the activities of human cellular proteins, including the regulation of cell growth (Chang and Laimins 2000), and thus may affect cellular aging.

In contrast with this later case, a clear connection between HTLV-1 infection and human aging has been proposed previously. Adult T-cell leukemia/lymphoma develops after a long period of HTLV-1 infection, and this phenotype is associated to host aging as well as to genetic abnormalities in infected cells (Kozako et al. 2022). Significantly, this long-term proliferation of HTLV-1 within humans relies upon viral manipulations of apoptosis and of replicative senescence of infected cells through mechanisms that are currently investigated (Harhaj and Giam 2018; Bellon et al. 2021; He et al. 2021). Similarly, HHV8/KSHV has been reported to trigger hallmarks of alternative lengthening of telomeres (Lippert et al. 2021) and to partly subvert autophagy in ways that dampen host antiviral defenses and allow infected cells to proliferate (Leidal et al. 2012). Moreover, HHV8/KSHV can overcome replicative senescence in primary lymphatic endothelial cells using vCyclin (DiMaio et al. 2020). Finally, chronic HCV infection is coupled to a marked up-regulation of cell cycle inhibitor and of senescence markers, and known to result in enhanced senescence of hepatic T cells compared with healthy liver tissues (Wandrer et al. 2018). These varied lines of evidence show that many candidate age distorters predicted by our analyses interfere with aspects of human aging. In addition to these oncoviruses, several empirically demonstrated oncosuppressive viruses, such as VACV, HAdV-5, and HAdV-2 (Pozzatti et al. 1988; Marcellus et al. 2000; Chen et al. 2011; Nguyen et al. 2018), also figure in our list of candidate age distorters. Although oncolytic viruses can in general rely upon very different modes of action, their presence in our list and our functional inferences based on their interactors among human proteins (supplementary fig. S9, Supplementary Material online) suggest that these viruses interfere with various aspects of aging, including cellular senescence and telomere attrition.

Influenza A, a Major Candidate Age Distorter Manipulating Human Cellular Senescence

Importantly, our list of viral age distorters also contains several candidates (e.g., H3N2, RSV) that, based on current published knowledge were less expected to behave as age distorters, and therefore may deserve greater considerations in future anti-aging therapies. This is especially true for the influenza A virus (subtype H1N1), which, based on its high scores in our tables, shows a significant genetic potential to interfere with human aging, alone or in co-infections, especially with HHV-4, HHV-8, HHV-1, or HIV-1 (supplementary fig. S8, Supplementary Material online).

First, we showed that H1N1 is connected to a remarkable number of human proteins for its genome size, to an extent comparable to that of HIV-1 (figs. 3 and 4). In details, the genome of HIV-1 is 8,955 bp long and encodes 9 ORFs, which produce 4 polyproteins and 15 final proteins, whereas the genome of H1N1 is 13,133 or 13,627 bp long, depending on the strain, and encodes 8 ORFs, which produce up to 17 known proteins. Both viruses however can interact with over a hundred human aging-associated proteins (142 for HIV-1, 130 for H1N1). In details, 253 interactions and 454 interactions with human proteins from the longevity network have been experimentally demonstrated for HIV-1 on the one hand and for H1N1 (compiling data from 20 strains in HVIDB, with 2 strains representing 90.5% of interactions) on the other hand. HIV-1 and H1N1 PPIs are very minorily dependent on yeast two-hybrid assays with high false positive rates (<5% each). Typically, HIV-1 interactions are mostly imported from Reactome curated data, whereas 95% of H1N1 interactions are supported by a variety of affinity-based assays. Both viruses are connected to 61 common human protein families, meaning that 43.4% of H1N1 human proteic interactors are shared with that of HIV-1, but these viruses do so using entirely different viral protein families. Finally, a comparison of the degree and closeness centrality metrics distributions of HIV-1- and H1N1-associated human proteins in the human longevity network, itself supported by a variety of molecular detection assays (see Materials and Methods), found no significant differences in centrality (two-sample Kolmogorov–Smirnov test for goodness of fit), meaning that both viruses can interact with equally central human proteins.

Interestingly, some published evidence on influenza A viruses (subtype H1N1) is compatible with our prediction that the flu virus could be a genuine human age distorter. Some influenza A proteins (up to three: HA, NS1, and M2) were demonstrated to interact with a few host proteins from the PI3K-AKT-mTOR pathway, for example, mTORC1 and mTORC2 (Shin et al. 2007; Murray et al. 2012; Kuss-Duerkop et al. 2017). In short, H1N1 proteins directly and indirectly activate mTOR, which supports viral replication, and consistently H1N1 replication is reduced when mTOR is inhibited (Wang et al. 2014; Jia et al. 2018), suggesting an evolutionary interest for H1N1 to interfere with mTOR (Kuss-Duerkop et al. 2017). As mTORC1 activation supports viral protein expression and replication, viral–human proteic interactions would probably be optimal for the influenza A virus midway through its life cycle, considering that these expressed viral

proteins are likely to support the late stages of influenza replication when infected cells undergo significant stress (Kuss-Duerkop et al. 2017). Although they support our claim that H1N1 can act as an age distorter, the above studies did not analyze the possible effects on host aging of the interplay between Influenza A virus proteins and these human proteins. However, although it is well-known that the primary targets of influenza viruses are airway epithelial cells, severe influenza infections result in virus-induced tissue destruction and dysregulated systemic inflammation (Jia et al. 2018), two phenotypes that could contribute to aging. Moreover, some temporal relationships between influenza A (subtype H1N1) infection and increased type 1 diabetes incidence have been reported (Nenna et al. 2011; Watanabe 2011; Valdés et al. 2013). If beyond this correlation, the causal role of influenza A in this increased type 1 diabetes incidence could be established (Ruiz et al. 2018), this would provide independent evidence that influenza A infection can contribute to human aging, because type 1 diabetes can be considered as a form of accelerated muscle aging (Monaco et al. 2019). Furthermore, another correlation appears compatible with the prediction that influenza A (H1N1 subtype) interferes with human aging. Recent reports show that the US cohort *in utero* during the peak of the 1918 influenza pandemic experienced higher rates of depression after age 50, higher rates of diabetes and ischemic heart disease after age 60 and higher mortality after age 65 (Easterlin et al. 2021). Likewise, the Taiwanese cohort exposed to influenza A (H1N1 subtype) *in utero* in 1919 experienced higher rates of renal disease, circulatory and respiratory morbidities, and diabetes after age 60, whereas the corresponding Swedish cohort experienced a higher morbidity at age 54–87, due to an excess of hospitalizations and an excessive male mortality from heart disease and cancer (Easterlin et al. 2021). However, it is impossible to conclude whether such significant phenotypic differences showing evidence of early decline in infected populations were due to exposure of these individuals to the influenza A (H1N1 subtype) virus itself, acting as an age distorter according to our hypothesis, or were more generally provoked by the stress associated with the pandemic environment (Easterlin et al. 2021).

Finally, as indicated above differential gene expression analyses comparing human gene expression in the transcriptomes of individuals infected by influenza A subtypes H1N1 and H3N2 strains as well as influenza B strains (fig. 5) provide another independent line of experimental evidence to demonstrate that influenza infection interferes with at least one feature of human aging: cellular senescence, suggesting that influenza A poses underappreciated threats to human aging.

Discussion

Evolutionary considerations predict that viral genomes coevolve with that of their hosts, in particular in the context of the evolution of strategies of hijacking of host processes by their viruses. Accordingly, we devised a systematic protocol based on interaction network analyses to test the general, worrying hypothesis that various pathways associated with human aging may be impacted by direct interactions with viral proteins from a broad diversity of viral sources. For this, we relied on the collection of experimentally demonstrated interactions between viral proteins and human proteins from HVIDB (Yang et al. 2021) to survey viral candidate age distorters of type 1, that is, viruses characterized by their genetic potential to encode proteins interacting with human proteins from aging-associated pathways. The quality of HVIDB allowed us to unveil candidate age distorters, but this database is surely not yet exhaustive. Inevitably, the limited experimental knowledge about under-studied viral proteins and human interactions limited our ability to detect all viral candidate age distorters of human aging. For instance, although influenza B strains appear to have similar associations as influenza A strains with cellular senescence biomarkers expression upon infection, we could not have predicted such a role based on interspecific PPI because HVIDB has only nine PPIs recorded for influenza B.

Nonetheless, bearing these limits in mind, we found that dozens of viruses from different phylogenetic groups harbor protein-coding genes whose products have been experimentally demonstrated, with the support of biochemical and biophysical assays (see Materials and Methods), to interact with human proteins associated with aging. This systematic analysis over a large phylogenetic diversity of viruses offers a strong argument to generalize the observation that some viruses, such as HIV-1 and SARS-CoV-2 contribute to accelerating human aging, beyond these well-known cases of viral suspects of "age distortion."

From an evolutionary viewpoint, the large phylogenetic diversity of candidate age-distorter viruses and the fact that, when they belong to different phyla, these viruses can use almost completely unrelated age-distorting gene families to interact with human proteins associated with aging, demonstrates a strong evolutionary convergence in the impact viruses might have on human aging. This may be explained by the fact that since mechanisms of viral hijacking generally target important human proteins, and since human proteins associated with aging are often central in human PPI networks (Bell et al. 2009; Fernandes et al. 2016), then viral hijacking should commonly interfere with human aging. In that sense, viral evolutionary success is likely to proceed at the cost of some alteration of human aging. However, it should not simply be assumed that any sort of viral illness, even if repeated or latent, will inevitably result in accelerated host aging. A host owns resources to fight viral infections and illnesses, even chronic ones. Surely, viral lytic infection substantially alters cellular physiology, provoking nutrient depletion, energy depletion, hypoxia and endoplasmic reticulum stress. But these alterations in stress signaling activate host mechanisms that can either alleviate the problem or induce apoptosis (Buchkovich et al. 2008). Therefore, although each new

viral particle depletes cellular lipidic, proteic, or nucleic resources, which need to be replaced to maintain cellular homeostasis, such an infection does not imply that the fight for limited macromolecules has to be (dramatically) lost by the host. In the case of some infections at least, substrate availability may not be a limit, for the virus and for the host (Smallwood et al. 2017). Consistently, the effects of human cytomegalovirus (HCMV) infections on accelerated immune senescence have been debated for a long time. Some recent studies demonstrated that a high infectious dose is a prerequisite for CMV-associated immune senescence (Redeker et al. 2018), and that HCMV infection results in telomere erosion and replicative senescence, faster and more frequently in $CD8^+$ cytotoxic T lymphocytes compared with $CD4^+$ T-helper cells (Humphreys et al. 2020), through continuous antigen exposure. Yet, a recent consensus is that CMV does not have a clear and measurable negative immune senescence impact (Nikolich-Žugich et al. 2020). Furthermore, the effects of bacteriophage infection on human health are still poorly known. Bacteriophages are abundant within our bodies (Popescu et al. 2021), forming phage colonies that are highly temporally stable, including circulating bioactive phages, remarkably well-tolerated immunologically. In addition, some phage genome transcriptions have even been reported in a eukaryotic system (Popescu et al. 2021), and some phages recently proved to play unanticipated roles in the mammalian and in the human body, including some ability to modulate the physiology of their host mammalian cells (Popescu et al. 2021), to the point that some authors foresee a growing field of phage–mammalian cell interactions (Bodner et al. 2021). Whether phage infection should necessarily lead to human aging is therefore an open question. Consequently, not all viruses may qualify as type 1 age distorters.

Getting back to the concept of age distorter, it must be recognized that the evolutionary reasons for which viruses interfere with apoptosis or with cellular senescence, for instance, are debated (Kelley et al. 2020). Our findings are consistent with the notion that, in some cases, the hijacking of important human proteins within those associated with aging, for example, when viruses interfere with very central proteins in human longevity networks, may be an adaptive strategy for the viruses. Typically, viral survival and reproduction can be enhanced by interspecific proteic interferences that weaken human antiviral defenses or that, by delaying cell death, generate human cell reservoirs for viruses. For instance, the ability to delay or prevent apoptosis provides viruses with more time and opportunities to replicate and assemble viral particles and promotes long-term survival of viruses in the host cell as well as their spread to surrounding hosts cells, which can lead to persistent infection. Thus, apoptosis induced by HIV-1 contributes, among many mechanisms, to the gradual T cell decline that occurs in HIV-infected patients, and programmed cell death of uninfected bystander T lymphocytes, including $CD4^+$ and $CD8^+$ T cells (Rex et al. 2022). The same is true for cellular senescence, often considered a part of the host cell response to fight viruses (Baz-Martínez et al. 2016; Kelley et al. 2020). Yet, on the other hand, many viruses replicate optimally in senescent cells. Indeed, senescent cells offer a hospitable microenvironment with persistently elevated cytosolic calcium, abundant intracellular iron, and low interferon type I. As a result, in infected hosts, virus-induced immune dysfunction and premature cellular senescence may predispose to aging-related disease such as neurodegenerative disorders (Osorio et al. 2022). Similarly, some viruses have been proposed to hijack the senescent machinery within the infected cell to downregulate the interferon pathway, to promote viral packaging and ultimately to enhance viral replication within the cell (Kim et al. 2016; Kelley et al. 2020). This is the case for the human papillomavirus or the varicella zoster virus which replicate more efficiently in senescent human bronchial epithelial cells or in human dermal fibroblasts than in non-senescent cells, and have evolved machinery to specifically overcome cellular senescence (Kelley et al. 2020). Likewise, Giannakoulis et al. (2021) recently reported that different isoforms of the hepatitis B virus X protein have different effects on senescence, yet promotes factors of the SASP phenotype, which may enhance telomere shortening, and thus trigger replicative senescence and cirrhosis in hosts. In addition, Camell et al. (2021) reported the SARS-CoV-2 S1 protein is a pathogen-associated molecular pattern that can trigger a hyperinflammatory state in senescent cells, and that senescent cells could promote SARS-CoV-2 pathogenesis by decreasing viral defenses and increasing expression of viral entry proteins in neighboring non-senescent cells through amplified secretion of SASP factors (Lee et al. 2021). These examples suggest that cellular senescence, in some host conditions, may enhance rather than oppose viral infection. Therefore, to distinguish between viruses that inadvertently trigger an immune response and viruses specifically causing apoptosis/cellular senescence for their own purposes, quantifying the effect of the manipulated host processes on viral fitness (e.g., by quantification of viral titers from supernatants of infected cells, or of the intensity of viral protein synthesis in senescent cells) would be useful. Our work makes one key step on that research road, by identifying a number of viruses with genetic potential to act as type 1 age distorters, even though our work does not allow to distinguish between two interpretations, that is, virally altered human aging as a side-effect of the hijacking of central human proteins versus a selected direct viral-manipulation of human aging. However, our work makes it clear that many viruses encode genetic potential to interfere with human aging and provides a broad, updated list of key viruses, key viral proteins and human proteins, repeatedly involved in interactions with these viral entities (supplementary table S1, Supplementary Material online), supporting testable predictions.

Importantly, this list of age distorters and age-distorting proteins is, in part comforted by the published literature and by experimental evidence. For instance, the report

of HIV-1 as well as that of many oncoviruses among the top candidate age distorters offers a proof of concept that our strategy succeeded in reporting first viruses known to interfere with host aging and with the human cell cycle. Interestingly, our broadscale functional inferences suggest that these top candidate age distorters may impact human aging in general, potentially contributing to multiple hallmarks of aging, and in particular, for some viruses, such as influenza A (subtype H1N1), to cellular senescence. These latter effects on cellular senescence are worth emphasizing, because virally-induced interference with cellular senescence is expected to affect global host aging beyond the fate of human infected cells. For instance, virally-induced manipulation of cellular senescence can contribute to age-associated diseases (Kelley et al. 2020), as it induces dysregulation of the host homeostasis, for example, when senescent cells accumulate faster than they are removed, and/or due to an aggravation of immunosenescence, caused by the known bystander effect exerted by senescent cells on their neighbors (Karin et al. 2019). With this in mind, our prediction that the influenza A virus (subtype H1N1) is likely to alter cellular senescence, reinforced by transcriptomic evidence, raises the possibility that, although H1N1 (but maybe not its genes [Tesoriero et al. 2016]) has usual short latency periods (Cori et al. 2012), it encodes a rich under-appreciated genetic potential to distort human aging. Therefore, although the majority of influenza infections are acute self-resolving episodes, the long-term effects on human aging of both recurrent infections by influenza A (Möst et al. 2019; Memoli et al. 2020; Wang et al. 2022) and of longer episodes of acute infections in some immuno-suppressed individuals (Pinsky et al. 2010) (but see [Tang 2010]) may deserve further investigations. In particular, it would be worth determining whether the severity of age distortion by H1N1 viruses, by aggravating the load of senescent cells and by provoking other host damages, may not be in itself an age-dependent process, for example, with stronger effects on aging in older infected humans. Indeed, as cellular senescence, particularly in cells of the immune system, is the hallmark of elderly adults, the further induction of immunosenescence may cause older individuals to be more susceptible to infection (Hsieh et al. 2020).

On that front, our original heatmap analysis of the differential gene expression of SenMayo markers upon viral infection provides novel evidence that many viruses beyond the influenza A virus affect cellular senescence, and may also contribute to host aging in an age-dependent way. Consistently, SARS-CoV-2 has been experimentally demonstrated (1) to indirectly induce cellular senescence in humans and (2) to have aggravated effects in elderly humans with respect to younger humans. These two observations have been causally connected in some papers that propose that because older humans already harbor an elevated proportion of pre-existing senescent cells in their tissues, the additional cellular senescence provoked by SARS-CoV-2, by aggravating the load in senescent cells and their SASPs beyond a certain threshold, leads to a switch past which there is an exacerbation of the infection, an aggravation of age-related pathologies and further immunosenescence (Camell et al. 2021; Lee et al. 2021; Lynch et al. 2021; Schmitt et al. 2022). This claim was further supported by the observation that treatments with senolytics, that is, drugs that remove senescent cells from aged organisms, can decrease the effects of SARS-CoV-2 infection, confirming that (pre-existing) senescent cells are critical mediators for the disease (Camell et al. 2021). In addition, such an accumulation of senescent cells, when insufficient to trigger an exacerbation of the disease during the course of the infection, may still have a longer term impact, as proposed (although debated) for "long Covid" (Schmitt et al. 2022). If that logic holds for other viruses that induce cellular senescence, either by direct viral protein interactions with human proteic interactors associated with cellular senescence pathways, or indirectly, by triggering an immune response that the host uses to clear the virus, then the effects of these viruses should be more dramatic when they infect hosts with higher proportion of pre-existing senescent cells. Consistently, the impact of viruses that induce cellular senescence should be higher on older individuals, as well as in some younger individuals affected by chronic diseases, who can also harbor higher proportion of pre-existing senescent cells in their tissues than healthy members from their age classes (Schmitt et al. 2022).

By bringing into light the large diversity of viruses that could genetically alter our aging, our predictions of candidate age distorters set the stage to subsequent experimental analyses of the contribution of viral age-distorting genes, of viral age distorters and of their human targets to human aging, to determine which are the major viral threats to our aging. It also sets the stage to determine which of the human proteic interactors of these viruses may, as a result of evolution, constitute human molecular Achilles' heels, leading to altered aging patterns upon viral infection. Indeed, as our approach supports the hypothesis that many viruses interfere with human aging and may genetically contribute to the progressive weakening of our organisms, by the same token, our protocol opens an avenue for the research of novel targets through innovative anti-aging therapies. Knowing which key proteic interactors in humans can be affected by age distorters is of high interest to shape evolutionary medicine, as it defines a pool of human cellular targets, critical for the success of viral infection, which may be used as (less evolutionarily dynamic) targets than the viral proteins for pharmacological interventions (König et al. 2010; Kuss-Duerkop et al. 2017). Alternatively, new medical anti-aging treatments could possibly be devised with the aim to counter the negative effects of some interactions between viral and human proteins, for example, by designing molecules mimicking human target proteins to alleviate the effects of viral proteins (Karoyan et al. 2021). Moreover, some existing vaccines developed to fight acute viral infections could be re-purposed to fight against virally-induced aging, leading to future novel health policies.

Likewise, it may appear desirable to routinely monitor the environmental load in viral age distorters and in viral

age-distorting genes using targeted metagenomics approaches, for instance to quantify the abundance of key viral age distorters or of key age-distorting genes in the environments (hospital, schools, public waters, etc.) to determine whether and where humans are being exposed to significantly high age-distorting threats. A similar procedure could also be used in the context of personalized medicine to monitor the dynamics of the load of age distorters associated with various individual medical conditions (e.g., through targeted -omics analyses of blood samples).

On a more theoretical level, recognizing that some viruses are age distorters could also change our perception of these viruses on our health, by recognizing that these viruses may cause more deaths than currently assumed. Quantifying the number of people that die from a virus (such as the seasonal flu) is both important from a medical and societal viewpoint and challenging from a demographic perspective (Charbonneau and James 2019). For seasonal viruses, measures of excess deaths during infection periods is a common strategy to address this problem (Iuliano et al. 2018; Paget et al. 2019). However, should influenza A (subtype H1N1) be considered as an age distorter as suggested by our work, this would mean that infections by influenza A may also lead to additional deaths, delayed in time, that is, occurring after, rather than during, the flu season, through host aging and aggravated senescence. This additional death-toll induced by influenza infection would then deserve to be accounted for, possibly by an explicit modeling of age-distorsion potential in demographic/epidemiological models, to quantify short- and long-term deaths induced by the influenza A virus. To conclude, because our strategy to mine for candidate age distorters and age-distorting genes is very generic, our work paves the way for future, phylogenetically expanded surveys of viral age distorters and viral age distorting, which are likely to be prompted by the ever-increasing flow of -omics viral (including bacteriophages) and human data. And beyond, by moving away from an anthropocentric view toward a more fundamental understanding of the impact of viral interactions on aging for a diversity of hosts across the Web of Life, we anticipate that our study could be extended to many other species for which genes and proteins have been associated with aging (currently, *Mus musculus*, *Caenorhabditis elegans*, *Saccharomyces cerevisiae*, etc.). Thereby, our work should further enhance the classic views on the locus of organismal aging from current mainstream evolutionary theories of aging (Johnson et al. 2019), moving it toward a more communal, ecological perspective to explain both the ultimate and proximal causes of aging, which could have implications for many fields, including evolutionary biology, aging research, virology, medicine and demography studies.

Materials and Methods

Construction of Aging-associated PPI Networks

The human PPI network used in this study was downloaded from the STRING ('Search Tool for Retrieval of Interacting Genes/Proteins') database v11.5 (https://string-db.org/, Szklarczyk et al. 2019). The CellAge set (Build 2) of 279 cell senescence human genes (http://genomics.senescence.info/cells/cellAge.zip, Avelar et al. 2020) and the GenAge set (Build 20) of 307 aging-related human genes (https://genomics.senescence.info/genes/human_genes.zip, Tacutu et al. 2018) were retrieved. A "longevity network" was derived from this human PPI network by keeping only the interactions between proteins corresponding to the cellular senescence-associated CellAge and longevity/aging-associated GenAge gene sets. Only edges indicating experimental support (see next section for details) were integrated in the longevity network.

Interspecific bipartite PPI networks were derived from PPI data from the HVIDB updated June 25, 2020 (http://zzdlab.com/hvidb/, Yang et al. 2021) restricted to interactions involving human proteins corresponding to the CellAge and GenAge gene sets. The HVIDB experimentally supported (see next section for details) human–virus PPIs (7,796 human proteins, 2,104 viral proteins, 48,643 human virus PPIs) was downloaded in June 2021 from the following URL: http://zzdlab.com/hvidb/download/HVIDB_PPIs.txt. To identify viral proteins interacting with senescence- and/or aging-related human proteins, PPIs involving human proteins encoded by genes present in the CellAge (212 human proteins, 771 viral proteins, 1,783 PPIs) and GenAge (269 human proteins, 913 viral proteins, 2,958 PPIs) gene sets, respectively, were extracted from the HVIDB PPI data set (forming a total of 4,154 total interactions). HIV-1- and H1N1-specific interspecific PPI networks were built by combining interactions from the STRING human longevity network with HIV-1-associated and H1N1-associated, respectively, HVIDB interspecific PPI interactions.

Details of the Experimental PPI Support

All PPIs used are supported by experimental data obtained using a large variety of molecular interaction detection techniques. Experimental data supporting STRING and HVIDB PPI were simplified using high level categories in the HUPO PSI's "experimental interaction detection" ontology (Hermjakob et al. 2004). These categories were "affinity technology" (immunoprecipitation assays; competition binding; display technology; enzyme linked immunosorbent assay; far western blotting; filter binding; interactome parallel affinity capture; luminescence-based mammalian interactome mapping; phage display; proximity ligation; pull down assays; saturation binding; solid phase assay; tandem affinity purification), "protein complementation assay" (adenylate cyclase complementation; barcode fusion genetics two hybrid; beta galactosidase complementation; beta lactamase complementation; bimolecular fluorescence complementation; cytoplasmic complementation assay; gal4 vp16 complementation; lex-a dimerization; lexa b52 complementation; mammalian PPI trap; prey pooling approach; protein three hybrid; split luciferase complementation; two hybrid; two-hybrid

array; two-hybrid bait; two-hybrid pooling approach; ubiquitin reconstruction), "imported from Reactome" (Reactome curated interaction data), and high confidence biochemical/biophysical assays grouped as "other techniques."

The detail of this supporting data is crucial to determine if these interactions are to be trusted: yeast two-hybrid-based techniques, for instance, tend to have high rates of false positives (Huang et al. 2007). PPIs in the human longevity network were selected because their "experiments" STRING score channel (comprised between 0 and 1000) was >0. The scores in the extracted PPI network ranged from 42 to 999, with a mean of 416.54 and a standard deviation of 246.45. 61.3% were of low confidence (score < 400), 21.3% of medium confidence ($400 \leq$ score < 700) and 17.4% of high confidence (score ≥ 700), using STRING criteria. To compute these scores, STRING integrated experimental support from 16,231 data sets from other protein interaction databases (BioGRID: 9409; IntAct: 5,530; HPRD: 810; PDB: 368; DIP: 114). 899 interaction data sets (5.5%) were constituted using only yeast two-hybrid (Y2H) techniques, whereas 10,816 data sets (66%) used more reliable affinity-based techniques (including coimmunoprecipitation, pull down, and tandem affinity purification). The remaining data sets used diverse biochemical and biophysical techniques to define PPIs. Similarly, two-thirds of HVIDB PPIs were supported by affinity-based assays (66,6% of 4,154 selected PPIs), with 4% being in addition supported by other categories of assays, and 16.5% were only based on protein complementation assays (685/4154). Overall, the experimental support for the STRING human PPIs and HVIDB interspecific PPIs gathered for this study is varied and does only marginally rely on Y2H-type screens.

Computation and Curation of Viral Protein Families

The sequences of the 1,031 viral proteins found to interact with human proteins involved in senescence and/or aging were retrieved from the Uniprot database via the following string concatenation: "https://www.uniprot.org/uniprot/" + Uniprot ID of the viral protein provided by HVIDB + ".fasta". Upon remapping of obsolete identifiers and removal of 197 sequences annotated as (Fragment), 834 viral sequences were then aligned to each other in an all-against-all BLASTP and families of viral proteins were defined as connected components in the sequence similarity network connecting proteins showing at least 30% identity over at least 80% mutual length coverage. 174 (Fragment) sequences were subsequently mapped to the families containing the corresponding complete sequences, and the remaining short fragments manually curated based on their annotation. Further curation identified multiple families corresponding either to unannotated incomplete sequences, low-complexity sequences failing to be aligned, to hypervariable proteins or to polyproteins, that were thus merged together: HIV-1/SIV/SIV-agm.gri/HIV-2: Nef; Tat; Vif; Vpu; Gag/Gag-Pol/Matrix protein P17, HHV-8/MuHV-4: Latent nuclear antigen and HHV-4: EBNA1. The resulting protein families were arbitrarily numbered from 1 to 314 to annotate viral proteins in supplementary table S1, Supplementary Material online.

Centrality Metrics Computation

The closeness and degree centrality metrics were computed for each human protein in the entire experimentally supported human PPI networks and in the derived longevity network using the NetworkAnalyser plugin in Cytoscape or the networkx Python module (https://networkx.org). In bipartite interspecific networks, the in-degree of human proteins represents the number of viral proteins, viruses, or viral families (as indicated) recorded interactions and the out-degree of viral proteins, viruses or viral families (as indicated) is the number of recorded human proteic interactors. In-degrees and out-degrees were also computed using networkx.

Identification of Human Aging-associated Proteins Connecting With Significantly High Numbers of Viruses

To determine whether some human proteins are significantly more connected than by chance to viral proteins in the interspecific bipartite PPI network, we generated a distribution of 1,000 random bipartite virus–human protein networks: in each random network, nodes representing viruses and human proteins were sampled at random from the set of all viruses and all human proteins, respectively, found in the reference network. The same number of edges than in the reference network was then connected at random to viral and human protein nodes. The in-degree of human protein nodes (number of viruses connected) was computed for each random network and compared with the reference in-degree (absent proteins in random networks had an in-degree of 0). For each human node, a counter was incremented each time the random in-degree value was greater than the reference value. Empirical *P*-values were then calculated by the ratio counter/1,000, and adjusted for multiple testing using the Bonferroni method.

Metrics Identifying Candidate Age Distorters in Single Infection and Co-infection

To determine the top 25 candidate age distorters, viruses were ranked by decreasing score, computed by multiplying the number of viral protein sequences able to interact with human proteins belonging to the indicated gene sets by the number of connected human proteins. The same formula was used to calculate a combined score for co-infections by any two viruses from these top 25 lists. For each pair of viruses, this score was obtained by multiplying the number of combined viral proteins from the two viruses with the number of combined connected human proteins. To measure the similarity between pairs of viruses in terms of virus-connected human proteins, we used their Jaccard index, calculated as the size of the

intersection of the two sets of connected human proteins divided by the size of the union of these two sets. We used bipartite random network permutations, as described above for the identification of proteins with significantly high in-degrees, to compute random values of combined scores and Jaccard indices, which were compared with the reference values. For each pair of viruses, a counter was incremented each time a random value was greater than a reference value. Empirical *P*-values were then calculated by the ratio counter/1,000, and adjusted for multiple testing using the Bonferroni method.

Determination of Viral Genome Sizes

For each virus in the HVIDB, a genome size was determined from the size of the corresponding reference genome in the NCBI genome database (listed at https://ftp.ncbi.nlm.nih.gov/genomes/GENOME_REPORTS/viruses.txt).

Identification of Biomarkers of Senescence Among Differentially Expressed Genes Associated With a Viral Infection

Published transcriptomic analyses were gathered from the literature, from the RNAseq HVIDB and from the Gene Expression Omnibus repository (https://www.ncbi.nlm.nih.gov/geo/), providing a list of differentially expressed genes (DEGs) for infected and non-infected humans for a selection of viruses, several found among our top 25 candidate age-distorting viruses (supplementary table S10, Supplementary Material online). For studies with published RNAseq gene expression count matrices only, differential gene expression analyses were performed using DESeq2 (https://bioconductor.org/packages/DESeq2/) using $f|\log_2 FC|>1$ and adjusted *P*-value <0.05 as cutoff. This $\log_2 FC$ and adjusted *P*-value filter, conservatively within the thresholds used in stringent studies, was also applied to standardize the significance thresholds used across published studies of predicted DEGs. When available in a given study, separated time points and/or replicates were treated as separate individual samples and the number of DEGs associated with each individual sample was computed. The resulting list of DEGs was intersected with the SenMayo senescence gene data set (Saul et al. 2022) to indicate which of these senescence biomarkers were differentially expressed during a given condition of viral infection.

Supplementary Material

Supplementary data are available at *Molecular Biology and Evolution* online.

Acknowledgments

This work was supported by an Emergence grant from Sorbonne Université (S21JR31001—IP/S/V2 EMERG-ESPA) to E.B. and J.M. and by a grant from the Ministère de la Recherche to C.B. The authors thank Prof. Takayuki Murata, Dr Sascha Schäuble, and Prof. Jürgen Löffler for sharing complete transcriptomic data sets, two anonymous reviewers for their constructive comments, and D. Sussfeld for critical reading.

Data Availability

The data underlying this article are available in the article and in its online supplementary material.

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