FOXO3A directs a protective autophagy program in haematopoietic stem cells.

Journal: Nature

Publication Year: 2013

Authors: Matthew R Warr, Mikhail Binnewies, Johanna Flach, Damien Reynaud, Trit Garg, Ritu Malhotra, Jayanta Debnath, Emmanuelle Passegue

PubMed link: 23389440

Funding Grants: Mechanisms Underlying the Responses of Normal and Cancer Stem Cells to Environmental and Therapeutic Insults

Public Summary:
How blood-forming hematopoietic stem cells (HSC) accommodate the different cellular stresses associated with their life-long activity remains elusive. Here, we identify the self-catabolic process of autophagy as an essential mechanism used specifically by HSCs, and not their downstream myeloid progeny, to combat metabolic stress and maintain their functionality. We show that HSCs are uniquely wired to mount a protective autophagy-mediated survival response through expression of a FOXO3a-driven pro-autophagy gene expression program that poises HSCs for rapid induction of autophagy following metabolic stress. This robust and rapid stress-response likely allows the HSC compartment to withstand growth factor and nutrient fluctuations that naturally occur in the bone marrow (BM) microenvironment. Our results form the basis for a better molecular understanding of how autophagy is wired within the cellular hierarchy of an organ, and how it contributes to the life-long protection of the stem cell compartment and maintenance of tissue homeostasis. They also demonstrate that autophagy is essential for the survival of HSCs in old mice. This is in striking contrast to the prevailing view in the aging field that impaired autophagy is a principal determinant of cellular aging. We show that the regulatory pathways that poise HSCs for rapid stress-induced autophagy remain intact during physiological aging, and that ongoing autophagy is essential for the continued survival of a largely expanded population of old HSCs. Our results demonstrate that autophagy acts as a double-edged sword for HSC function. On the one hand, autophagy helps maintaining blood homeostasis by protecting adult HSCs from metabolic stress, yet on the other, it contributes to the aging of the blood system by allowing the survival of damaged old HSCs, which are bad actors for the development of age-related blood disorders. This article was previewed in Nature (494: 317-318, 2013), and selected for Faculty of 1000 Biology.

Scientific Abstract:
Blood production is ensured by rare, self-renewing haematopoietic stem cells (HSCs). How HSCs accommodate the diverse cellular stresses associated with their life-long activity remains elusive. Here we identify autophagy as an essential mechanism protecting HSCs from metabolic stress. We show that mouse HSCs, in contrast to their short-lived myeloid progeny, robustly induce autophagy after ex vivo cytokine withdrawal and in vivo calorie restriction. We demonstrate that FOXO3A is critical to maintain a gene expression program that poises HSCs for rapid induction of autophagy upon starvation. Notably, we find that old HSCs retain an intact FOXO3A-driven pro-autophagy gene program, and that ongoing autophagy is needed to mitigate an energy crisis and allow their survival. Our results demonstrate that autophagy is essential for the life-long maintenance of the HSC compartment and for supporting an old, failing blood system.