Spermidine Enhances Thymic Regeneration and Ameliorates Immunosenescence Through Autophagy Activation in Aged Mice

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Abstract

With advancing age, the progressive functional decline of the immune system—known as immune senescence—is a core factor contributing to increased susceptibility to infections, diminished vaccine responses, and chronic inflammatory states in older individuals. The thymus, as the primary lymphoid organ crucial for T cell development, undergoes progressive atrophy (thymic degeneration) with aging. This represents a hallmark event of immune senescence, directly leading to reduced output of naive T cells and disrupting the diversity and homeostasis of adaptive immunity. In recent years, cellular autophagy has been identified as playing a crucial role in maintaining tissue homeostasis and delaying aging. Its diminished activity is closely associated with the onset and progression of various age-related diseases. Consequently, exploring intervention strategies that can safely and effectively activate autophagy and specifically reverse aging in immune organs has become a frontier hotspot in anti-aging research.This study investigates how the natural polyamine spermidine enhances the aging immune system's capacity to rebuild adaptive immunity through autophagy mechanisms. In aged mice, spermidine treatment significantly mitigated age-related thymic atrophy, restored thymic architecture, and enhanced thymic function. This was manifested by increased thymic weight, elevated FOXN1 and AIRE protein expression in thymic epithelial cells, and enhanced output of naive T cells. These effects correlated with a remodeled peripheral T cell compartment, characterized by an increased proportion of naive T cells and a decreased proportion of memory T cells. Molecularly, spermidine enhances autophagic flux by activating the AMPK/mTOR signaling pathway. The critical role of autophagy was confirmed, as its pharmacological inhibition completely abolished spermidine-induced thymic regeneration and functional recovery. Furthermore, spermidine treatment demonstrated favorable safety in aged mice, with no significant hepatic or renal toxicity observed. This study confirms that spermidine primarily drives thymic regeneration and restores peripheral T-cell homeostasis by activating autophagy, offering a promising translational strategy for enhancing immune function in aging.

Keywords

Spermidine, Autophagy, Thymic Regeneration, Immunosenescence, Aging