REVIEW

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An Aging Program at the Systems Level?

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Many genes and pathways are known to modulate lifespan in various organisms, but it remains unclear whether there exists a common aging program, and how individual variations of lifespan can occur in an isogenic population. Recent studies on aging regulation at the systems and epigenetic levels point to the possibility of regulating and potentially reversing the aging epigenome and transcriptome, resulting in differential aging status and aging rate in different individuals. Here, the author summarize some of these findings and discuss the possibility of integrating multiple layers of aging regulation at the systems level, to identify an aging program that can explain lifespan variations introduced by environmental and developmental history. **Birth Defects Research (Part C) 96:206–211, 2012.** © 2012 Wiley Periodicals, Inc.

Key words: aging; systems biology; epigenetics; regulatory network

AGING IS A PROCESS OF SYSTEM DESTABILIZATION

Aging is a major risk factor for many complex diseases, including neural degenerative diseases, type 2 diabetes, cardiovascular diseases, and various cancers (Campisi, 2005; Chien and Karsenty, 2005; Kirkwood, 2005; Harman, 2006; Longo and Kennedy, 2006).

The aging process is, however, very heterogeneous among different individuals, as indicated by the fact that any lifespan curve of a population does not precipitate at 90° (Fig. 1, a typical lifespan curve vs. an ideal squared lifespan curve), that is, not all individuals die at the same age. Instead, the mortality rate (or failure rate of the system) increases only after midlife and continuously increases toward the maximum lifespan of the population.

The increased mortality rate (e.g., from an increased susceptibility to many common diseases) and the high degree of heterogeneity and uncertainty in this process indicate that, rather than being precisely controlled, aging may in fact be a process of system instability or disintegration. Network analysis supports this hypothesis. By integrating interactome data with age-dependent gene expression data, an active subnetwork for aging can be extracted using protein–protein interactions (PPIs) that occur between proteins whose encoding genes are positively or negatively transcriptionally correlated during the aging process (Xia et al., 2006; Xue et al., 2007). The modules in either human brain aging, or fruit fly aging network, correspond to sets of transcriptionally anticorrelated genes representing alternative cellular states, such as proliferation versus differentiation states or oxidative metabolic versus reductive metabolic states. The genes linking these transcriptionally anticorrelated gene modules via PPIs are highly enriched for lifespan regulators—genes that when perturbed, extend or shorten life span. In silico removal of these module-connector genes from the networks destabilizes the network structures. This suggests that aging preferentially targets the regulators controlling the organization and coordination of temporal switches (Xia et al., 2006; Xue et al., 2007). Destabilization of the transcription regulatory network has also been suggested from the increase in gene expression variations with aging among different individuals (Somel et al., 2006). In addition, the transcriptional modules that change in the aging stage are also predominantly those that are actively regulated in the developmental stage (Somel et al., 2009).

These observations support a regulatory network, in which interactions precisely regulate development, but shift or transit toward a different loosely controlled status, from a young to old age (Fig. 2), and also raise the question of whether or not there is a program that leads to such system instabil-

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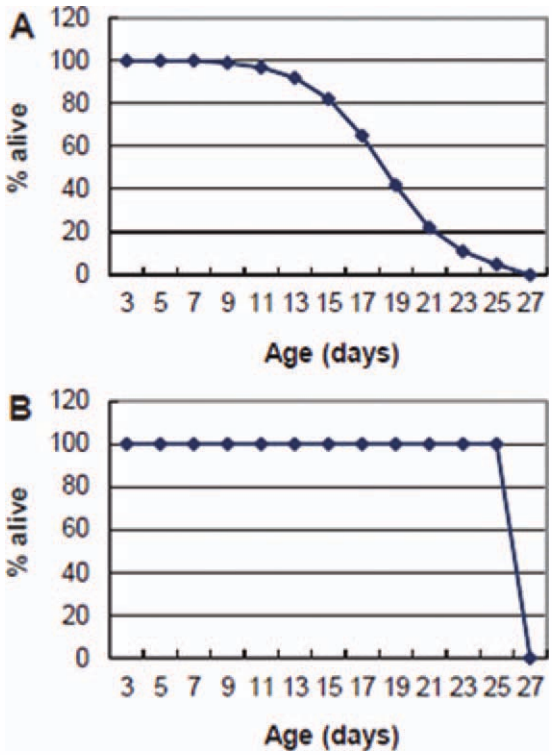

Figure 1. A typical lifespan curve (**A**) and an ideal squared lifespan curve (**B**) in the isogenic N2 strain *C. elegans*.

ity and network state change, controls when it starts, prevents it from happening, or could even reverse it.

AGING IS A CONTROLLABLE PROCESS

Even though aging itself is characterized by random accumulation of damage, the rate of this process differs drastically between species. For example, maximal lifespan varies more than fivefold among genetically similar bat species. Furthermore, humans are ~94% identical at the genome level to old world monkeys, such as macaques, but have 2.5–3 times longer maximal lifespan. These large differences in life expectancy between closely related species suggest a central "aging program" that is easily susceptible to modulation with natural selection.

Within species, aging rate can be modified by external factors, such as caloric restriction (CR) and genetic perturbations. This phenomenon suggests that the rate of aging is not a fixed parameter simply due to wear and tear, but a subject of regulation. Indeed, several such mechanisms have already been delineated in model organisms.

Several housekeeping processes, such as DNA repair, telomere maintenance, ribosome biogenesis, autophagy, and redox metabolism, are now known to be involved in aging/lifespan alterations (Kenyon, 2010).

The insulin/IGF-1 signaling (IIS) pathway stands out as a highly conserved and critical pathway among various animals, regulating both organism development and aging (Kenyon, 2005; Antebi, 2007). It is initiated at the IGF-1 receptor (*IGF1R*) (*daf-2* in *Caenorhabditis elegans*), and through a cascade of kinases, it inhibits the longevity-promoting activity of *FOXO* (*daf-16* in *C. elegans*).

The target of rapamycin pathway is another highly conserved lifespan regulatory pathway and is also a key nutrient sensing pathway. In the presence of nutrients, Tor activates S6 kinase (S6K) and 4EBP to upregulate translation and inhibit autophagy (Kenyon, 2010).

AMP-activated protein kinase (AMPK) is an immediate sensor of the adenosine monophosphate (AMP) / adenosine 5' triphosphate (ATP) ratio and mediates the lifespan extension observed with middle age dietary restriction (Kenyon, 2010).

CR is perhaps the only universal intervention that consistently prolongs lifespan in most organisms examined (Kenyon, 2005; Fontana et al., 2010). How CR increases lifespan is currently under intensive investigation, but all of the signaling pathways listed above have been implicated in one way or another, as sensors for nutrient level and modulators of several aging-related housekeeping activities.

INDIVIDUAL VARIATION IN THE RATE OF AGING

Stochastic individual variations in lifespan can be predicted at the individual and whole systems level. For example, an individual worm's level of induction of the *hsp-16.2* gene, in response to heat shock in early adulthood, can predict its lifespan and aging rate (Rea et al., 2005). Moreover, such individual differences occur at the whole body or whole systems level. For example, DAF-16 nuclear translocation is consistent across each whole worm (i.e., if one cell has predominately nuclear or cytoplasmic localization of DAF-16, all cells will have the same pattern) but vary greatly among individual worms (Padmanabhan et al., 2009; Jin et al., 2011). One explanation could be that DAF-16 is regulated by IGF-1-like circulating hormones. Similar patterns are also evident for *hsp-16.2* gene expression (Rea et al., 2005). It will be interesting to see if these molecular markers reflect the biological age of the animals.

Recent studies have shown that individual variation of the phenotypes resulting from loss of function of a gene (i.e., penetrance) can be buffered by the expression of paralogous genes, which are induced by the loss of the gene and also by genetic hubs such as chaperones or heat shock proteins

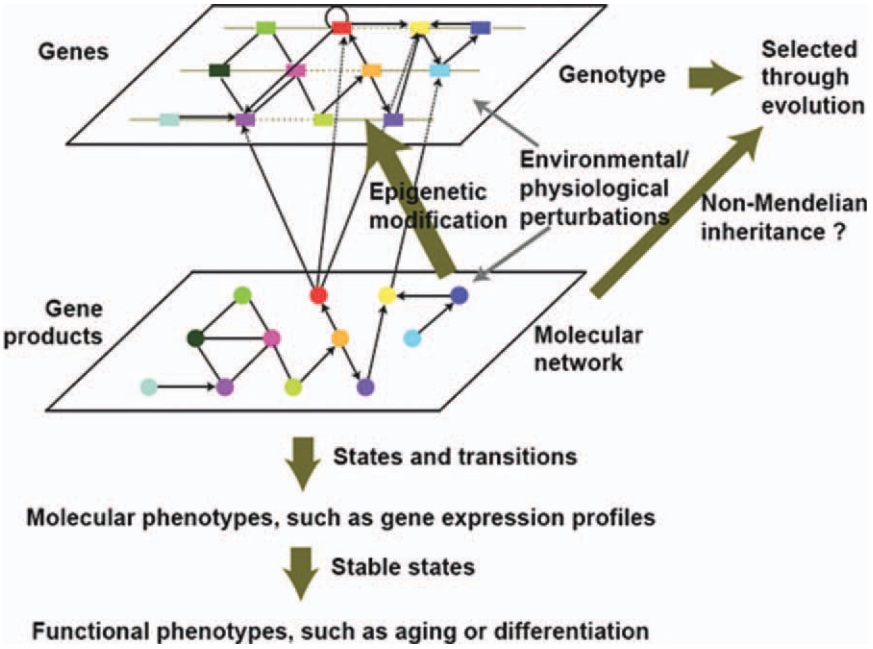

Figure 2. Heterogeneity or individual variation of aging-associated phenotypes as a result of network state drift or shift. Heterogeneity or individual variation of aging-associated phenotypes is likely due to the differential states of the developmental and aging regulatory network. This network will consist of coding and noncoding gene products interacting with each other under the influence of both endogenous and environmental signals. The genome (except the regulatory sequences of the genes) does not directly participate in the molecular interactions. Rather, it encodes the potential interaction patterns (or what the molecular network is capable of doing) and allows Mendelian inheritance from generation to generation. Such a regulatory network template only ensures the robustness of the network through development and reproduction. Both the genetic template (the genome) and the actual steady states of the molecular interaction network are subjected to changes by environmental factors and developmental histories. When these changes affect the germlines of an organism, they may become inheritable and play a role in evolution. See text for details.

(Burga et al., 2011). The first mechanism is a specific or local mechanism that reflects local feedback controls between paralogous genes. The second is a general or global mechanism coordinated among all the chaperones examined (Burga et al., 2011), which may also be under hormonal regulation, for example, by IGF-1. As such buffering mechanisms make a biological system more robust toward perturbations, they should also buffer against stochastic events during the aging process. Indeed, both mild heat shock and the induction of heat shock factors are able to extend lifespan in *C. elegans* (Gems and Partridge, 2008). Therefore, the strength of buffering genetic interactions can at least partially explain some of the individual variations in the rate of aging and level of stress tolerance (Fig. 2).

Intriguingly, in addition to chaperones, the most prominent genetic hubs identified in a whole genome-wide screen for genetic interactions in *C. elegans* are chromatin and epigenetic modifiers (Lehner et al., 2006). Given that epigenetic modifications serve as an interface between the environment and the genome, and as a nuclear memory of cellular history, different epigenetic modification states are also likely to account for individual variations in phenotypes, such as the rate of aging and stress tolerance in isogenic populations.

EPIGENETIC REGULATION OF AGING AND LIFESPAN

Network analysis has also revealed a most intriguing feature of the lifespan regulators: in both the full PPI network and the active subnetwork for aging, the known lifespan regulators tend to be inhibitory hubs connecting the transcriptionally anticorrelated modules—that is, hubs showing negative gene expression correlation with their binding partners (Xue et al., 2007). This feature of life span regulators implies that aging can be, at least partly, attributed to the derepression of expression of genes targeted by such inhibitory hubs, or in more general terms, disruption of the balance between alternative cellular states. Among the module-connecting genes identified in our network analysis, we found not only transcription factors but also epigenetic regulators, such as DNA methyltransferase DNMT1, various histone deacetylases, the H3K27 methyltransferase, and EZH2 (Xia et al., 2006). EZH2 is a component of the PRC2 complex, which catalyzes the formation of the transcriptionally repressive mark H3K27 trimethylation (H3K27me3) and plays a critical role in ''locking in'' the transcription regulatory status during development (De Santa et al., 2007; Lee et al., 2007; Swigut and Wysocka, 2007). One suggestive hint that such epigenetic modifications also play a role in the aging process comes from the Hutchison–Gilford Progeria Syndromes. In these patients, the repressive marks H3K27me3 and H3K9me3 are significantly reduced, compared with age-matched normal controls (Shumaker et al., 2006). A Bayesian network, reversed engineered from ChIP-seq data obtained from human T cells, predicts that H3K9me3 changes can be induced by H3K27me3 changes (Yu et al., 2008). Therefore, the important question now is what causes these changes in H3K27me3, and does this epigenetic mark also plays a role in normal aging?

Histone methylation is controlled by the balanced activity of histone methyltransferases and demethylases. In the case of H3K27me3, this is controlled by the methyltransferase, EZH2, and two H3K27me3 demethylases, JMJD3 and UTX. By analyzing a published

microarray array dataset, Jin et al. (2011) found that only the UTX gene displayed a significant age-dependent expression increase in the human brain. We went on to show that this aging-dependent increase also exists for the *C. elegans* ortholog *utx-1* gene, and if *utx-1* gene expression is reduced with RNAi, this delays the aging process, and extends *C. elegans* lifespan by ~30%. This lifespan extension required a functional *daf-16* gene and could not further extend the lifespan of the already very long-lived *daf-2* mutant, suggesting that UTX-1 acts through the IGF-1 pathway. Consistent with DAF-2 being the primary target of UTX-1 regulation during aging are the following findings: *daf-2* gene expression increases dramatically during aging, *utx-1* RNAi greatly reduced the expression level of *daf-2* and enhanced the nuclear translocation of the DAF-16 protein, and the H3K27me3 mark was increased on *daf-2*/*IGF1R* by *utx-1*/*Utx* RNAi in *C. elegans* and a mouse cell line. This regulation of *daf-2*/*IGF1R* by *utx-1*/*Utx* is likely to be conserved across the mammalian aging process as H3K27me3 on *IGF1R* is significantly reduced in the muscle and brain of aged macaques compared with young macaques. Our findings therefore support a model where *utx-1* RNAi increases the level of H3K27me3 on *DAF-2*, thereby promoting a younger epigenetic state of the IGF-1 pathway, which ultimately leads to longer lifespan in animals (Jin et al., 2011). Epigenetic modulations are also an important interface for receiving and memorizing cues from the environment to allow heritable and conditionally programmed gene expression from the genome. It is conceivable that epigenetic modifications at least partially mediate the lifespan modulation by environmental factors such as dietary interventions. In the case of *utx-1*, it would be interesting to see if it is subjected to various environmental and developmental modulations.

In addition to H3K27me3, other epigenetic modifications also play important roles in locking in transcriptional states (Berger, 2007; Klose and Zhang, 2007; Li et al., 2007; Yu et al., 2008; Wu and Zhang, 2009) and cellular states during development of the organism (Brosch et al., 2008; Jiang et al., 2008; Weishaupt et al., 2010).

Before identification of the role of H3K27me3, and its demethylase utx-1, in the regulation of aging (Jin et al., 2011; Maures et al., 2011), a link between epigenetic modification and aging was already beginning to emerge following observation of longevity effects of the yeast *Sir2* gene and its mammalian homolog, *SIRT1* (Guarente and Picard, 2005; Oberdoerffer et al., 2008; Dang et al., 2009), and the recent finding that high levels of germline histone H3 lysine 4 trimethylation (H3K4me3) decreased *C. elegans* lifespan (Greer et al., 2010). Sir2/SIRT1, a nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylase, has been proposed as a sensor of cellular metabolic states (Lin et al., 2000). Its reduction increases genome instability (Oberdoerffer et al., 2008), and its substrate H4 lysine 16 acetylation (H3K16ac) has been shown to regulate replicative lifespan in yeast (Dang et al., 2009). Nevertheless, resveratrol, a potential activator of Sirt1 does not affect normal lifespan, although overexpression of Sirt1 partially rescued the short lifespan of high-fat-diet mice (Baur et al., 2006). Peleg et al. (2010) have also shown that deregulated H4K12 acetylation is involved in memory impairment in old mice.

GENETIC VERSUS EPIGENETIC REGULATION OF AGING

Although the large interspecies differences in maximal lifespans are likely to be determined genetically, the intraspecies variations in individuals' lifespans are more likely attributable to the interplay between the environment and genetics. In particular, in an isogenic population, variation will mostly be due to variation of environmental or developmental history, or the stochasticity of the molecular networks that impinge more on the epigenome than the genome of the individuals. Such epigenomic variations (heritable or otherwise), which persist throughout the lifespan of an individual, may therefore determine the mean lifespan rather than the maximal lifespan of the species.

The regulation of the insulin/IGF-1 pathway by the H3K27me3 epigenetic modification and its modifier, *utx-1*/*UTX*, is a perfect example of interaction between the epigenetic and genetic regulation of aging and lifespan (Jin et al., 2011; Maures et al., 2011). This is certainly not the only interaction between epigenetic and genetic regulation during aging, and it is likely that more and more will be revealed in the future. In addition to UTX-1, the *Drosophila* H3K27me3 methyltransferase E(Z) (orthologous to human EZH2), the *C. elegans* H3K4me2/3 demethylases LSD-1 and RBR-2, and H3K36me3 demethylase T26A5.5 (orthologous to human LSD-1, RBR-2, and KDM2B, respectively) have all been shown to regulate lifespan (McColl et al., 2008; Greer et al., 2010; Siebold et al., 2010). How these epigenetic regulators receive and store information from the environment would seem to be the next key question to be solved.

AN AGING PROGRAM AT THE SYSTEMS LEVEL?

The million dollar question is how these multiple layers of regulation and intervention converge on an aging program (if there is one) to regulate aging and lifespan? Do they have common targets or do they affect different aspects of aging in parallel?

As an organism essentially has the same genomic sequences in young and old ages, the so-called aging program could be ultimately implemented at the network level, such as a transition (gradual or switch-like) and stabilization (by feedback control) of an alternative expression status and/or levels of aging regulatory pathways from a young to an aged state (Fig. 2) (Han, 2008), or the epigenetic level, such as *utx-1*'s modification of the epigenetic status of the IIS pathway, which might be

induced by transition and stabilization of a feedback control regulating *utx-1* expression level. The ability of network circuitry to maintain the network states is also referred to as ''trans-epigenetic'' regulation (Rando and Chang, 2012). At least some of the lifespan changes resulting from epigenetic regulations may be inherited through yet unknown mechanisms (Greer et al., 2011).

Do lifespan regulatory pathways all affect the epigenome to lock in gene expression to an aging status? If not, what proportion of the network transitions and stabilization toward the aging state require epigenetic lock-down? The interplay between the network and epigenetic states of the aging might be mutually dependent as depicted in Figure 2. The network might be very robust during development, as it has been under stringent evolutionary selective pressures, which is indicated by the strong tolerance to various environmental and cellular stresses. However, it becomes fairly fragile and loosely regulated after the reproductive period due to lack of selective pressure. When additional cellular damage accumulates, the network transits into another stable state, the ''aged'' state. However, the rates of the decline in robustness and state transition are under the influence of the developmental history of the individual and environmental cues, such as diet and stress, and stochastic events in the activity of gene products and the strength of interactions. All of these aspects differ even within an isogenic population, and therefore may play an important role in individual variation in the rate of aging. Epigenetic changes, either as the result or the cause of network state changes from a young to old stage, may permanently (if not reprogrammed) lock in the aging state and reinforce the feedback controls in the network (Fig. 2).

So ultimately, can the aging network, epigenome, and the aging organism be reprogrammed back to the young or ''naïve'' status? Emerging pieces of evidence suggest that, like cellular pluripotency, aging might be reprogrammable (Rando and Chang, 2012). In a similar way to reprogram differentiated cells to pluripotent stem cells (iPSCs, induced pluripotent stem cells), reprogramming the aging organism, if at all possible, will probably be achieved through a systems approach (Olshansky et al., 2002). The success in derivation of iPSCs has taught us that reprograming is achievable, and that a systems approach with a combination of computational and experimental analyses will be the key. Yamanaka et al. (2009) identified the core iPSC factors first by a bioinformatic search for transcription factors uniquely and highly expressed in stem cells, and then by narrowing down the most effective combinations through targeted experiments (Takahashi and Yamanaka, 2006; Yamanaka, 2009). In theory, one should first be able to follow in the footsteps of Yamanaka et al. to identify the master reprogramming transcription regulators for aging. Thus, erasing the epigenetic marks set up in the developmental stage should reverse the developmental trajectories (Boyer et al., 2006; Huangfu et al., 2008; Yamanaka, 2009), and reestablishing the naïve status of epigenetic marks in the old individuals may also help reverse the aging status.

To achieve these goals, one must first know the common differences between the young and old transcriptomes and epigenomes and infer the master regulators that confer such differences. One must also know how to measure the reversal phenotypes, in a similar way to the agreed standards of the stem cell reprogramming community. There are at least two types of biomarkers and/or phenotypes required to measure aging; one to measure the onset of aging and one to reflect biological age, for example, as a function of the average chronological age of a species. The dramatic increase of *utx-1* at midlife from a nonexistent level in young worms (Jin et al., 2011) makes it a candidate marker for the onset of aging. So far the search for a marker that reflects biological age, by gene expression analysis, has largely failed. The only relatively consistent metric of aging, in most organisms studied, is the decrease in oxidative phosphorylation gene expression (Zahn et al., 2006). Therefore, identification and confirmation of faithful and quantitative molecular and phenotypic markers for biological or physiological age, or for the onset of aging, remain a prerequisite for endeavors toward reprogramming aging.

The advent of new technologies, such as deep sequencing and nanotechnologies, brings plenty of growth opportunities for aging systems biology to mature into its adolescence. By building on these technologies and combining them with detailed mechanistic studies, aging systems biology may eventually help reprogram aging, or at least move us toward minimizing the individual variations resulting from system destabilization, and closer to the ''squared'' lifespan curve for a population (e.g., Fig. 1B).

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