SUPPLEMENTARY MATERIALS

Supplementary Results

Human, largest healthspan pathway, further details

We further investigated the miRNAs that are statistically enriched in the largest healthspan pathway using the TFmir webserver [1]. Notably, hsa-mir-34 stands out as a regulator of the *Notch* genes, and it is implicated in cancer, intracranial aneurysm and heart failure (Supplementary Figure 1, Supplementary Table 9). Additionally, hsa-mir-30 regulates many genes of this healthspan cluster/pathway, including NOTCH2, and it is implicated in the epithelial-mesenchymal transition (EMT), cancer, heart failure and obesity. In fact, the EMT is known to be involved in kidney disease and cancer, mediated by Notch signalling [2–4]. It is also associated with human longevity [5]. Furthermore, miRNA 34 has been associated with schizophrenia [6], and miRNA 34a has been associated with Alzheimer´s Disease [7], and its upregulation was found 30 minutes after fear conditioning in the amygdala, transiently downregulating Notch signaling. Finally, according to Wikipedia's community annotation facilitated by miRBase and Rfam, hsa-mir-34 and hsa-mir-30 are both linked to cancer, see also [8, 9].

Human, second-largest healthspan pathway

The genes in the second-largest pathway/cluster, related to cell proliferation (with links to inflammation and apoptosis) feature downregulation as expected, affecting NFKB1, STAT1, STAT5a and GSK3B, with likely beneficial effects. Specifically, JAK/STAT pathway inhibition is considered to alleviate the cellular senescence-associated secretory phenotype and frailty in old age [10]. Furthermore, [11] demonstrated that the hypothalamus is important for the development of whole-body ageing in mice, and that the underlying basis involves hypothalamic immunity mediated by IKBKB (IkB kinase-b, IKK-b) and NFKB. Zhang et al. developed several interventional models and could show that ageing retardation and lifespan extension were achieved in mice by preventing ageing-related hypothalamic or brain IKBKB and NFKB activation. Further mechanistic studies revealed that IKBKB and NFKB inhibit gonadotropin-releasing hormone (GnRH) to mediate ageing-related hypothalamic GnRH decline, and GnRH treatment amends ageing-impaired neurogenesis and decelerates ageing. For the second-largest pathway, a miRNA enrichment analysis by TFmir highlights hsa-mir-146a, which interacts with NFKB1 and STAT1 in particular, and is implicated in many immunity-related diseases (Supplementary Figure 2, Supplementary Table 10). According to Wikipedia's community annotation, miR-146 is primarily involved in the regulation of inflammation and other processes related to the innate immune system, see also [12].

Human, third-largest healthspan pathway

The third-largest healthspan pathway/cluster features the strong downregulation of APOE, and to a lesser extent also of APOC1. The APO family proteins are all lipid transporters, and severe decreases are detrimental, as they lead to hypercholesterinemia [13]. On the other hand, APOE4 has been widely implicated in the formation of amyloid plaques in Alzheimer's Disease [14], and experimental downregulation showed a protective effect in an Alzheimer Disease mouse model [15]. A supplementary interpretation of the CR-related downregulation found for this healthspan pathway is that fasting reduces lipid load, and hence induces a downregulation of the corresponding transporter proteins.

Human, further gene expression data mapping

The three largest healthspan clusters/pathways were further investigated by mapping aging- and disease-related gene expression data onto them, as published or collected by [16], see Supplementary Methods. In the largest (Notch-related) healthspan pathway (see Supplementary Figure 3), gene expression changes in aging blood clearly show the expected upregulation of Notch genes and LRP1, and the same holds for skin except for Notch3. In the second-largest (proliferation-related) healthspan pathway (see Supplementary Figure 4), most genes are upregulated as expected; again, the signal is stronger in blood than in skin. Finally, the downregulation of lipid-associated genes by CR we observed in the third pathway (see Supplementary Figure 5) is matched by an upregulation of all 4 genes in blood as well as in skin, with the single exception of APOE in skin, the downregulation of which may impair wound healing, since it does so in mice [17]. Furthermore, we mapped disease-related gene expression changes onto the healthspan pathway map, including one cancer entity (pancreatic cancer), coronary disease and Alzheimer disease (AD), see Supplementary Figure 6. We found the genes in the Notch-related healthspan pathway upregulated most consistently in case of Alzheimer disease, whereas genes in the proliferation-related and the lipid-related healthspan pathways were upregulated most consistently in coronary disease. All three healthspan pathways discussed here consist mostly of genes that

are, for higher values of gene expression, affecting health in negative ways; they are mostly downregulated by CR and upregulated by aging and disease.

C. elegans, next-largest healthspan pathways based on genetic/intervention data

In case of the mitochondrial and the hormone response cluster, the rapamycin-induced gene expression changes are not discussed since these are weak; in the *dauer*/dormancy cluster, the daf-16 inhibitor hcf-1 [18] is the most strongly downregulated gene. In the regulation cluster, the strongest changes consist of the downregulation of heat shock response genes hsp-16-41 and hsp-12-3.

C. elegans, next-largest healthspan pathways based on *WormBase* gene expression effect of intervention data

The ER/peroxisome-related pathway features upregulation of phy-2, daf-22 and acox-1. Specifically, phy-2 is essential for survival and embryonic development [19], while daf-22 catalyzes the final step in the peroxisomal β-oxidation pathway and is essential for *dauer* pheromone production [20], whereas acox-1 is essential for the prevention of fat accumulation [21]. The correlation of fat content and health maintenance was described several times: Fat accumulation in *C. elegans* was found to be decreased in phytochemically treated healthy nematodes [22] [23], during life-prolonging CR [24], or during increased autophagy [25]. Moreover, *ectopic* fat deposition is found in ageing worms and is discussed as a cause of ageing itself [26]. On the other hand, increased fat content was described in long-lived daf-2 mutants [27] and in germline ablated nematodes [28]. Moreover, acox-5 (aka drd-51), which is implicated in starvation-sensing and is downregulated by dietary restriction [29], is downregulated by rapamycin as well. The lysosome-related pathway is dominated by upregulated genes involved in fertility/development (gsp-3, gsp-4, frk-1 and spe-1). Finally, the six genes in the cluster related to morphogenesis are all upregulated (unc-52, involved in neuron differentiation [30] and muscle development [31], is upregulated the strongest), whereas the six genes in the cluster related to biosynthesis and transcription are all downregulated by rapamycin.

Overlap of healthspan pathways, first network alignment (Figure 5, left)

Notably, the serine/tyrosine kinases involved in the alignment are all known to be involved in proliferative processes, albeit in complex ways. The five kinases highlighted by our analysis include pro- and anti-proliferative genes, that is, tumor drivers as well as tumor suppressors. Control of proliferation is arguably the most important aspect of staying healthy, enabling stem cells to perform their function, while avoiding cancer. Accordingly, the independent expression data based on caloric restriction/rapamycin intervention data reflect that proliferation/biosynthesis is generally, but not completely, going down by pro-longevity interventions. Naturally, the phosphorylation status of these kinases would be more informative than their expression at the transcript level. Also, not much is known about the role of PAK4, BRSK2 and MELK in human health or aging. PAK4 is considered to protect cells from apoptosis [32], and a positive role in supporting stem cells is possible [33]. In context of cancer, however, upregulation of PAK4 has been associated with high-grade human breast cancer [34] and with malignancy in a variety of cancer cell lines [35], [36]. PAK4 can positively mediate cell survival and proliferation as well as enhance cell migration and invasion [35], [37], [38]. The inhibition of PAK4 reduced cell proliferation, migration and invasion of gastric cancer cells [35]. Further, depletion of PAK4 is considered to increase cell adhesion dynamics in breast cancer cells; due to its RhoU stabilizing function, it promotes the focal adhesion disassembly via phosphorylation of paxillin [34]. Furthermore, PAK4 modulates Wnt signaling by ß-Catenin regulation, increasing cell proliferation. Concordantly, the Wnt signaling pathway itself promotes intrinsic processes such as cell migration, hematopoiesis and cell polarity, and organogenesis during embryonic development [39], [40] . Concerning BRSK2, which is usually expressed in brain, testis and pancreatic tissue, an enhanced activity in response to DNA damage was reported [41], [42], [43]. In brain, BRSK2 is significant for proper regulation and formation of neuronal polarity in the developing nervous system [43], [44]. Finally, MELK as a stem cell marker is expressed in several types of progenitor cells and hematopoietic stem cells, and it plays key roles in cell cycle, embryonic development and in other crucial cellular processes [45] supporting stem cell function. In turn, upregulation of MELK has been associated with tumor progenitor cells of different origin and direct knock down of MELK leads to significant apoptosis induction [46]. In general, MELK is preferentially upregulated in cancer [47]. Overall, the overlap described highlights a cluster of genes held together mostly by shared protein domains in both species, with alternating evidence for their relation to health.

Overlap of healthspan pathways, second network alignment (Figure 5, right)

In the second alignment, all genes are considered health-related based on the *C. elegans* gene expression data in *WormBase*. The genes acox-1 and daf-22 are involved in the ER, peroxisome and microbody health

cluster (see above), whereas the genes cat-4 and pept-1 were found to be related to ion transport and homeostasis (in a smaller cluster of the original healthspan pathway map, Figure 3). All four genes are differentially regulated in a long-lived sir-2.1 overexpression strain [48] and in nematodes suffering from down-regulation of nhr-49, a key regulator of fat metabolism [49]. Moreover, differential translational regulation of cat-4, pept-1, acox-1, and daf-22 was observed in wildtypes during osmotic stress [50], underlining their role in health- and lifespan regulation. Interactions in *C. elegans* are all based on co-expression, while in human they are based on co-expression, co-localization and physical interaction (except for the interaction of SLC5A1 and GCH1, which is genetic). The independent gene expression data describing the effect of rapamycin in *C. elegans* are plausible for the ER/peroxisome genes acox-1 and daf-22 (see above). For cat-4, no data related to its role in health or survival is available, though the gene is involved in dopamine biosynthetic processes and is a target of the transcription regulator skn-1, which is known to be indispensable for proper stress response [51]. Finally, healthspan-promoting treatments like tannic acid [52], colistin exposure [53], or life-prolonging fasting [54] were shown to induce pept-1 transcription. The expression data in case of human, reflecting caloric restriction effects, are matching expectations (SCP2), are not available (SLC15A1), or are of unknown significance (ACOX1, GCH1; see also [55]). Overall, the overlap described here highlights a cluster of genes held together mostly by co-expression in both species, with a demonstrated relation to health in *C. elegans* only.

Supplementary Discussion

Biological interpretation of the lack of evolutionary conservation

In some sense, the lack of overlap between healthspan pathways in *C. elegans* and humans should not be surprising, and relates to our definition of health as the absence of undesirable conditions (that is, disease and dysfunction). Biologically speaking, each such undesirable condition may have its own etiology, or may partially share an etiology with others, such that depending on environmental factors the prevalence may vary greatly. For example, heart disease appears to be largely absent in Tsimane hunter-gatherers [56], but is a major cause of mortality in modern societies. Any heart disease pathway would thus have a major impact on healthspan in modern societies, but not in the Tsimane. Similar challenges apply to the comparison of healthspan pathways across modern populations as well [57]. It is thus to be expected that healthspan pathways will differ not just across distantly related species, but also among populations of a given species, depending on the environmental factors that push some pathways to more or less important roles in determining healthspan.

Of course it is still possible that there are shared healthspan pathways that operate across populations and species. Indeed, the conservation of genetic pathways related to aging (mTOR, sirtuins, insulin signaling, etc.) [58], [59] strongly implies the existence of shared healthspan pathways, since it is expected that these known aging pathways are also healthspan pathways. The more interesting question is thus whether there might be conserved healthspan pathways that are not also lifespan pathways: pathways that affect health much more than survival. The preliminary answer from this study is that there are few, if any, though we must consider that variation in causes of healthspan deterioration across populations and species might hide some more subtle effects.

From an evolutionary perspective, the question is how selection might act to create and maintain pathways that regulate healthspan. In the case of lifespan, it has been suggested that conserved pathways regulate a mechanism to allow individuals to put reproduction on hold during lean times, increasing lifespan at a cost to reproduction (a "trade-off"), and leading to diverse downstream mechanisms of aging with a shared control switch [60]. One possibility is that healthspan might undergo a similar trade-off, with individuals sacrificing reproduction in order to maintain health, or vice versa, though there is not yet evidence one way or another. If such a trade-off were facultative (i.e., regulated within the lifespan of an individual), we should see variation in gene expression across individuals even in the absence of allelic variation. If it were an obligate trade-off, we might see allelic variation in healthspan pathways. Allelic variation in healthspan could thus either imply (a) that there is some unknown benefit, through the trade-off, to having a shorter healthspan; or (b) that the population is not at evolutionary equilibrium, i.e. is in an environment for which healthspan regulation has not been optimized [61].

Supplementary Methods

Gene sets associated with health, based on WormBase differentially expressed genes

The *basic search* for *expression clusters* in WormBase (http://www.wormbase.org/species/c_elegans/expression_cluster#1-0-5) was used (status: 13th December 2017), to find transcriptomic data for healthspan-promoting compounds in *C. elegans*. For this purpose,

the search term "treated OR treatment OR exposure" was used, which resulted in a total of 323 expression clusters comprising about 100 different chemical, physical, and biological treatments of various kinds (differing by exposure time or dosage, and including RNAi treatment). In order to focus on small molecules, only studies with RNAi-untreated wild type animals were selected. The treatment had to lead to at least one enhanced health-related endpoint such as stress resistance or locomotion. The data sets covered the following substances (with results each described in an accompanying WormBase paper): Allantoin (WBPaper 00048989), astaxanthin (WBPaper00049979), cocoa-peptide 13L (WBPaper00042404), colistin (WBPaper 00045673), 2-deoxy-D-glucose (WBPaper00044434 and WBPaper00031060), garlic extract (WBPaper00046741), hydrogen sulfide (WBPaper00040285), lithium (WBPaper00046415), quercetin (WBPaper00040963), rapamycin (WBPaper00048989), resveratrol (WBPaper00026929), rifampicin (WBPaper00046496), and tannic acid (WBPaper00040963). All differentially expressed genes (DEGs) in the selected gene expression studies were compiled and duplicates were deleted, resulting in 11312 genes that are mentioned in at least one data set. For all genes annotated to at least one GO term (based on the ontology browser in WormBase), the exact number of associated GO terms was determined, by entering all 7646 genes in the search field of the "MGI Gene Ontology Term Finder" (http://www.informatics.jax.org/gotools/MGI_Term_Finder.html). The number of GO terms per gene was counted, and the count of each gene in all DEG lists (regulated, up-regulated only or down-regulated only, respectively) was determined. Finally, all genes were chosen which appear in at least four DEG lists in total or in at least three lists of up-regulated DEGs or in at least three lists of down-regulated DEGs, and which are annotated to at least 14 GO terms. These filter criteria were used to yield a manageable number of annotated genes; the resulting list of 58 genes was then used further. For acox-1.1 and acox-1.5, their alternative nomenclature names acox-1 and acox-5 were used.

Overlaying of expression data onto pathway maps

We searched the GEO (Gene Expression Omnibus) database in December 2017 for datasets/series where effects on healthspan or healthy aging in human or *C. elegans* were actually observed following an intervention. We found two gene expression series describing the effects of caloric restriction, or its mimetic rapamycin, that featured at least 3 replicates, as follows. For *C. elegans,* from GSE64336, "Expression data of worms under different caloric restriction mimetic treatments", we selected 1) wild type versus 2) rapamycin treatment, since the accompanying paper [62] claimed the largest number of differentially expressed genes for this compound (in comparison to the other compound tested, allantoin). For humans, from GSE38012, we selected all 25 samples, 1) Western diet versus 2) caloric restriction diet (for both series, we checked the box plots but we found no outlier distribution of expression values for any sample). We then used the GEO2R tool [63] to compute fold-changes using default parameters, downloaded the resulting tables, imported these into Excel (using "Text" column format for the gene names), removed genes with logFC equal to NaN and sorted, smallest to largest, by absolute fold change so that for genes with more than one probe, the probe with the largest fold-change is taken when the table is imported using Cytoscape. Selecting the "Gene.symbol" column as key column of the table and selecting the "gene name" column created by GeneMANIA as the "Key column for network", we established matching gene names (in case-insensitive mode) in the GEO2R and GeneMANIA tables as the common reference, to then import the tables into Cytoscape. Finally, we adjusted the "Style" of the resulting networks so that the logFC values from GEO2R are mapped continuously to a yellow-blue color scale with the appropriate max/min settings, adding a handle to map a logFC of 0 to white.

Further, we took [16] as reference publication for aging- and disease-related datasets. We took the human aging data published alongside the article, contrasting blood and skin in 24-29 and 45-50 versus 60-65 and 75-80 year-old humans. We took publicly available disease-related datasets listed in Supplementary Table 5 of [16]: for cancer we selected pancreatic cancer (GSE28735) as the only entity with paired data available at GEO; as cardiovascular disease we selected coronary artery disease as the only entity with paired data (taking plaque biopsy data rather than blood), and for neurodegenerative disease, we took Alzheimer Disease data based on brain biopsies. In the latter two cases we chose the tissues directly affected by the respective disease.

Overlap of healthspan pathways

Figure 4 (middle) summarizes the overall approach. The human health-related gene list based on Supplementary Tables 1-3 (Supplementary Table 6) and the health-related gene-expression-based gene list from wormbase (Supplementary Table 8) were investigated jointly. More specifically, both lists were submitted to Wormhole (wormhole.jax.org) on Jan 29, 2018, with "Limit results to ortholog pairs" set to "Do not filter (keep all results)" and with the "Reciprocal best hits (RBHs) only" option, to map from human to *C. elegans* and from *C. elegans* to human, respectively. The two

resulting tables were downloaded, and the ortholog genes were used to obtain two new gene lists: one list consisting of the human health gene list from Supplementary Tables 1-3 supplemented with the human orthologs of the *C. elegans* genes implicated by gene expression in WormBase, and a second list consisting of the health-related gene-expression-based *C. elegans* gene list supplemented with the *C. elegans* orthologs of the human health genes. Both new gene lists were submitted to GeneMANIA with default parameters[1], and the two GeneMANIA reports were exported[2]. From the two GeneMANIA reports, the two interaction networks and the two new lists of genes/nodes in the network were extracted. As input for the GASOLINE network aligner [64], each network was then written to a text file, and a single table of ortholog mappings was created by (a) submitting each of the two new lists of genes/nodes to Wormhole (with parameters as above), converting the "WORMHOLE Score" from 0 (worst) to 1 (best) into an E-value-like score as expected by GASOLINE (using the ad-hoc formula E-Value-substitute=1/WORMHOLE_Score*1E-20, which results in values roughly the same as given in the BLAST-based tables offered by the GASOLINE website as sample input data), and (b) concatenating both Wormhole ortholog tables into a single text file. Submitting the two network files[3] and the single table of ortholog mappings to GASOLINE with default parameters resulted in no alignment of subnetworks, but changing the GASOLINE "density threshold" from 0.8 to 0.5 resulted in the two alignments presented. Finally, the gene expression data describing effects of caloric restriction and of rapamycin were both imported, mapping the expression data to the alignments, and setting node colors, all as described above. Whenever data were processed by Excel, column formats of gene names were set to "Text".

All genes displayed in Supplementary Tables 1-5 and those derived from WormBase gene expression data are summarized in Supplementary Tables 6–8, including GenAge information [65] (https://genomics.senescence.info/genes/; GenAge Build 19; release date: June 24, 2017), if available.

The **web presentation** accompanying this paper employed Cytoscape version 3.6.1 to export the networks and its views as a CytoscapeJS object, employing a library used in version 3.29 (http://js.cytoscape.org) together with an Apache 2 web server [66]. The dynamic highlighting of genes and GO terms in the pathway was implemented in JavaScript. The transcriptional profile of user-selected genes can be inspected in GEO expression data aggregated by the multi-experiment matrix (MEM, https://biit.cs.ut.ee/mem/) [67]. Queried with single genes, the MEM service shows all the transcriptomics experiments of a selected platform and, underneath, all the genes with which the query gene is correlating in its expression [68]. The resulting list is ranked and differences between experiments with respect to the observed correlation are indicated graphically. When queried with a set of genes, specifically with all genes of a healthspan pathway, only correlations of transcripts assigned to these genes are shown. This tell us, in which experiments the genes included in our healthspan pathways interact, and for which conditions there is no concerted action of the healthspan-associated genes. One can thus obtain a characterization of a healthspan pathway in the light of a large set of gene expression experiments.

[1] which ignores some duplications introduced into the lists by a wormhole bug; non-nomenclature gene names for IL-6 and IL-12 were processed correctly.

[2] due to a GeneMANIA feature, reports for the same input gene lists may vary slightly in the last decimal places of some of the scores.

[3] first the C. *elegans* and then the human network; uploading networks the other way around results in slightly different output due to a GASOLINE feature.

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