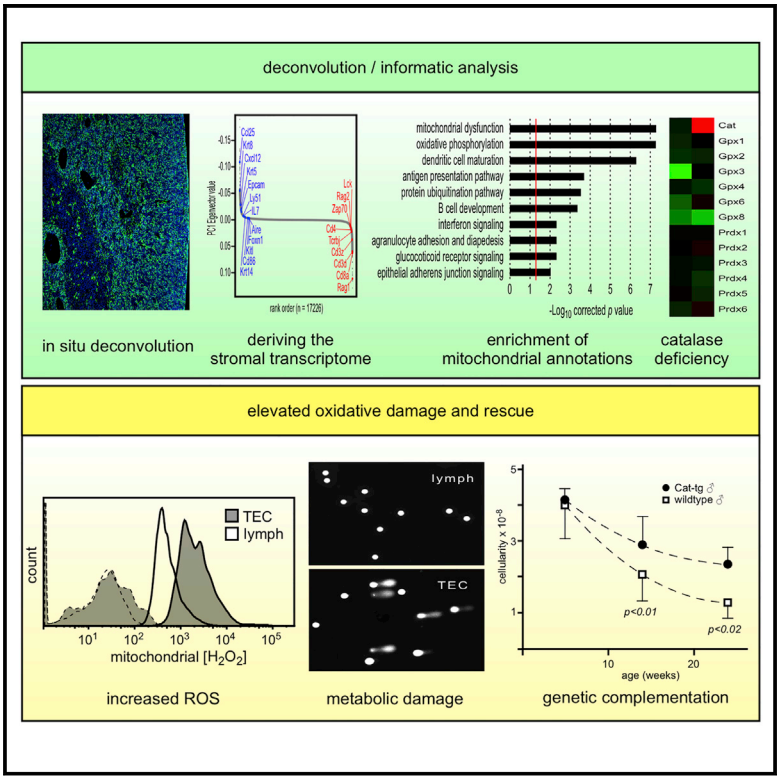
Report

Cell Reports

Metabolic Damage and Premature Thymus Aging Caused by Stromal Catalase Deficiency

Graphical Abstract



Highlights

- The thymus exhibits accelerated atrophy with age due to changes in stromal cells
- Global transcriptome analysis reveals that stromal cells are deficient in catalase
- Stromal cells showed elevated H_2O_2 levels and multiple hallmarks of oxidative damage
- Genetic or biochemical restoration of antioxidant activity ameliorates thymic atrophy

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In Brief

Thymic function is essential for maintenance of immunity but decreases with age. Griffith et al. show that stromal deficiency in catalase leads to mitochondrial dysfunction and DNA damage in stromal cells and that atrophy is ameliorated by genetic complementation of catalase or biochemical antioxidants.

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Metabolic Damage and Premature Thymus Aging Caused by Stromal Catalase Deficiency

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SUMMARY

T lymphocytes are essential mediators of immunity that are produced by the thymus in proportion to its size. The thymus atrophies rapidly with age, resulting in progressive diminution of new T cell production. This decreased output is compensated by duplication of existing T cells, but it results in gradual dominance by memory T cells and decreased ability to respond to new pathogens or vaccines. Here, we show that accelerated and irreversible thymic atrophy results from stromal deficiency in the reducing enzyme catalase, leading to increased damage by hydrogen peroxide generated by aerobic metabolism. Genetic complementation of catalase in stromal cells diminished atrophy, as did chemical antioxidants, thus providing a mechanistic link between antioxidants, metabolism, and normal immune function. We propose that irreversible thymic atrophy represents a conventional aging process that is accelerated by stromal catalase deficiency in the context of an intensely anabolic (lymphoid) environment.

INTRODUCTION

T lymphocytes, like all hematopoietic cells, are continuously lost and must be replaced throughout life by the thymus. Developing lymphocytes are present in the thymus only transiently, and the durable identity of the thymus is thus established by its stable (stromal) components, consisting mainly of epithelial cells with lesser contribution by mesenchymal, myeloid, neuronal, and vascular cells (reviewed in Petrie and Zúñiga-Pflücker, 2007). Stromal cells provide most of the signals for T lineage differentiation (Petrie and Zúñiga-Pflücker, 2007) and regulate lymphoid cellularity by providing limited numbers of niches for lymphopoietic progenitors (Prockop and Petrie, 2004). Consequently, the integrity of thymic stroma is critical for the maintenance of thymic function.

The thymus reaches maximum size around the time of puberty, followed by rapid, progressive atrophy (reviewed in Montecino-Rodriquez et al., 2005). Since T cell production is proportional to thymic mass (Haynes et al., 2000), age-related atrophy results in progressive diminution of new T production by the thymus (Hale et al., 2006). While frank lymphopenia is masked by the ability of peripheral T lymphocytes to duplicate themselves (Surh and Sprent, 2008), the end result is a gradual drift toward immunologic memory, especially representing latent or persistent viral infections (Nikolich-Zugich and Rudd, 2010). In contrast, response to new antigens becomes progressively more limited, resulting in well-recognized consequences for the aging population.

The biological pressure and mechanisms of accelerated thymic atrophy remain unclear, although we have recently shown that it is primarily a stromal effect (Griffith et al., 2012) that results in fewer lymphoid cells via the niche effect described above. Sensitivity to sex steroids, especially androgens, remains the most popular theory for stromal atrophy, based on compelling but nonetheless correlative findings, including maximum size prior to puberty (Domínguez-Gerpe and Rey-Méndez, 2003), increased atrophy in males (Aspinall and Andrew, 2001), and reduced atrophy when androgen response is impaired (Olsen et al., 2001) or ablated (Henderson, 1904). Castration also induces robust regeneration of the atrophied thymus (Utsuyama and Hirokawa, 1989; Goodall, 1905; Sutherland et al., 2005). However, such regrowth is transient even though androgen reduction is permanent (Griffith et al., 2012). Thus, while the thymus is exquisitely responsive to sex steroids, they cannot explain irreversible age-related atrophy of the thymus or why it is so dramatically accelerated compared with other tissues.

Among obstacles to working with stromal cells are that they are rare (<0.1% of thymic cellularity), difficult to isolate (because of formation of tight junctions and desmosomes), and most importantly, change dramatically upon removal from their native context, including downregulation of Notch ligands that are critical for T cell development (Mohtashami and Zúñiga-Pflücker,