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It is becoming increasingly evident that aging is controlled by both genetic and epigenetic factors. Histone modifying enzymes and their modifications comprise one of the main components of epigenetic mechanisms which have been directly linked to lifespan regulation in many organisms.[1] Studies in diverse species have highlighted changes in the distribution or abundance of certain histone marks during the lifespan of a cell or an organism, leading to alterations in gene expression. In some cases, this aging-dependent patterning of histone modifications affects the expression of key longevity genes while, in other cases, they drive large-scale transcriptome changes that eventually contribute to functional decline and other hallmarks of aging.[1] Since epigenetic factors, including histone modifications, are malleable to environmental signals, it was reasonably hypothesized that the epigenome could act as a platform through which external signals control lifespan via gene regulation.[2] However, evidence connecting an environmental stimulus to a specific histone modification and the subsequent alteration of a particular gene expression program influencing lifespan was lacking. Using the genetically tractable eukaryote *Saccharomyces cerevisiae* we have recently reported that histone H4 N-terminal acetylation (N-acH4), a modification catalyzed by the N-terminal acetyltransferase Nat4, responds to calorie restriction (CR) in order to enable the expression of genes which directly delay aging.[3]

In yeast, CR is commonly modeled by a dietary regimen that reduces glucose concentration in the media from 2% to 0.5% or lower. By subjecting yeast to glucose starvation we observed a reduction in the cellular levels of Nat4, and consequently of nucleosomal N-acH4, leading to the induction of a specific cohort of CR-regulated genes which prolong lifespan. Among the genes activated is nicotinamidase Pnc1 whose involvement in longevity in response to CR (and that of its mammalian functional ortholog NAMPT) is well established.[4] Of note, we have shown that the response of Nat4 and N-acH4 to CR is necessary for the induction of Pnc1 and ultimately longevity. Specifically, by introducing the Nat4 gene under the control of a constitutive CR-insensitive promoter we, firstly, showed that CR was not able to reduce the levels of N-acH4, secondly, the induction of *PNC1* and that of other stress-response genes was compromised and thirdly, the extension of replicative lifespan normally stimulated by glucose deprivation was limited in yeast cells.[3] Thus, our study proposes that N-acH4 mediated by Nat4 is an epigenetic barrier to longevity that can be removed by CR to promote its life-extending effects (Fig. 1). Certainly, important questions remain to be addressed in future studies: How exactly glucose starvation signals the reduction of Nat4 expression?, are other Nat4 substrates (i.e. histone H2A) involved in this signaling pathway?, and is this mechanism conserved in other eukaryotes and especially humans?

Transcriptional regulation by N-acH4 involves an interplay with its adjacent methylation mark at histone H4 arginine 3. In particular, the presence of N-acH4 in chromatin prevents the deposition of H4R3 asymmetric dimethylation (H4R3me2a), thus regulating ribosomal DNA silencing.[5] The crosstalk between these two modifications, which is a common functional characteristic of histone marks, was previously demonstrated to operate in response to CR.[5] Consistent with this antagonistic relationship between N-acH4 and H4R3me2a, we found that absence of an arginine residue at position 3 in histone H4 (H4R3K) and abrogation of arginine methylation confers a significantly shorter cellular lifespan.[3] Altogether, these findings implicate a specific histone modification cross talk in a pathway that controls aging as a result of an external signal. In the future, it will be interesting to explore whether cross talks among other histone modifications occur in response to diet or other environmental stimuli to regulate lifespan (Fig. 1).

Apart from the well-documented and conserved connection between diet and longevity[6], other environmental stimuli impinge on lifespan and also modulate the epigenomic landscape. For instance, robust circardian rhythms promote longevity and are linked to epigenomic regulation, such as the periodic deposition of specific histone modifications at circadian gene promoters. Furthermore, exercise, inter-individual interactions, social caste, hormones and pheromones constitute other environmental inputs that have been implicated in longevity and at the same time associated with epigenome changes.[2] Hence, according to what we have observed with CR and N-acH4, we propose that linear relationships may exist connecting these environmental signals to specific alterations in histone modifications that, ultimately, lead to defined transcriptional outputs which impact on longevity (Fig. 1). Deciphering the pathways that link external signals to specific epigenome and transcriptional changes will be crucial for better understanding the aging process but also for intervening to delay aging and improve healthspan. It is interesting to note that effective therapeutic compounds targeting histone modifying enzymes have already been developed[7] and therefore, determining the above mechanisms could provide insights as simple as repurposing some of the existing epigenetic drugs for the prevention and therapy of aging-related diseases.

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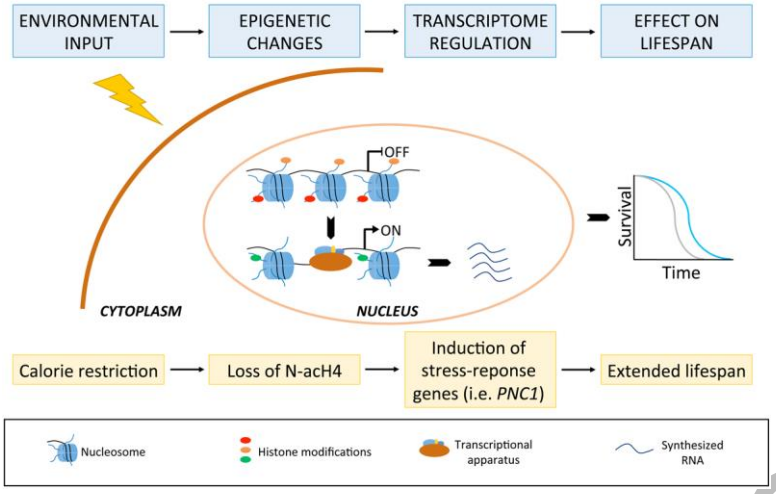

Figure 1. Epigenetic linkage of environmental inputs to life expectancy. An extracellular stimulus (i.e. calorie restriction) initiates a linear cascade of events involving certain epigenetic changes (i.e. loss of H4 N-terminal acetylation [N-acH4]) that translate to specific alterations in the transcriptome (i.e. induction of stress-response genes), culminating in a particular lifespan effect.