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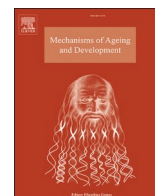
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Interspecific interactions and aging: Prediction of gerogenic bacteria and critical human protein targets of microbial infections

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ABSTRACT

Bacteria permeate every niche of the human body with major consequences on our health and senescence that have not been fully described. Here, we predict which bacteria and which bacterial proteins could interfere with proteins associated with human aging using bipartite networks showing interspecific protein interactions coupled with investigations of published experimental evidence and transcriptomic data. We introduce the term of “gerogenic” bacteria, literally bacteria that could induce some aging in their host and discuss the mechanisms by which such bacteria could serve as age-distorters of humans. *Salmonella*, *Escherichia* and *Shigella* appear as major candidate age-distorters, characterized by a higher experimentally demonstrated potential than other bacteria to interact with human proteins associated with human aging and human cellular senescence. Our analysis also highlights an evolutionary convergence among bacterial and viral candidate age-distorting proteins, since 14 human proteins associated with aging can be commonly targeted by bacteria and viruses in case of microbial infection. Since infections are common and *Salmonella*, *Escherichia* and *Shigella* are frequently found as pathogens in our microbiomes, characterizing bacterial influence on our aging and our cellular senescence through molecular hijacking could enhance the understanding of the causes of aging and suggest new anti-aging therapies.

1. Introduction

Aging is a multifaceted intricate process, marked by a myriad of physiological changes over time that affects not only tissues and organs but also cells and subcellular organelles (Phillip et al., 2015). Aging is commonly explained by three major evolutionary theories (Johnson et al., 2019). The mutation accumulation theory attributes aging to the relaxed selection against late-acting deleterious mutations (Mueller, 2021). The antagonistic pleiotropy model suggests that genes conferring early-life benefits may have harmful effects later (Mitteldorf, 2019). The disposable soma theory proposes a trade-off in resource allocation favoring reproduction over somatic maintenance (Van Den Heuvel et al., 2016).

While these mainstream theories have been fruitful in the field of aging, they mostly focused on individuals, treating the environment as an undifferentiated source of pressures and resources (Johnson et al.,

2019). However, organisms do not develop in isolation and no species exists in an ecological vacuum. Moreover, aging may be the cause of infection but infection can also be the cause of aging through mechanisms such as heightened inflammation, pathogen-induced tissue damage, or accelerated cellular aging due to increased cell turnover (Gavazzi and Krause, 2002). Therefore, it is essential to include the influence of interspecific interactions to better understand the aging process (Bapteste et al., 2023). This realization led Teulière et al. to propose the concept of age-distorters (be they viruses, microorganisms, or multicellular organisms) that interact with the aging of a host from another species for their own evolutionary benefit (Teulière et al., 2021).

Taking age-distorters into account extends the disposable soma theory into the realm of interspecific relationships, by suggesting that part of a host's body, whose aging would be altered due to these interactions, could be analogous to an extended disposable soma for its microbial age-distorters. The notion of age-distorters also enhances the

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Mutation Accumulation theory and the Antagonistic Pleiotropy theory, when microbes are the sources of late expressed deleterious genes and of antagonistic pleiotropic genes (Teulière et al., 2021). More precisely, Teulière et al. proposed to identify two categories of age distorters: Type 1, which directly alter their host's aging pathways by molecular interferences, and Type 2, which indirectly affect aging by influencing the balance of accumulated damage in their hosts. Accordingly, dozens of viruses were predicted as human Type 1 age distorters, including the influenza A virus (IAV) subtype H1N1 (Teulière et al., 2023). These hypotheses were corroborated by experimental evidence in mice infected by IAV, highlighting the importance of considering interspecific protein interactions in the study of aging. This broader focus not only enriches our understanding of aging's complexities but also emphasizes the evolutionary interconnectedness of life and aging.

To further refine this research beyond viruses, we shifted our focus to another category of candidate age-distorters: bacteria, which pervade every corner of the human body, forming a complex ecosystem with their host through continuous bacterial-host interactions. Already, some evidence suggests that some bacteria play a significant role in influencing aspects of human aging. *Helicobacter pylori* infection induces changes in the DNA methylation of its host, leading to a permanent activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), which results in chronic inflammation of the gastric mucosa, even after the elimination of this bacterium by antibiotics (Delval et al., 2023; Fischer, 2020; Gao et al., 2017; Goplen et al., 2020). Moreover, *H. pylori* infection promotes gastric epithelial cell senescence through inflammatory C-X-C motif chemokine receptor 2 (CXCR2) signaling, forming a feedback loop with p53. Notably, senescent cells of humans were detected throughout the gastric mucosa, including progenitor and stem cells in the gland base. This cellular aging likely contributes to gastric atrophy by disrupting cellular differentiation and renewal (Cai et al., 2021). Likewise, *Listeria monocytogenes* induces host DNA damage and delays the host cell cycle to promote infection, inducing host cell genomic instability, impairing DNA repair, and promoting tumor development through bacterial persistence (Leitão et al., 2014).

By analogy with the term "oncogenic" bacteria, whose infection increases the risk of cancer in their host, we will refer to bacteria whose infection increases the risk of aging of their hosts as "gerogenic bacteria". This group includes bacteria that trigger aging-related processes such as cellular senescence, genomic instability and chronic inflammation. Although a growing body of evidence (Abavisani et al., 2025; Reyes et al., 2023; Teulière et al., 2021) highlights the significant impact of candidate gerogenic bacteria on humans, a comprehensive census of these bacteria and a prediction of their modes of action remains lacking. In particular, no systematic prediction of type 1 bacterial age-distorters in humans has been achieved, despite the existence of -omics data to address this question over a large range of bacterial species. To fill in this important knowledge gap, we used the Human Longevity PPI Network created from the STRING database (Szklarczyk et al., 2023), the Host-Pathogen Interaction Database [HPIDB] (Ammari et al., 2016) and the IntAct database (del Toro et al., 2022) to develop a bipartite network analysis of human and bacterial protein interactomes with the aim of identifying bacterial proteins that have been experimentally confirmed to interact with human proteins known to be associated with aging or with cellular senescence. This *in silico* approach assumes that when a bacterial protein was demonstrated to interact with some human proteins in carefully controlled experimental set-ups, then this protein has the potential to interfere with the same host proteins during bacterial infection (Teulière et al., 2023). This allowed us to provide the first systematic prediction of candidate age-distorting bacterial proteins. Moreover, we investigated the potential modes of action of these bacterial proteins on human aging, by analyzing biomarkers of cellular senescence amongst differentially expressed genes and enrichment analyses associated with these bacterial infections.

2. Results

2.1. Bacterial targets in human aging- and longevity-associated proteins

We first constructed a reference human aging and longevity PPI network, which features proteins associated with human aging (and with cellular senescence) as their nodes and represents the whole set of experimentally demonstrated human protein-protein interactions that are also well supported by other channels of evidence (experimental score > 0 , combined score ≥ 500) as direct edges (see Materials and Methods). In brief, this aging and longevity network was derived from the STRING human Protein-Protein Interaction (PPI) network (Szklarczyk et al., 2023), filtering protein nodes by their association with cellular senescence or with human longevity/aging as recorded in the CellAge (Avelar et al., 2020) and GenAge (Tacutu et al., 2018) databases, respectively. The resulting human aging and longevity network contains 1074 proteins and 16021 interactions.

We then determined the set of bacterial proteins experimentally demonstrated to interact with proteins from this human aging and longevity network using the HPIDB Host Pathogen Interaction Database (HPIDB 3.0) and IntAct (version:1.0.4 - October 2023), which are the most comprehensive resources to date that provide data on protein-protein interactions between hosts and pathogens. We only selected the most trustworthy interactions above a MIscore threshold of 0.4 (Villaveces et al., 2015) to create a bipartite bacterial protein-human protein network. The resulting bipartite network reveals 99 interspecific interactions between 81 bacterial proteins from 28 different genera and 69 proteins from the human longevity network (Fig. 1). Among these 69 human proteins, 41 are associated with cellular senescence (Avelar et al., 2020), 10 to organismal aging (Tacutu et al., 2018), and 18 are common to both types of senescence (supplementary figure S1 A, B). Therefore, the vast majority of connections suggests a potential influence primarily on cellular aging. Functional enrichment analyses (supplementary figure S1 C) show that these interspecific PPI could affect different aging pathways. In addition, we compared the list of 69 human protein putative targets of candidate bacterial age-distorters with the list of 69 human proteins identified by prediction (Teulière et al., 2023) as being convergently manipulable by viruses. The two lists shared 14 proteins (20 % in common): CDK1, EEF1A1, EGFR, EP300, GAPDH, GRB2, HSPA1A, HSPA5, HSPA8, HSPD1, RB1, TGFB111, TP53 and YWHAZ. Among those proteins, 12/14 proteins (CDK1, EEF1A1, EGFR, EP300, GAPDH, GRB2, HSPA5, HSPA8, HSPD1, RB1, TP53 and YWHAZ) are essential genes (Luo et al., 2021), crucial for basic cellular functions and survival. Notably, in aging mice, HSP70 (HSPA1A, HSPA5, HSPA8) basal levels increase in mitotic tissues like the liver and renal medulla, but decrease in post-mitotic tissues like the heart, renal cortex, cerebral cortex, spleen, and peritoneal immune cells in aging mice (De Toda et al., 2016). Additionally, Cdk1 and related cell cycle regulators increased significantly with aging in the gastric mucosa of rats (Barbaro et al., 2022). EGFR mRNA levels and production of new transcripts decreased during human aging (Kim et al., 2021). And EP300 activity is attenuated in ageing mice (Bedford and Brindle, 2012; Li et al., 2002).

Bacterial genera were ranked by age-distorting potential (Fig. 1), determined based on their genetic potential to interact with central human proteins from the human aging and longevity network, which we estimated by the average degree of the human proteins that could be targeted by each bacterial genus in the human longevity network (see Materials and Methods), shown in Fig. 2. In this representation, each node represents a human aging and longevity protein with which one or several bacterial proteins can interact. These nodes are colored based on the Taxonomy of the targeting bacterial protein. Notably, three human aging-associated proteins (ZCCHC10, SYT1 and SPARC) lack interactions with other human aging-associated proteins, while the others are interconnected. We also computed a Gerogenic score, GS, for each bacterial genus, calculated based on the number of human proteins

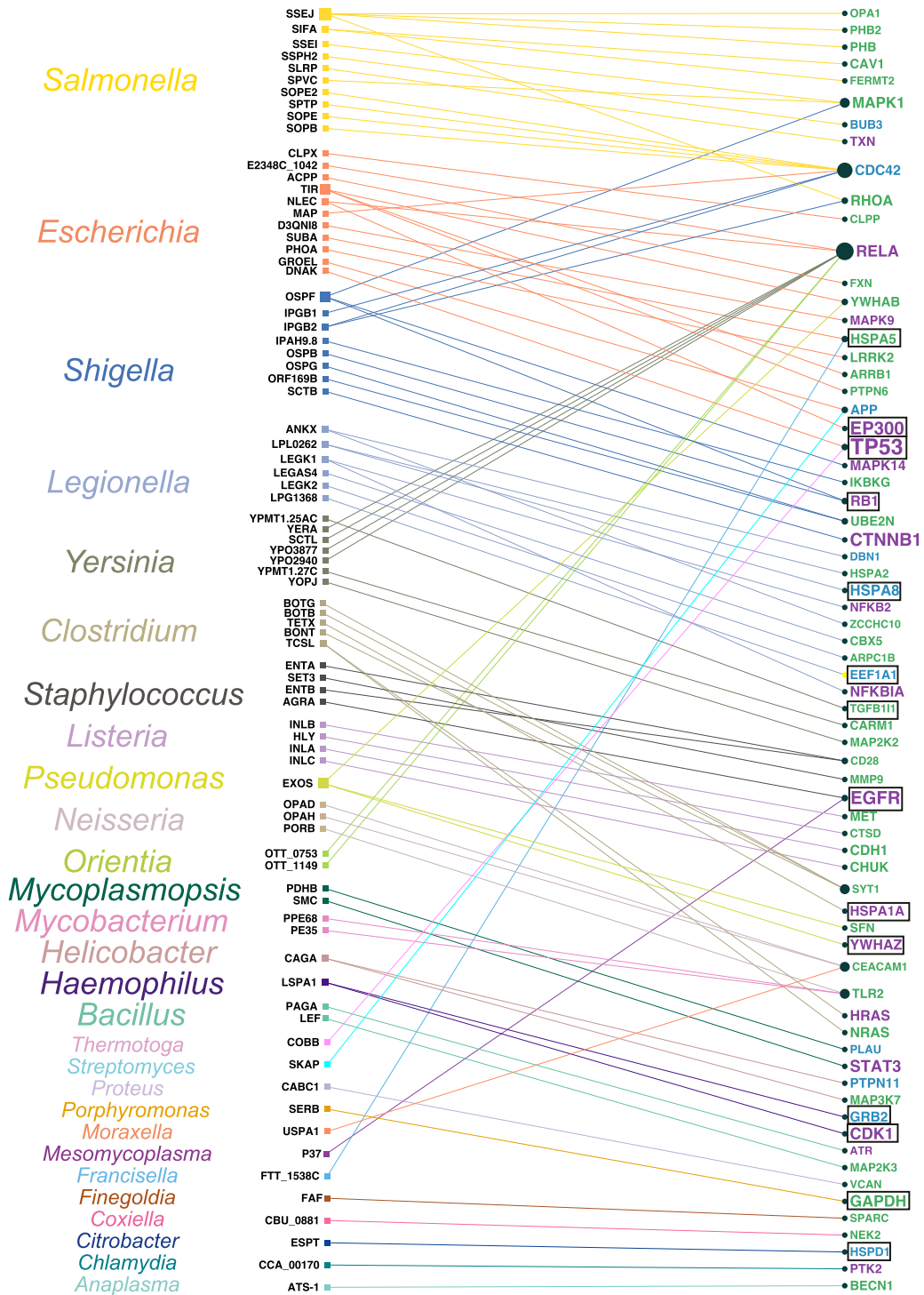


Fig. 1. Bacterial-human proteins longevity bipartite network. The bacterial-human longevity bipartite network was extracted from HVIDB and IntAct, focusing on human proteins associated with longevity and the interaction with high MIscore (≥ 0.4). The 69 proteins from the human aging and longevity network (circular black nodes) are displayed on the right, and the 81 bacterial proteins linked to human proteins on the left (colored square nodes), grouped from top to bottom by the number of interactions in the same genus and color-coded by genus. Both types of nodes are connected by a total of 99 interspecific protein-protein interactions, represented by edges whose color reflects the bacterial genus involved in the interaction. Node degree in the bipartite network is indicated by node size. The label font size of human proteins corresponds to the degree of the node in the human aging and longevity network: the larger the label font, the more central the protein is in the human aging and longevity network. The label colors of nodes represent the types of proteins as follows: black indicates bacterial proteins, green represents proteins associated with cellular aging, blue signifies proteins linked to gene aging, and purple denotes proteins involved in both cellular and gene aging. Labels enclosed in a black box indicate genes that are critical human protein targets in cases of viral and bacterial infections (a total of 14 proteins are highlighted).

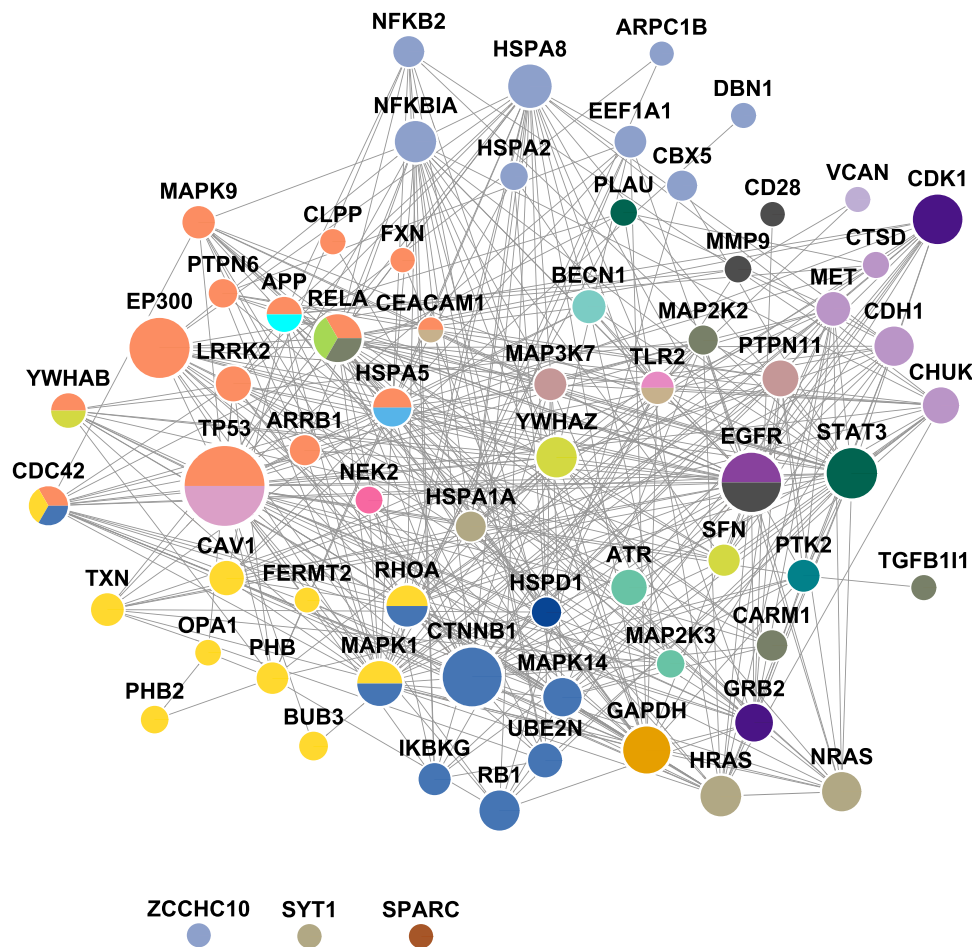


Fig. 2. Sub-network of the human aging and longevity protein-protein interactions with which bacterial proteins can interact. This sub-network of the human aging and longevity PPI network is filtered to display only human proteins that could interact with bacterial proteins, based on experimental evidence. Nodes representing human proteins are colored by sector according to the bacterial genera they could interact with, while node size represents the human protein degree within the human aging and longevity network. The legend on the right lists bacterial genera, ordered by decreasing number of interactions with human proteins.

connected to each bacterial genus multiplied by the average degree of the human proteins in the aging and longevity network (see Materials and Methods). Among 28 bacterial genera, three stand out due to their high GS: *Escherichia*, *Shigella* and *Salmonella* (Table 1), commonly found as pathogens.

Furthermore, proteins from phylogenetically distant and unrelated candidate age-distorting bacteria have a convergent potential to interact with the same human proteins (e.g. several proteins from *Yersinia*, *Escherichia* and *Orientia* are connected to the RELA human protein, Fig. 2). Two of these bacterial proteins are homologs, while others are unrelated, as assessed by a BLAST search over the 81 bacterial proteins identified (see Materials and Methods). Notably, the SpvC protein from *Salmonella* and the OspF protein from *Shigella* are homologs that present 63.5 % identity and an E-value of $< 2.5E-84$. These bacterial proteins exhibit the same phosphothreonine lyase activity on host mitogen-activated protein kinase (MAPK) (Choi et al., 2010) and directly interact with human MAPK1 (Fig. 1). In contrast, two non-homologous proteins, *Escherichia* DnaK protein and *Thermotoga* CobB protein interact with human TP53. The latter is a key regulator of numerous target genes involved in cell cycle arrest, DNA repair, cellular senescence and apoptosis and plays a critical role in maintaining genomic integrity. TP53 dysfunction leads to chromosomal instability, triggering either cellular senescence or apoptosis (Mijit et al., 2020).

2.2. Transcriptomic evidence of cellular senescence associated with candidate gerogenic bacterial infection

To test our predictions, we mined published transcriptomic data and evaluated the potential of our candidate gerogenic bacteria to interfere with cellular senescence in humans, as previously performed for viruses (Teulière et al., 2023). More precisely, we monitored the expression levels of 125 biomarkers of human cellular senescence, referred to as SenMayo biomarkers (Saul et al., 2022), by performing analyses of differentially expressed genes (DEGs) within 34 published transcriptomes of humans infected and non-infected by the candidate gerogenic bacteria *in vivo*. In the heatmap summarizing the results of this meta-analysis (Fig. 3), the vertical axis represents genes from the SenMayo gene set, ordered by the number of samples showing significant differential expression. Among the SenMayo genes, the cysteine X cysteine ligands (CXCL) CXCL-1/3 and CXCL-8, that have been shown to be key mediators of inflammation (Han et al., 2022) and chronic inflammation (Zhou et al., 2023), exhibit the highest number of samples with overexpression (Fig. 3, line 1–3,4). An enrichment analysis of Senescence SenMayo genes performed by comparing non-infected and infected samples also defined gene sets that were significantly highly enriched (normalized enrichment scores NES > 1.5 and nominal p-value < 0.05 (Subramanian et al., 2005) in most samples infected by gerogenic bacteria, indicative of cellular senescence induction.

Table 1

Bacteria with potential to interact with human longevity and aging-associated proteins in the HVIDB and IntAct databases. Legend: Bacteria: Names of bacterial genera. Bacterial proteins: number of bacterial proteins interacting with CellAge/GenAge proteins in HPIDB and IntAct with high miscore (>0.4). Human proteins: number of CellAge/GenAge proteins interacting with bacterial proteins in HPIDB. Degree: The average degree of human proteins in the longevity network is indicated. Gerogenic scores: the gerogenic score calculated based on the number of the interaction and average degree of the nodes in each bacterial genus (interactions* average degree in each genus). In the table, the bacteria were ordered by decreasing score.

Genera	Human proteins	Bacterial proteins	Interactions	Average degree	Gerogenic scores
<i>Escherichia</i>	13	11	14	100.714	1409.996
<i>Shigella</i>	8	8	11	101.909	1120.999
<i>Salmonella</i>	10	10	14	72.071	1008.994
<i>Yersinia</i>	4	7	7	98.429	689.003
<i>Legionella</i>	9	6	9	44.778	403.002
<i>Thermotoga</i>	1	1	1	349	349
<i>Orientia</i>	1	2	2	151	302
<i>Clostridium</i>	4	5	6	48	288
<i>Listeria</i>	4	4	4	62.75	251
<i>Staphylococcus</i>	3	4	4	61.75	247
<i>Haemophilus</i>	2	1	2	123.5	247
<i>Mesomycoplasma</i>	1	1	1	219	219
<i>Pseudomonas</i>	3	1	3	71.667	215.001
<i>Mycoplasmopsis</i>	2	2	2	91	182
<i>Porphyromonas</i>	1	1	1	147	147
<i>Helicobacter</i>	2	1	2	62.5	125
<i>Mycobacterium</i>	1	2	2	55	110
<i>Francisella</i>	1	1	1	90	90
<i>Neisseria</i>	2	3	3	23.667	71.001
<i>Streptomyces</i>	1	1	1	70	70
<i>Anaplasma</i>	1	1	1	60	60
<i>Chlamydia</i>	1	1	1	51	51
<i>Citrobacter</i>	1	1	1	38	38
<i>Bacillus</i>	2	2	2	13	26
<i>Coxiella</i>	1	1	1	20	20
<i>Proteus</i>	1	1	1	9	9
<i>Moraxella</i>	1	1	1	8	8
<i>Finegoldia</i>	1	1	1	4	4

2.3. Evidence for *in vivo* candidate gerogenic bacterial-human interspecific protein interactions

The interactions listed in HPIDB are experimentally confirmed, but this does not necessarily mean that they occur *in vivo*. Indeed, the methods to identify these interactions are *in vitro* techniques, such as co-immunoprecipitation, yeast two-hybrid based systems, or affinity chromatography. One first step to test the likelihood of these interactions is to examine if they are topologically possible, i.e., whether the bacterial and human proteins could colocalize in the same cellular compartment during bacterial infection. For this, we first mined the literature to determine which bacteria within our list of candidate bacterial age distorters could be localized intracellularly during infection. A substantial number of these bacteria are intracellular: only 3/28 are considered as strictly extracellular genera (*Clostridium*, *Streptomyces*, *Thermotoga*), whereas *Escherichia*, *Salmonella*, *Shigella*, *Yersinia*, *Legionella*, *Listeria*, *Staphylococcus*, *Pseudomonas*, *Helicobacter*, *Neisseria*, *Orientia*, *Mycobacterium*, *Bacillus*, *Mycoplasma*, *Haemophilus*, *Proteus*, *Porphyromonas*, *Moraxella*, *Mesomycoplasma*, *Francisella*, *Finegoldia*, *Coxiella*, *Citrobacter*, *Chlamydia* and *Anaplasma* can eventually enter host cells and possibly use their bacterial proteins to manipulate host processes to their advantage (supplementary table S2). Among our candidate gerogenic bacteria, *Yersinia* and *Salmonella* harbour a type III secretion system (T3SS) that translocates a set of effectors such as YOPJ and SseJ and SopE2, respectively, into infected host cells (Matsuda et al., 2019; Viboud and Bliska, 2005). In addition, the pathogenic strains of *H. pylori* use Cag T4SS to deliver the effector protein CagA to the host cells (Wu et al., 2023). However, detailed evidence for the subcellular localization is still lacking for many other candidate age-distorting proteins in our list.

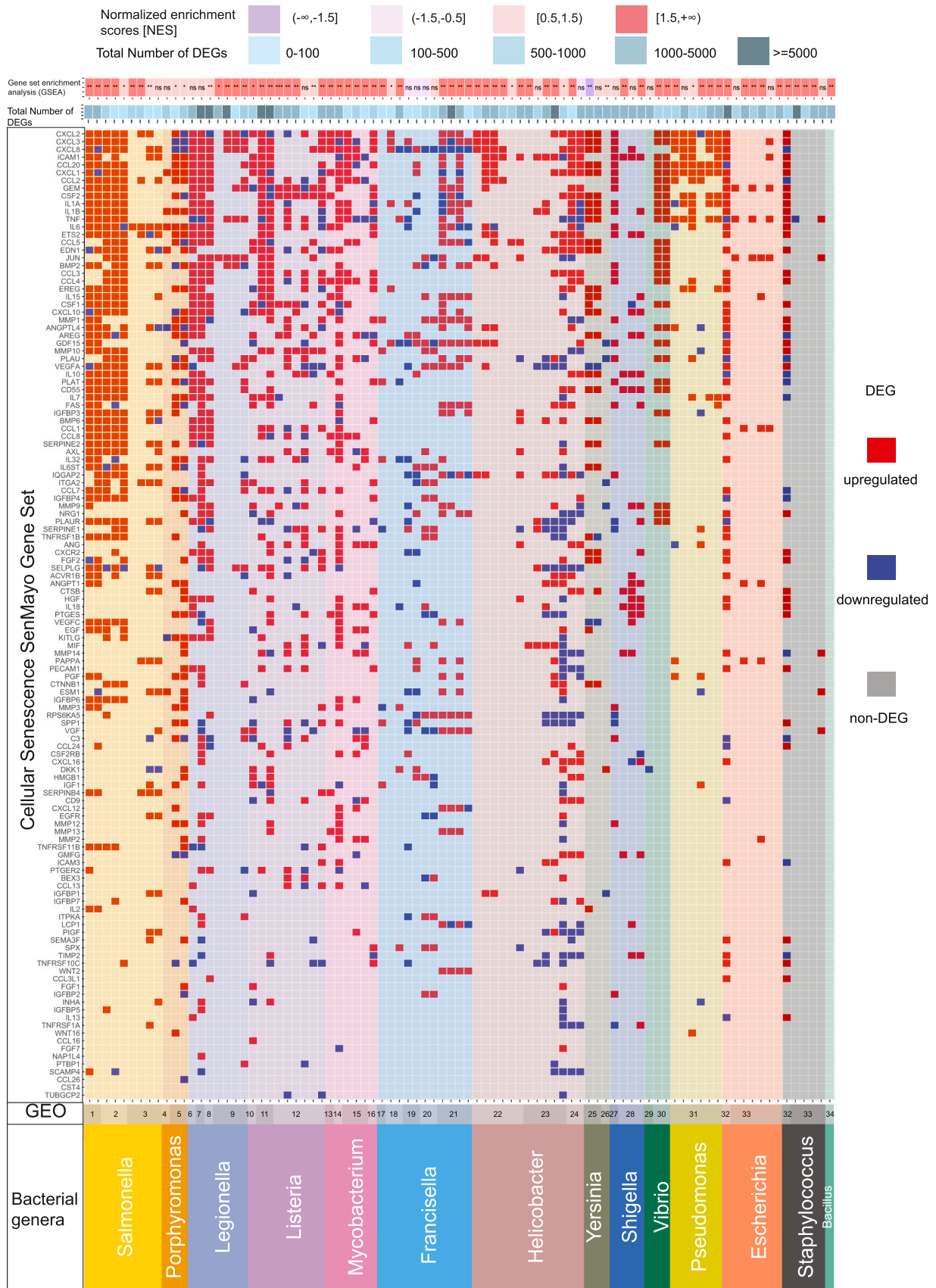
Finally, to gain further knowledge of the possible subcellular localization of each target and bacterial protein during infection, we used bioinformatic approaches to predict the cellular location of these bacterial proteins. Specifically, we analyzed the presence or absence of a

signal peptide (SP) in our set of candidate age-distorting bacterial proteins. In bacteria, translocation of proteins across the cytoplasmic membrane into the periplasm or the extracellular space is typically mediated by the interaction of their N-terminal signal peptides (SP) with the protein secretion machinery (Honn et al. 2017). Consistently, we identified informative signal peptides, providing indirect evidence that a secreted bacterial protein enhances its capacity to interact with human proteins *in vivo*. We detected signal peptide (SP) for 18 bacterial proteins from 11 genera (supplementary table S3). Of note, all proteins of *Listeria* were detected to present signal peptides, and nearly all belong to the internalins (Inl) family that contain leucine-rich repeats. Inl proteins in *Listeria monocytogenes* have drawn attention for their role in facilitating the bacterium's entry and spread in human cells by interacting with host receptors to cross critical barriers like the intestinal, blood-brain or placental barriers (Ireton et al., 2021). Specifically, InlA enhances the efficiency of host cell invasion by *L. monocytogenes* through its cooperation with *Listeriolysin O* (LLO). LLO has been predicted as an age-distorting protein in our list due to its ability to induce and facilitate proinflammatory reactions (Phelps et al., 2018).

3. Discussion

Our work systematically searched for bacterial proteins that could interact with human aging- and longevity-associated proteins by constructing a bipartite bacterial-human protein interactions network based on STRING (Szklarczyk et al., 2023), and on various experimental evidence of interactions between bacterial and human proteins recorded in HPIDB and IntAct database. Bacteria integrated into this bipartite network have some genetic potential to act as type 1 age-distorters, a potential that we used to classify these bacteria as gerogenic. If our prediction holds, these bacteria could perform direct molecular interference with human aging pathways, which could result in an aggravated or accelerated biological aging of their hosts.

We observed that *Salmonella*, *Escherichia*, *Shigella*, stand out due to



(caption on next page)

Fig. 3. SenMayo gene set expression during infection by bacteria predicted to interfere with human cellular senescence. Each line represents the expression profile of a given SenMayo biomarker. Each column represents a condition of infection. The bacterial genera names are at the bottom of the figure. The total number of DEGs associated with each sample is indicated by the shade of blue at the top of the figure. SenMayo gene set enrichment analysis (based on normalized enrichment scores [NES] and p values) are shown in the top row of the figure; positive NES values are represented in red, while negative values are shown in purple. The values correspond to the enrichment p-value: NS = not significant, * $p < 0.05$, ** $p < 0.01$. Bacterial genera are ordered by the mean number of the DEGs within the SenMayo biomarker genes associated with their infection from left to right in the heatmap. Data sources are numbered and visually delimited by an alternance of light-gray/dark-gray backgrounds, with some sources providing several samples in different time points or with different cell on the right side of the figure: 1) GSE81046 2) GSE161854 3) GSE60144 4) GSE192887 5) GSE218606 6) GSE135803 7) GSE207487 8) GSE190376 9) GSE205648 10) GSE184729 11) GSE174689 12) GSE60216 13) GSE211974 14) GSE227851 15) GSE207456 16) GSE164287 17) GSE185270 18) GSE190449 19) GSE149092 20) GSE162056 21) GSE243405 22) GSE155970 23) GSE37416 24) GSE12108 25) GSE194118 26) GSE116725 27) GSE8636 28) GSE69529 29) GSE125453 30) GSE184077 31) GSE199424 32) GSE237960 33) GSE232159 34) GSE14390.

their high Gerogenic Score, reflecting the high number of interactions characterized for these microbes with potential to directly influence certain proteins associated with human aging or longevity. Moreover, transcriptomic analyses of human host gene expression during bacterial infections indicated that infections by most of these bacterial genera predicted to be gerogenic is associated with an over-expression of biomarkers associated with human cellular senescence, consistently with the hypothesis that these bacteria may aggravate cellular senescence and influence aging-related processes. However, as most transcriptomic data are limited to within 24 hours post-infection, with the exception of one condition, an infection by *Listeria monocytogenes* for 3 days (fig3 column 10) that extends beyond this window, while these results are compatible with a potential for these bacteria to induce senescence in host cells, it remains unclear whether the observed substantial over-expression of inflammatory and senescent cell markers indicates a transient response of the host immune system to the infection, or a long term effect that could contribute to general human aging by aggravating the host load in senescent cells. Further analyses are needed to elucidate the long-term effects on cellular senescence and aging-related processes of these bacterial infections.

Our investigation of age-distorting proteins also highlighted a well-documented case which provides a proof of concept of the predictive value of our approach. CagA has been reported to lead to the up-regulation of p21 in an ERK-dependent manner, that in turn induces cellular senescence (Lewinska and Wnuk, 2017; Reyes et al., 2023). Additionally, CagA upregulates spermine oxidase (SMO) in host cells, converting spermine to spermidine and generating hydrogen peroxide, a ROS, which activates the DDR and contributes to genomic instability (Abavisani et al., 2025). These findings reinforce our prediction of the roles of *H. pylori* as an age-distorter and of CagA as age-distorting. Moreover, although the proteins of these bacteria are not directly represented in the interspecific bipartite network, parallel evidence from the literature supports their potential gerogenic effects. The three bacterial genera: *Salmonella*, *Escherichia*, and *Shigella*, exhibiting high Gerogenic score, have already been reported to play significant roles in inducing cellular senescence. *Salmonella* genotoxins, specifically the typhoid toxin (CdtB and PltA), act on human immune cells by damaging mitochondrial DNA, which leads to mitochondrial dysfunction and oxidative stress. This damage triggers the release of mitochondrial DNA into the cytosol, activating the cGAS-STING pathway and stimulating the production of type I interferons. The resulting inflammatory response induces T cell senescence, fostering a proinflammatory environment that may be associated with aging (Chen et al., 2024). In addition, approximately 5 % of *Salmonella typhi* infections result in chronic carriers due to biofilm formation and immune evasion in the gallbladder, leading to long-term bacterial carriage, ongoing epithelial cell damage and potential transmission (Jahan et al., 2022). In addition, the protein of CdtB and PltA from *Salmonella* have been reported to play a role in aging pathways, but only been documented once in human bacterial interaction in the IntAct database, highlighting the lack of available data to confirm this hypothesis. Similarly, *Escherichia coli* B2 produces colibactin, which induces DNA damage in human cells and activates repair pathways such as FANCD2 and ATR kinase. Some infected cells survive, displaying senescence markers like SA- β -gal

activity and secreting inflammatory molecules such as IL-6 and IL-8. This process promotes the spread of senescence to neighboring cells, exacerbating age-related tissue dysfunction (Humphreys et al., 2020). In the case of *Shigella*, the production of *Shiga* toxin causes DNA lesions that result in genome instability, which may indirectly contribute to aging and its associated pathologies (Benedetti et al., 2021). Our approach complements these early findings and sheds light on novel pathways, uncovering mechanisms and interactions that have not been extensively studied.

From an evolutionary point of view, distantly related bacteria may influence human aging-related pathways through common molecular targets in the human aging and longevity network. The high centrality of these human proteins and the convergence of multiple bacteria on them as targets suggests that there is a selective advantage for bacteria to interfere with these important human proteins in order to hijack multiple critical pathways. Additionally, the structural constraints imposed by their high centrality in the complete human PPI network (see Materials and Methods) and numerous interactors limit the possibilities for mutations in these proteins over generations, making it challenging for them to escape bacterial targeting. Moreover, although data on bacterial-human protein interactions are more limited compared to data on viral-human protein interactions, resulting in fewer known interactions (Teulière et al., 2023), our analyses could still identify some evolutionary convergence amongst the common human protein targets of these bacterial age-distorters and of viral age-distorters. We propose that 14 human protein (CDK1, EEF1A1, EGFR, EP300, GAPDH, GRB2, HSPA1A, HSPA5, HSPA8, HSPD1, RB1, TGFB11, TP53 and YWHAZ) associated with aging and longevity may have evolved into molecular Achilles' heels (Teulière et al., 2023), potentially influencing aging patterns during microbial (viral and bacterial) infections. However, specific allelic variants of these genes associated with bacterial infection susceptibility have not yet been documented in the current literature, and it's usually impossible to determine whether some of these Achilles' heels are more resistant than others to bacterial manipulation. Therefore, we encourage further investigation into the genetic polymorphisms of these 14 proteins, focusing on their functional consequences after bacterial and virus infections and aging. This includes conducting genome-wide association studies (GWAS) and allele-specific expression analyses to identify variants that may influence susceptibility, immune response, and disease outcomes in host-pathogen interactions, as well as their potential roles in modulating age-related cellular processes and longevity. However, 12 of these 14 proteins are known to be encoded by essential genes, which means these targets are likely always present in humans, which possibly makes them targets of choice for microbial manipulation. Accordingly, many bacterial pathogens, such as *Helicobacter pylori*, *Pseudomonas aeruginosa*, *Chlamydia trachomatis* and *Shigella flexneri* have been reported to manipulate TP53 to evade the host's defense mechanisms (Abavisani et al., 2025; Siegl and Rudel, 2015). These bacteria can inactivate or degrade TP53 to prevent the host cell from initiating apoptosis, allowing the bacteria to survive longer within the host cell and replicate (Siegl and Rudel, 2015). In addition, studies have shown that stabilization and activation of TP53 by the anticancer drugs Nutlin-3 and etoposide resulted in strong inhibition of *Chlamydia trachomatis* growth, which may offer an interesting new

approach in the treatment of potential age-distorsion by intracellular pathogens (Siegl et al., 2014).

Moreover, the increased vulnerability to bacterial infections in the elderly (Kline and Bowdish, 2016; Theodorakis et al., 2024) is attributed to several well-documented factors, including immunosenescence, alterations in the microbiome with an increasing presence of pathobionts, and the accumulation of senescent cells in older individuals, etc. For instance, the prevalence of *Helicobacter pylori* infection rises with age due to the immunosenescence (Reyes et al., 2023). Similarly, the susceptibility to *Salmonella typhimurium* infection increased with aging in human (Chen et al., 2016) and in mice (Ren et al., 2009). Likewise, the differential expression of our predicted molecular Achilles' heels with host aging or in aging cells may be an important factor increasing vulnerability to bacterial and virus infections. Specifically, one study demonstrates that the efficiency of the TP53 pathway declines with host age, leading to reduced DNA repair capacity and an increased fixation of mutations due to impaired p53-mediated apoptosis, particularly in response to stress. This progressive decline in TP53 function (Feng et al., 2007) may contribute to the increased risk of infections in older individuals (Siegl and Rudel, 2015).

Because of its current limitations, our study opens a new avenue of research. First, our prediction of gerogenic bacteria and of their potential age-distorting proteins are based on *in vitro* interaction data from databases like HPIDB and IntAct. Therefore, although we filtered the interactions between bacterial and human proteins by a quality score to select the more trustworthy protein-protein interactions from these databases, these high scores do not prove by themselves that these interactions experimentally demonstrated *in vitro* also occur *in vivo*. Consequently, additional experimental analyses are now required to validate our predictions, to evaluate the long-term effects of the many bacteria that persist in the human body on human aging, to obtain a more comprehensive view of the impact of these bacterial interactions on the aging process. Second, the most investigated bacterial species logically appear higher in our list of candidate age-distorters, precisely because more experimental analyses have been conducted on these bacteria. Thus, the observation that *Salmonella* and *Escherichia* rank first and third in terms of interaction abundancy within the list of candidates gerogenic bacteria may result, at least in part, from this research interest bias. Other less investigated bacteria may be more effective age-distorters than our current top predicted species, but so far research regarding the interspecific interactions of proteins from these genera with human proteins are too limited to identify them as gerogenic by a bioinformatic approach. We consistently advocate for further systematic experimental research on bacterial-host interaction studies and longitudinal transcriptomic data, both in the presence and absence of bacterial infection, to deepen our understanding of the interplay between bacterial infections and aging.

4. Materials and methods

4.1. Collection database

We used the STRING database (version 12.0, downloaded from <http://string-db.org/>), a rich repository of known and predicted protein interactions (Szkłarczyk et al., 2023) to extract the human PPI network and focus on experimentally verified interactions (STRING experimental score > 0) with high global confidence score (STRING combined score ≥ 500) (Szkłarczyk et al., 2023). We also harnessed specialized datasets for aging, specifically the 949 genes from CellAge (Avelar et al., 2020) and 307 genes from GenAge (Tacutu et al., 2018) (updated August 28, 2023) to investigate cellular senescence and general aging, respectively. From these aging gene sets, we constructed a human aging and longevity PPI network with a total of 32042 total interactions between 1074 aging genes.

Data for the human-bacterial PPI network were retrieved from Host Pathogen Interaction Database version 3.0 (HPIDB 3.0) (Ammari et al.,

2016) (updated juillet 2016) and from IntAct (del Toro et al., 2022) (version:1.0.4, updated October 2023). These databases compile experimentally demonstrated interactions collected from different experiments and obtained by different methods. Therefore, to construct the most trustworthy PPI networks, we filtered the bacterial-human protein interactions by MIscore that assess the confidence in molecular interactions by evaluating their detection method, the type of interaction, and the quantity of supporting publications with a preference for experimental evidence (Villaveces et al., 2015). The optimal cutoff value for MIscore proposed by IntAct is 0.45. However, in order to conserve more proteins that have the potential to be age-distorting, we decided to lower the threshold slightly to 0.4, a value that still filters out a large number of false positive interactions, such as the interaction only detected by yeast two-hybrid (Y2H) techniques. This protocol produced a bacterial protein-human protein bipartite network with 'reliable' weighted edges.

4.2. Construction of a bacteria-human longevity protein-protein interaction (PPI) network

To construct a bacteria-human aging and longevity protein-protein interaction (PPI) network, we mapped by Diamond BLASTP (Buchfink et al., 2021) between the human proteins of HPIDB and IntAct network and of human longevity PPI network to avoid the identity in the two databases being different, filtering with an e-value threshold of $1e-5$ and a minimum identity of 90%. Consequently, our bacteria-human longevity PPI network is comprised of 99 interactions between 81 bacterial proteins and 69 human proteins.

4.3. Network analyses

Degrees were computed for each protein node using the package networkx (version 3.2.1). Two values were calculated: degrees in the bipartite network (Bacterial-human proteins aging and longevity bipartite network, Fig. 1) and degrees in the complete human longevity network (1074 longevity genes and 32042 interactions). We performed the BLASTP and filtering with an e-value threshold of $1e-5$ to identify homologs of 81 bacterial proteins. The gerogenic score was calculated based on the number of the interaction between bacteria and human protein multiplied by average degree of human proteins in the longevity network in each bacterial genus (interactions * average degree).

4.4. Identification of biomarkers of senescence among differentially expressed genes associated with bacterial infection

We conducted a comprehensive analysis of differentially expressed genes (DEGs) between transcriptomes of humans infected or non-infected by candidate bacterial age-distorters, sourced from the Gene Expression Omnibus repository (Barrett et al., 2012), from 34 experiments. For data with whole transcriptomes and RNA-seq with gene expression count matrices (29 datasets: GSE81046, GSE161854, GSE192887, GSE218606, GSE135803, GSE207487, GSE190376, GSE205648, GSE184729, GSE174689, GSE211974, GSE227851, GSE207456, GSE164287, GSE155970, GSE194118, GSE185270, GSE190449, GSE202165, GSE149092, GSE162056, GSE243405, GSE125453, GSE184077, GSE199424, GSE237960, GSE232159, GSE60144, GSE60216, GSE69529), we employed DESeq2 (Love et al., 2014) to identify DEGs, utilizing a threshold of $|\log_2FC| > 1$ and adjusted P-value < 0.05. For microarray data (5 datasets: GSE37416, GSE12108, GSE14390, GSE8636, GSE116725), we used the limma package with identical thresholds for $|\log_2FC|$ and adjusted P-values (Ritchie et al., 2015) with the same threshold to ensure consistency in the stringency of our analyses across different methodologies (Tong, 2021). In studies where multiple time points, different types of human cell targets and different bacterial strains were available, each condition was then treated as an independent sample. For each sample, the

number of DEGs between the transcriptomes of infected and non-infected humans and human cells was calculated based on the previously defined threshold, as shown at the top of Fig. 3. Subsequently, these DEGs were compared with the SenMayo senescence gene dataset to identify which senescence biomarkers exhibited differential expression under specific bacterial infection conditions as in (Teulière et al., 2023). In addition, to investigate the enrichment of SenMayo senescence gene set in our dataset, we utilized the fgsea R package (1.26.0) (Korotkevich et al., 2016) and log2 fold changes (log2FC) from differential expression analysis. This analysis yielded the Normalized Enrichment Score (NES), which quantifies the extent to which the SenMayo gene set is overrepresented at the top or bottom of the ranked list of genes and the nominal p-value (not corrected for multiple testing). Since only a single, predefined gene set was tested, correction for multiple comparisons was not necessary (Saul et al., 2022; Subramanian et al., 2005).

4.5. Detection of signal peptide (SP) in bacterial proteins

For each bacterial protein interacting with the human aging and longevity-associated proteins, we predicted whether it presents a SP site using the SignalP v 6.0 (Teufel et al., 2022) with default parameters, that use a machine learning model to detect five SP types.

CRediT authorship contribution statement

Louis-Patrick Haraoui: Writing – review & editing, Supervision, Funding acquisition. **Philippe Lopez:** Supervision. **Eric Baptiste:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **dai yuping:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Jérôme Teulière:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Ni Boussagnet:** Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Elphège Budzinski:** Writing – review & editing, Investigation. **Hugo Bonnefous:** Writing – review & editing, Methodology.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.mad.2025.112076](https://doi.org/10.1016/j.mad.2025.112076).

Data availability

Data will be made available on request.

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