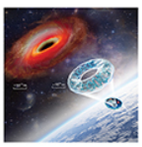
Autophagy



Autophagy

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The curious case of polyamines: spermidine drives reversal of B cell senescence

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ABSTRACT

Spermidine, a polyamine that induces macroautophagy/autophagy, exhibits anti-aging properties. It is thought that these properties of spermidine are primarily due to its ability to modulate autophagy, but the mechanistic details were hitherto unclear. Studying the effects of spermidine on B lymphocytes, Zhang *et al* uncover the molecular mechanism that places spermidine at the crossroads of autophagy and immune senescence. Their work highlights the role of spermidine as an anti-aging metabolite that exerts its effects through the translational control of autophagy.

Abbreviations: EIF5A, eukaryotic translation initiation factor 5A; HC, hematopoietic cell; ODC1, ornithine decarboxylase 1; PBMCs, peripheral blood mononuclear cells

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Immune senescence is characterized by the inability of the immune system to elicit adequate responses to infection, malignancy and vaccination due to several age-related deteriorative changes [1]. A defining strength of the adaptive immune system is its capacity to maintain long-term memory against pathogens. Utilizing this feature of the immune system, vaccines provide effective protection against many types of infection. The aged population is particularly vulnerable to infectious diseases, and vaccination is an efficient means to combat this susceptibility. However, the immune response to vaccines decreases with age – particularly due to the inefficient production of stimulus-specific antibodies by long-lived plasma B cells. Hence, it is important to find methods to enhance the immune response that has been dampened by aging [2].

Autophagy is a highly conserved cellular catabolic process wherein damaged and/or superfluous intracellular material is degraded. Long-lived lymphocytes are prone to accumulate intracellular waste, and autophagy is an important quality control, recycling pathway that eliminates unwanted cytoplasmic components and maintains cellular homeostasis in these cells [3]. Multiple studies have highlighted the observation that aging is accompanied by a reduction in autophagic efficiency, and this decrease in autophagy is speculated to lead to cellular and immune senescence [2,4]. In agreement with this hypothesis, $CD8^+$ T cells from aged mice and humans have reduced autophagy, and the upregulation of autophagy in these cells restores their immune responses back to a level similar to that seen in "young" cells [5]. Hence, drugs that induce autophagy have the potential for reversing immune senescence [2].

Recently, spermidine has emerged as an important metabolite that links cellular aging and autophagy [6]. Spermidine is a naturally occurring polyamine involved in biological processes such as cell growth and proliferation, tissue regeneration and translation regulation, making it a critical regulator of cellular homeostasis. Spermidine also exhibits anti-inflammatory and anti-aging properties. External supplementation of spermidine improves longevity [7], which may be attributed to its ability to exert cardioprotective [8] and neuroprotective [9] effects, as well as reducing immune senescence [5]. Spermidine is thought to exhibit many of these anti-aging properties due to its role in inducing autophagy; however, many questions remain unanswered in this regard. For example, what is the molecular mechanism behind the induction of autophagy by spermidine, and how does spermidine-induced autophagy prevent immune senescence? In the article highlighted here, Zhang *et al* provide mechanistic insights into the role of spermidine in regulating autophagy and B lymphocyte function [10].

These authors found that spermidine levels decline in human PBMCs with age. Furthermore, aging results in the decrease of autophagic flux in murine and human B lymphocytes, which can be rescued by exogenous supplementation with spermidine. An interesting fact about spermidine is that it serves as a unique substrate for the hypusination of EIF5A (eukaryotic translation initiation factor 5A) [11]. Hypusine is an unusual amino acid found in all eukaryotes, and EIF5A is the only known protein that contains this amino acid modification. Hypusination of EIF5A is dependent on spermidine availability [10] and is an important modification that regulates the translation of proteins rich in proline repeats [12]. To dissect the role of spermidine in regulating autophagy, the authors hypothesized that spermidine regulates autophagy via hypusination of EIF5A. Indeed, genetic knockdown of EIF5A results in reduced autophagic flux, and a similar result is seen with inhibition of EIF5A hypusination

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by genetic and pharmacological methods. Exogenous supplementation with spermidine fails to rescue autophagic flux when EIF5A hypusination is inhibited, suggesting that spermidine induces autophagy by hypusinating EIF5A.

Hypusination of EIF5A is required for the efficient translation of proteins that contain hard-to-read motifs such as polyproline. Due to their geometry, polyproline motifs slow down ribosome elongation, and EIF5A stimulates the translation of such proteins. The authors found that TFEB, a transcription factor involved in autophagosomal and lysosomal biogenesis, contains one specific motif with potential ribosome-pausing effects (SPPPVP) and requires hypusinated EIF5A for efficient translation. Furthermore, they found that spermidine depletion reduces TFEB protein, similar to that seen with hypusination inhibition. Restoration of TFEB protein levels by spermidine supplementation is dependent on hypusinated EIF5A. Taken together, these findings indicate that spermidine regulates the cellular TFEB levels via EIF5A hypusination.

Zhang and colleagues found that in human B lymphocytes obtained from aged donors, a decrease in antibody responses can be correlated with a decrease in spermidine levels, hypusinated EIF5A, TFEB protein levels and autophagic flux. Exogenous supplementation with spermidine can rescue autophagic flux by efficient translation of TFEB via hypusinated EIF5A. Importantly, spermidine supplementation restores IgG responses of B lymphocytes, hence restoring its function.

In summary, Zhang and colleagues demonstrate a mechanism by which autophagy is regulated at the translational level. They determined that in "young" B cells, the polyamine metabolite spermidine promotes the hypusination of EIF5A, which regulates the translation of TFEB, which in turn regulates autophagosomal and lysosomal biogenesis. In "old" B cells, decline in spermidine levels leads to loss of a hypusinated EIF5A-TFEB-autophagy axis and results in the loss of antibody responses of B lymphocytes. Exogenous supplementation with spermidine can reverse the age-dependent decline of the hypusinated EIF5A-TFEB-autophagy axis and restore B cell function. An important contribution of this study is the identification of the EIF5A pathway as a potential blood biomarker for aging. Importantly, this pathway can be restored by replenishing spermidine levels, thereby boosting the immune responses of B cells. Therefore, spermidine has direct clinical translational relevance as a metabolite that might reverse immune aging.

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