CellPress

Shockingly Early: Chromatin-Mediated Loss of the Heat Shock Response

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http://dx.doi.org/10.1016/j.molcel.2015.08.004

In this issue of *Molecular Cell*, Labbadia and Morimoto (2015) show that there is a precipitous decline in stress resistance at the onset of reproduction in *C. elegans* and that this transition is regulated by changes in repressive chromatin marks.

During aging, early decline in one biological process could trigger the dysfunction of other longevity insurance pathways in a domino effect. What are the biological processes that change first, and what is their contribution to aging? One hypothesis is that stress resistance fails early during aging. Increasing stress resistance through genetic and pharmacological intervention extends life span (Bjedov et al., 2010; Hsu et al., 2003), suggesting that a decline in stress resistance plays a functional role in aging (Lithgow and Walker, 2002; Vilchez et al., 2014). A major way to improve stress resistance is to prevent protein misfolding and aggregation through changes in the proteostatsis network (Vilchez et al., 2014). Interestingly, proteostasis (protein homeostasis) deteriorates relatively early in life and precedes other aging markers in *C. elegans* and *Drosophila* (Ben-Zvi et al., 2009; Demontis and Perrimon, 2010). Thus, stress tolerance and proteostasis may be among the earliest biological processes to decline during aging and their loss may be causative. What is completely unknown is exactly when, why, and how stress tolerance starts to decline.

To investigate the timing and mechanism of age-associated decline in stress responsiveness, Labbadia and Morimoto (2015) studied the *C. elegans* heat-shock response (HSR). Exposure to heat stress results in the activation of the highly conserved transcription regulator HSF-1, which then activates the transcription of chaperones that combat protein misfolding. Labaddia and Morimoto find that, when reproduction begins, the HSR sharply declines both in terms of chaperone induction and tolerance to thermal and other stresses. HSR deficiency may be one of the first changes to occur during aging. Indeed, HSR decline occurs when more than 85% of the worm's total life and nearly 100% of the worm's adult life remains. The timing of this change is fascinating not only because of how early it is (Figure 1), but because it may indicate a switch in priorities leading to higher resource allocation for the next generation.

Where in the pathway does the reduction in HSR occur? Surprisingly, the authors show that HSF-1 can still translocate to the nucleus in older worms, when

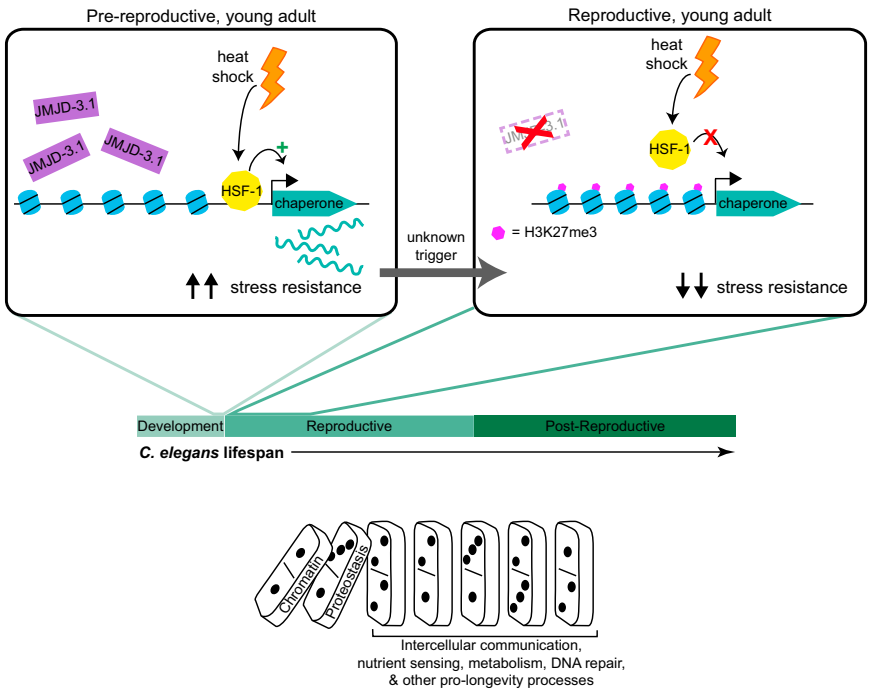

Figure 1. Loss of the H3K27me3 Demethylase JMJD-3.1 Mediates an Early-in-Life Decline in Stress Resistance
Prior to reproduction (upper left panel), worms are highly stress resistant. The conserved transcription factor HSF-1 upregulates chaperone genes in response to stress (e.g., heat). Shortly after the onset of reproduction (upper right panel), the chromatin landscape at these chaperone genes changes due to loss of the H3K27me3 demethylase JMJD-3.1. This prevents HSF-1 from binding chaperone gene promoters even under stressful conditions and, as a result, these reproductively mature animals are less stress resistant. Chromatin state and proteostasis may be the earliest biological processes to fail during aging, which could in turn trigger the loss of other longevity insurance pathways (lower panel).

HSR declines. HSF-1's ability to bind its DNA recognition sequence in vitro was not impacted, either. However, in aging worms, less HSF-1 is bound to the upstream regulatory sequences of its target chaperone genes compared to young worms. These findings raise the exciting possibility that chromatin is a key player in the decline of the HSR. Indeed, the authors find that the upstream regulatory regions of two key HSR genes become less accessible to DNase I digestion and have increased levels of trimethylation of histone H3 on lysine 27 (H3K27me3), a repressive chromatin mark (Figure 1). The *C. elegans* genome encodes four H3K27 demethylases (*utx-1, jmjd-3.1, jmjd-3.2,* and *jmjd-3.3*), and their specific (or redundant) functions in *C. elegans* remain mostly unknown. These genes are orthologous to the mammalian UTX, UTY, and JMJD3. In *C. elegans,* UTX-1 is the best-studied member of this group and is an important regulator of longevity (Jin et al., 2011; Maures et al., 2011). Labbadia and Morimoto show that a single H3K27me3 demethylase, *jmjd-3.1*, is a key regulator of the HSR decline. Mutating *jmjd-3.1* reduces the HSR, and overexpression of *jmjd-3.1* results in the maintenance of a more youthful HSR and chromatin landscape at the HSR genes. Overexpression of *jmjd-3.1* also increases the worm's life span, although it is unclear if this is solely due to changes in the HSR or to other effects of this demethylase. Interestingly, expression of only *jmjd-3.1*, and not the other H3K27me3 demethylases, decreases with age. *Jmjd-3.1*, therefore, appears to be the only family member playing a role in the HSR decline. Each demethylase may have a specific function, perhaps by acting in specific tissues or at selective loci. For example, increased levels of *jmjd-3.1* promote longevity, whereas decreased levels of *utx-1* extend life span (Jin et al., 2011; Maures et al., 2011). As H3K27me3 has been shown to increase during aging in muscle stem cells in mice (Liu et al., 2013) and in the brain of the African killifish (Baumgart et al., 2014), it will be important to understand the relative contribution of H3K27me3 regulators to the aging of different cells and tissues across species. It is intriguing that the regulation of the HSR occurs through changes in chromatin rather than changes in transcription factor activity because chromatin marks are generally more stable than modulations in transcription factor activity. Thus, this chromatin change may represent a long-lasting shift in biological strategy from accurate development and somatic protection to reproduction.

But what is the molecular signal that triggers the JMJD-3.1-mediated decline in HSR? Given that the timing is coincident with the onset of reproduction, one possibility is that the presence of mature oocytes or fertilization initiates signaling that triggers the decline. The authors use a series of genetic mutants in an attempt to identify the cells that may produce this signal. They find that genetic mutants defective in the production of germline stem cells maintain a more youthful chromatin state at HSR genes in a *jmjd-3.1*-dependent manner. However, in the absence of mature sperm or oocytes, the decline still occurs. Thus, while HSR decline occurs at the same time as reproductive maturity, fertility is not necessary. One of the next major challenges will be to identify the exact cell type, timing, and molecular signal that trigger JMJD-3.1 loss, HSR decline and, perhaps, the onset of the aging process.

Regardless of the precise nature of the signal that triggers HSR decline, it is clear that it occurs in a stereotypical manner that can be perturbed by genetic manipulations. Unlike development, aging is generally not considered to be programmed. However, several studies, including this report by Labbadia and Morimoto (2015), have shown that there exists a "program" that downregulates longevity insurance pathways. Why might such a program exist, and how did it evolve? In this case, the timing coincides with the onset of reproduction, when the animal shifts from developing somatic and germline tissues to expending its resources on producing progeny. Thus, one possibility is that the HSR decline is a response to a shift in biological strategy, and its detrimental effect on longevity and stress resistance is a consequence of this shift. Important future directions will be to determine whether males (which invest less in their progeny) also use this strategy and whether this strategy is conserved and used in other species, such as mammals (which have fewer progeny than *C. elegans*). Changes in the chromatin landscape and the resulting loss of proteostasis may be the first dominos to fall in the progression of aging, triggering a more general failure of other longevity insurance pathways (Figure 1). Understanding these early changes, and how they relate with each other, may provide new avenues to slow aging and age-related diseases.

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