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Born to survive

Autophagy in hematopoietic stem cell maintenance

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Hematopoietic stem cells (HSCs) are unique in their ability to self-renew and produce all mature blood cells.[1] Thus, HSCs are central for the lifelong maintenance of the blood system, and considerable evidence suggests that HSCs are equipped with unique survival mechanisms that ensure their protection throughout life. These include localization to specialized hypoxic niches in the bone marrow (BM) cavity and maintenance of HSCs in a quiescent, slow cycling state.[2] However, these strategies primarily function to minimize stress and production of damaging reactive oxygen species (ROS) associated with replication and cellular respiration. In contrast, less is known about the mechanisms used by HSCs to cope with stresses occurring in the BM cavity. Recently, we showed that HSCs could survive metabolic stress by inducing a robust protective autophagy response.[3]

Autophagy (Greek for "self eating") is an evolutionarily conserved process through which cellular materials are targeted to the lysosomes for degradation.[4] Autophagy primarily serves as a "garbage disposal" mechanism, eliminating damaged components that threaten cell integrity, but also acts as a major adaptive stress response pathway, with functions ranging from energy regulation in starving cells to warding off microbial attacks. Autophagy is important for the development of the blood system, as shown by the deregulated fetal and postnatal hematopoiesis observed in mice lacking the essential autophagy gene *Atg7*.[5] We expanded upon these results by showing that autophagy also plays a critical role in the adult blood system by protecting HSCs from starvation.[3] We used both genetic mouse models and pharmacological means to examine the autophagy response of HSCs and myeloid progenitors following ex vivo cytokine withdrawal or in vivo caloric restriction. We found that HSCs, and not their short-lived myeloid progeny, are uniquely poised to mount a robust protective autophagy response. Moreover, we demonstrated that the transcription factor FOXO3A is essential for maintaining a pro-autophagy gene program that poises HSCs for rapid autophagy induction. Our results demonstrated that HSCs are uniquely wired to use autophagy as an adaptive stress response mechanism. However, how HSCs sense metabolic stress and activate autophagy is still unclear.

The mammalian target of rapamycin (mTOR) is activated by signaling through the PI3K/AKT pathway in response to mitogenic factors such as nutrients, cytokines and amino acids. When activated, mTOR promotes cell growth, proliferation and survival but also potently blocks autophagy by directly inactivating critical proteins involved in its induction.[4] Although, we did not observe differential mTOR signaling between HSCs and myeloid progenitors,[3] it is likely that the PI3K/AKT/mTOR pathway plays an important role in sensing metabolic stress and triggering autophagy induction in HSCs. A potential mechanism could be via PI3K inactivation in response to a decreased local concentration of nutrients and cytokines, resulting in a subsequent block in mTOR activity. Alternatively, mTOR inactivation may be triggered by other means, such as AMPK activation, under reduced cellular energy via an AMP-mediated conformational change and action of the upstream kinase LKB1.[4] In fact, we and others have shown that both catalytic subunits of AMPK, *Prkaa1* and *2*, are highly expressed in HSCs, with the expression of *Prkaa2* being FOXO3a-dependent.[3,6] Thus, HSCs may be particularly poised to activate AMPK in an environment of reduced cellular energy, hence inactivating mTOR and rapidly driving the induction of autophagy. In support of this hypothesis, genetic mouse models that are either deficient in FOXO family members or display constitutive mTOR activation both result in HSC depletion and loss of function.[1] It is therefore tempting to speculate that an inability of these mutant HSCs to trigger an adaptive autophagy response could play an important role in these phenotypes.

With age, the blood system undergoes considerable functional decline, resulting in reduced adaptive immunity, anemia and an increased incidence of myeloid malignancies.[7] Since aging has been associated with decreased autophagy,[8] we directly examined the ability of HSCs isolated from old mice to use autophagy. In stark contrast to HSCs isolated from young mice, we found that old HSCs rely on high basal levels of autophagy for their survival.[3] Much of the evidence linking aging with decreased autophagy comes from longevity defects observed in autophagy-defective organisms, which might be distinct from a role for autophagy in maintaining tissue integrity during physiological aging as studied here. It might also reflect a unique role for autophagy in tissues with high turnover rates, like the blood system. While we did not find evidence for oxidative stress, we observed that old HSCs were less efficient in taking up nutrients than young

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HSCs and were constitutively metabolically stressed. Importantly, we showed that the killing effects of autophagy inhibition in old HSCS could be rescued by adding methyl-pyruvate, a cell-permeable form of pyruvate that provides energy in the absence of nutrient uptake. It will now be important to understand whether such compromised metabolic features are cell-intrinsic characteristics of old HSCs, or byproducts of a less supportive aging BM environment in which old HSCs reside. Taken together, our results indicate that autophagy not only preserves HSCs from starvation in a young organism, but also supports an old HSC compartment that faces unique metabolic challenges and maintains a frail, aging blood system.

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