How stem cells get “turned on”

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Recent research began to link autophagic processes to the functional integrity of certain stem cells. A novel study published in this issue of *The EMBO Journal* reports on autophagic flux as crucial checkpoint to meet the energy demands during muscle stem cell activation.

See also: **AH Tang & TA Rando** (December 2014)

Macroautophagy (hereafter, “autophagy”) is an evolutionarily conserved mechanism employed by cells to recycle cellular building blocks, effect protein quality control, and generate energy during times of nutrient deprivation. This catabolic strategy involves the engulfment of cellular organelles and other cytoplasmic components into specialized double-membrane vacuoles called autophagosomes, which deliver their contents to the lysosome for degradation to generate amino acids and other macromolecules that are used for protein synthesis and energy production (Singh & Cuervo, 2011). Autophagic processes have been implicated in many physiological processes, including cell survival, differentiation, regulation and activation of immune responses, and cellular responses to oxidative, metabolic, ER- and pathogen-induced stress. In aging cells, breakdown of autophagy is thought to represent a common pathway that leads to cell and organ dysfunction (Lopez-Otin *et al*, 2013).

Additional work has begun to highlight a potentially unique role for autophagy in controlling the activity of stem cells and tissue regenerative potential. For example, Passegue and colleagues reported last year that autophagy protects hematopoietic (blood-forming) stem cells from apoptosis during metabolic stress induced by nutrient deprivation following cytokine withdrawal

or fasting (Warr *et al*, 2013). Interestingly, induction of autophagy in this system was a distinctive, FOXO3A-driven response of stem cells that was not shared by their more differentiated progeny. Autophagy may also

serve a tumor suppressor function in the hematopoietic system, as hematopoietic cell-specific ablation of the essential autophagy gene *Atg7* in mice led to a severe depletion of hematopoietic stem cells from the bone

Figure 1. Satellite cells (green) are regenerative stem cells for skeletal muscle that are tightly associated with mature muscle fibers (red).

In undamaged (resting) muscle, these cells are small in size and quiescent, with low autophagic flux, low mitochondrial content and activity, low metabolic rates, and low levels of ATP. Upon muscle injury, satellite cells become activated, a change that is accompanied by an increase in satellite cell size as well as enhancement of autophagic flux, metabolic rate, mitochondrial content/activity, and ATP concentrations. This cellular and metabolic reprogramming induced in activated satellite cells is coordinated in part by SIRT1, a nutrient sensor induced by activated satellite cells that promotes autophagy in part through deacetylation of Atg7, a component of the autophagic machinery, and via activation of AMPK, which can signal both directly and indirectly to upregulate autophagy. Enhanced autophagy is important to meet the increased energetic and biosynthetic demands of satellite cell activation. Model based on (Tang & Rando, 2014).

marrow and a myeloproliferative expansion reminiscent of human acute myeloid leukemia (AML) (Mortensen *et al*, 2011a,b). In this issue of *The EMBO Journal*, Tang and Rando identify yet another role for autophagy in stem cell function, demonstrating that this catabolic response is a critical step in the activation and differentiation of muscle-forming stem cells (also known as satellite cells) (Tang & Rando, 2014; Fig 1).

Using complementary *in vitro* and *in vivo* models, Tang and Rando first showed that a substantial increase in autophagic flux occurs during the early stages of activation of normally quiescent muscle satellite cells as they respond to tissue damage. The authors further determined that this enhanced autophagic activity is required to effect the metabolic reprogramming of satellite cells, increasing mitochondrial activity and ATP content to meet the increased bioenergetic and biosynthetic demands associated with myogenic differentiation. Significantly, when the authors inhibited autophagy, via chemical agents or satellite cell-specific ablation of key autophagy genes, they observed impaired metabolic reprogramming and delayed satellite cell activation, which could be partially rescued by the provision of an exogenous energy source. These studies suggest that sufficient availability of bioenergetic substrates, ensured in part through enhanced autophagy, represents an important “check-point” for stem cell activation.

To investigate the signaling mechanisms through which autophagy might be regulated to coordinate the metabolic state of muscle

stem cells with their activation state, the authors turned to SIRT1, an NAD⁺-dependent protein deacetylase that links cellular energy status with nuclear gene expression and cell physiological responses (Chalkiadaki & Guarente, 2012). Genetic and pharmacological inhibition of SIRT1 activity delayed satellite cell activation in part via reduced mitochondrial activity. These results are consistent with prior work, indicating that satellite cells from animals exposed to a calorie-restricted diet show enhanced satellite cell activity in concert with increased levels of SIRT1 and greater mitochondrial abundance (Cerletti *et al*, 2012).

In summary, this new study by Tang and Rando reveals a novel function for autophagy and the conserved nutrient sensor SIRT1 in stem cell regulation: in addition to protecting stem cells from metabolic stresses induced upon starvation (Cerletti *et al*, 2012; Warr *et al*, 2013), autophagy also plays a key role in the normal process by which stem cells support tissue homeostasis and repair through the generation of differentiated daughter cells (Tang & Rando, 2014). Significantly, as inhibition of autophagy delays but does not prevent satellite cell activation, it seems likely that additional processes, such as increased glycolytic flux or fatty acid oxidation, are also engaged to meet the energy demands of myogenic differentiation. Further clarification of how stem cells adjust their metabolic programs to respond to regenerative cues and how metabolic signals may influence stem cell fate decisions will no doubt reveal additional complexity in these responses, and may also

uncover novel metabolic vulnerabilities that may be targeted to boost stem cell activity for regenerative medicine.

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