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Mitochondria and FOXO3 in stem cell homeostasis, a window into hematopoietic stem cell fate determination

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Abstract

The production of all blood cells from hematopoietic stem cells (HSC) is highly sensitive to reactive oxygen species (ROS). Cumulating evidence suggests that mitochondria are critical for HSC fate determination. FOXO are known regulators of antioxidant response and key to the maintenance of HSC. Recent works indicate that FOXO3 is implicated in the control of mitochondrial function beyond regulating levels of ROS in HSC. Here we review these findings and discuss implications for homeostatic blood formation and stem cell fate determination.

Keywords

FOXO; FOXO3; ROS; HSC; Stem cell; Mitochondria; UPR

Mitochondrial regulation of stem cell fate

Increasing evidence suggest that mitochondria are implicated in regulating stem cell fate by multiple paths. For instance, hematopoietic stem cells (HSC) have relatively high numbers of mitochondria that are overall metabolically inactive and produce limited ATP (Simsek et al. 2010; Norddahl et al. 2011). As a result mitochondrial respiration is lower in HSCs relative to downstream progenitors (Simsek et al. 2010; Norddahl et al. 2011). In their quiescent state, HSC rely on glycolysis to maintain their pool and the role of mitochondria had been mostly associated with oxidative phosphorylation in committed stem cells. However, functional mitochondria are required for adult stem cells' proper maintenance (Chen et al. 2008; Gan et al. 2010; Gurumurthy et al. 2010; Nakada et al. 2010; Maryanovich et al. 2012; Tai-Nagara et al. 2014). The need to constantly survey and maintain the health and numbers of mitochondria within stem cells may be central to stem

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cell biology. Growing evidence raise the possibility that mitochondria might reach far beyond oxidative phosphorylation and be implicated in sustaining the delicate balance between maintaining adult stem cell pool and preventing stem cell exhaustion and, stem cell differentiation to continually replenish downstream lineages.

Dormant stem cells including HSC are highly sensitive to oxidative stress that is the imbalance in the generation versus detoxification of ROS (Ito et al. 2004; Ito et al. 2006; Tothova et al. 2007; Miyamoto et al. 2007; Yalcin et al. 2008; Miyamoto et al. 2008). Unbalanced elevated ROS is frequently but not always associated with impaired HSC function in vivo (Ito et al. 2004; Kocabas et al. 2012; Zheng et al. 2014) and with HSC differentiation and increased production of their immediate progenitors (Jang and Sharkis 2007). In many of these models, the in vivo administration of N-acetyl-cysteine (NAC) - a glutathione precursor that reduces ROS levels - rescues HSC ability to reconstitute all blood cells for a long period of time in a mouse in which blood is ablated (Rimmele et al. 2015), also known as long-term competitive repopulation ability, restores quiescence and reduces DNA damage. These findings suggest that ROS modulations might constitute a stem cell sensing mechanism for gauging mitochondrial health and activity.

Transcription factors FOXOs (Forkhead Box O 1/3/4) and specifically FOXO3 are essential for controlling ROS levels in HSC. The evolutionary conserved functions of FOXOs in stress response including oxidative stress are implicated in organismal longevity (Lin et al. 1997). FOXO3 is key for the maintenance of HSC pool. FOXO3 loss is associated with compromised HSC long-term repopulation ability, loss of HSC quiescence, accumulation of DNA damage, myeloid biased production of progenitors, lymphocyte defects and reduced red blood cell production (Miyamoto et al. 2007; Miyamoto et al. 2008; Yalcin et al. 2010; Marinkovic et al. 2007). FOXO3 regulation of HSC has been attributed to its ability to inhibit oxidative stress in quiescent cells at least partly by direct transcriptional control of expression of anti-oxidant genes including superoxide dismutase (SOD2) and catalase (Kops et al. 2002; Nemoto and Finkel 2002; Oh et al. 2005; Murakami and Johnson 2001; Ookuma et al. 2003; Murphy et al. 2003; Lee et al. 2003). However evidence suggests that FOXO3 might coordinate a number of fundamental processes beyond oxidative stress to regulate stem cell fate. Among these the regulation of ATM that is key in coordinating stem cell cycling with ROS levels (Yalcin et al. 2008), regulation of autophagy (Warr et al. 2013; Liang et al. 2015), control of pentose phosphate pathway (Yeo et al. 2013) and mitochondrial metabolism are noteworthy (Rimmele et al. 2015).

Despite elevated ROS involvement in many of *Foxo3*$^{-/-}$ hematopoietic stem and progenitor cell (HSPC) defects (Yalcin et al. 2008; Yalcin et al. 2010; Marinkovic et al. 2007; Bigarella et al. 2017), the compromised *Foxo3*$^{-/-}$ HSC ability to reconstitute all blood cells for a long (in contrast to short) period of time in a mouse in which blood is ablated is ROS-independent (Rimmele et al. 2015). Instead, loss of FOXO3 is associated with reduced oxygen consumption (by half) and ATP depletion (by half) in long-term HSC (LT-HSC) suggesting that mitochondrial respiration is reduced in *Foxo3*$^{-/-}$ LT-HSC (Rimmele et al. 2015). Despite the notion that the mitochondrial proton gradient generated by the respiratory chain drives ATP synthesis (Chen 1988), the low ATP in *Foxo3*$^{-/-}$ LT-HSC is associated with increased mitochondrial membrane potential (Rimmele et al. 2015). Loss of HSC

quiescence – as it is observed in *Foxo3*$^{-/-}$ HSC – is frequently associated with reduced glycolytic flux and increased oxidative phosphorylation. In contrast, *Foxo3* mutant HSCs exhibit a shift in the ATP production from oxidative phosphorylation to glycolysis. These paradoxical metabolic phenotypes in *Foxo3*$^{-/-}$ HSC are also associated with enhanced mitochondrial fragmentation (Rimmele et al. 2015), collectively depicting a picture in which loss of FOXO3 is associated with accumulation of faulty mitochondria. Damaged mitochondria are removed by mitophagy, a process that involves autophagic recycling of mitochondria and compromised in the absence of FOXO3.

Indeed, FOXO (FOXO3) are essential for the process of autophagy (Warr et al. 2013; Liang et al. 2015; Sandri et al. 2004; Chiacchiera and Simone 2009; Mammucari et al. 2007; van der Vos et al. 2012; Zhao et al. 2010) by regulating the transcription of many autophagy-related genes. Autophagy mediates the consumption of damaged or old cellular proteins and components and serves as a source of energy for maintaining HSC homeostasis during cellular stress and starvation (Warr et al. 2013; Yang and Klionsky 2010; Mortensen et al. 2011). FOXO3 was identified as the main transcription factor regulating autophagy gene expression and autophagy in HSC (Warr et al. 2013). FOXO3 is also a critical regulator of mitophagy (mitochondrial clearance by autophagy) a process required for HSC self-renewal (Ito et al. 2016) at least in some hematopoietic cells (Liang et al. 2015). Accumulation of defective mitochondria as a result of impaired mitophagy ((Liang et al. 2015), *Liang and Ghaffari, Oct 2015, unpublished findings*) in *Foxo3*$^{-/-}$ HSC may compromise HSC long-term stem cell activity in vivo, enhances ROS levels and result in apoptosis resistance in *Foxo3*$^{-/-}$ HSC (Bigarella et al. 2017). ROS elevation in *Foxo3*$^{-/-}$ HSC is however responsible at least partially for loss of quiescence and accumulation of damaged DNA in HSC (Bigarella et al. 2017).

ROS elevation results also in damage to mitochondrial DNA leading to mitochondrial misfolded and protein aggregates in response to which the cells mount mitochondrial unfolded protein response (UPR^{mt}). The goal of UPR^{mt} activation is to return to mitochondrial protein homeostasis. UPR^{mt} is triggered by mitochondrial-to-nuclear stress-signaling which is generated by an imbalance between mitochondrial protein production from nuclear (n)DNA) versus mitochondrial (mt)DNA. Mitochondrial misfolded proteins trigger an increase in anti-oxidant defense that is promoted by activation of both FOXO (FOXO3) and sirtuin (SIRT)3 deacetylase (Papa and Germain 2014) and possibly other sirtuins. Sirtuins are deacetylase for histones and other proteins that are evolutionary conserved in their regulation of healthy aging. Activation of mUPR is also implicated in the control of longevity (Mouchiroud et al. 2013; Mohrin et al. 2015).

SIRT1, another sirtuin of the family of seven mammalian sirtuins, is also a deacetylase for FOXO3 (Brunet et al. 2004; Motta et al. 2004). SIRT1 deacetylation maintains FOXO3 in an active form in HSC and protects HSC from aging-like damages (Rimmele et al. 2014; Liang et al. 2016). SIRT3 is also implicated in shielding HSC from stress-induced damages during aging (Brown et al. 2013).

In addition to SIRT1 and SIRT3 (Rimmele et al. 2015; Brown et al. 2013), the maintenance of longevity and healthy aging of HSCs requires SIRT7 that is also implicated in mUPR

activation (Mohrin et al. 2015). It is noteworthy that FOXO3 is implicated in regulating HSC longevity. Hematopoietic stem and progenitor cell defects in *Foxo3*$^{-/-}$ mice are reminiscent of defective hematopoiesis generated by old HSC (Miyamoto et al. 2007; Miyamoto et al. 2008; Rimmele et al. 2014). Collectively these findings suggest that elucidating the precise role of mitochondrial function including metabolism, dynamics and mUPR and their regulation by FOXO3 in cross talks with sirtuins will be of critical implications for HSC health and longevity and for understanding malignancies.

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