Editorial

Stem Cell INVESTIGATION

IFN-1 Bid crosstalk: foe or friend to stem cells

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Provenance: This is an invited Editorial commissioned by Editor-in-Chief Zhizhuang Joe Zhao (Pathology Graduate Program, University of Oklahoma Health Sciences Center, Oklahoma City, USA).

Comment on: Tasdogan A, Kumar S, Allies G, *et al*. DNA Damage-Induced HSPC Malfunction Depends on ROS Accumulation Downstream of IFN-1 Signaling and Bid Mobilization. Cell Stem Cell 2016;19:752-767.

Received: 14 January 2017; Accepted: 07 February 2017; Published: 27 February 2017.

doi: 10.21037/sci.2017.02.06

View this article at: http://dx.doi.org/10.21037/sci.2017.02.06

Under steady-state approximately 70% of the hematopoietic stem and progenitor cells (HSPC) in the bone marrow are quiescent, with low metabolic activity fueled by glycolytic metabolites (1). However, in response to exogenous demands such as cell loss or damage, or infection, they become highly proliferative and can efficiently and quickly expand or reconstitute the blood and immune systems (2,3). Stem and progenitor cell activation and proliferation relies primarily on mitochondrial oxidative phosphorylation (4). Intracellular reactive oxygen species (ROS) are a by-product of mitochondrial oxidative phosphorylation that are generated by the respiratory chain primarily in the form of superoxide anions (O_2^-) and are immediately transformed by mitochondrial superoxide dismutase (MnSOD) to hydrogen peroxide (H_2O_2) (5). HSPCs are highly sensitive to ROS and under normal physiological condition; ROS levels are tightly regulated to prevent hematopoietic cell damage (6-8). Accumulating evidence indicates that the inability to regulate high levels of ROS can lead to impaired stem and progenitor cell homeostasis and bone marrow failure (6-9). Evidence also suggest a role for chronic oxidative stress in the progression of radiation-induced acute and late hematopoietic syndromes (10,11), stem cell aging and (12) degenerative diseases (13), whereas ROS scavengers improve HSPC function and engraftment (9,14). Recently, genetic deletion of the core DNA damage response transcription factor *Atm* identified supra-physiological elevation of ROS as a key mediator of stem cell exhaustion, shorter lifespan and premature aging (6). However, to date, there has been little compelling molecular mechanisms that link this unrelated gene mutation to detrimental intracellular accumulation of ROS.

Chronic exposure to type 1 interferon (IFN-1), a primary effector cytokine against viral infection, can cause hematopoietic stem cells to exit quiescence and induces extensive stem cell proliferation that can lead to functional defects (2,15). IFN-1 signaling increases phosphorylation of signal transducer and activator of transcription 1 (STAT-1) and the serine/threonine-specific protein kinase B, Akt, which enhance expression of IFN-1 target genes and lead to cell cycle progression in HSPCs (2). Thus, even though associations between IFN-1 signaling and deficiencies in stem and progenitor cell function have been established, the molecular events linking IFN-1 signaling and defects in hematopoietic cell function are not well understood. In a recent issue of *Cell Stem Cell*, an elegant study by Tasdogan and co-workers (16) demonstrates that chronic activation of INF-1 signaling as a consequence of DNA damage mobilizes mitochondrial Bid resulting in exaggerated intracellular accumulation of ROS that leads to functional defects in HSPCs, thus establishing a novel role for IFN-1 and Bid cross talk in hematopoietic cell function. To identify factors/mechanisms involved in the DNA damage response that mediate altered hematopoietic function, the group performed functional analysis of HSPCs in $Mll5^{-/-}$ mice with inherited inefficient DNA repair machinery. In this model, massive DNA damage, excessive cell-cycle and elevated ROS were detected in all major subpopulations of lineage negative, Sca-1 positive, c-kit positive (LSK) cells, the population of mouse cells that

contain stem and progenitor cells, whereas treatment with the radical scavenger N-acetyl-L-cysteine (NAC) resulted in substantial reduction of ROS in these cells and effective correction of the hematopoietic deficits in Mll5$^{-/-}$ mice. Analysis in Mll5$^{-/-}$ and IFNar1$^{-/-}$ double-deficient mice, lacking both effective DNA repair and IFN-1 receptor signaling provided conclusive evidence that exaggerated ROS accumulation and HSPC functional abnormalities in Mll5$^{-/-}$ mice are primarily due to chronic activation of IFN-1 signaling. Further studies pointed to the involvement of mitochondria in the accumulation of ROS in HSPCs, as Mll5$^{-/-}$ HSPC exhibited increased mitochondrial membrane potential and elevated levels of intra-mitochondrial ROS. Higher mitochondrial ROS in Mll5$^{-/-}$ mice was correlated with substantial mitochondrial accumulation of full length Bid, which has previously been identified as an inducer of mitochondrial ROS and a key player in preserving hematopoietic cell function (17,18). Genetic deletion of Bid in Mll5$^{-/-}$ mice revealed 90% reduction in supra-natural ROS in HSPC and improved key hematopoietic anomalies including long-term repopulation ability of HSCs and hyper-proliferation of HSPC. Furthermore, lack of IFNar1 signaling resulted in substantial lower levels of full-length Bid and ROS in mitochondria and substantially improved hematopoiesis in Mll5$^{-/-}$ mice. Taken together, these novel findings identify that supra-natural mitochondrial ROS accumulation in response to IFN-1 signaling-mediated Bid mobilization plays a key role in hyper-proliferation and function of HSPCs. These findings have critical implications for understanding the mechanisms that promote malignant transformation and aging of blood stem and progenitor cells where the DNA damage response is compromised and offers exciting therapeutic opportunities by which the manipulation of Bid mobilization and ROS levels in stressed hematopoiesis, such as during inflammation, radiation exposure, aging and malignant transformation, may preserve normal hematopoiesis.

While mitochondrial BID mobilization appears to be the central culprit for toxic accumulation of ROS and altered function of HSPCs in response to DNA damage, several questions remain. A key question is how does mitochondrial Bid mobilization translate into toxic accumulation of ROS? It is possible that Bid modulates mitochondrial ROS levels by interaction with its receptor, mitochondrial carrier homolog 2 (MTCH2). MTCH2 is a surface-exposed outer mitochondrial membrane protein that is important for Fas-induced liver apoptosis (19). In addition, MTCH2 is also identified in a genome-wide association study as a new gene locus associated with body mass index in humans (19). Thus, MTCH2 may also be involved in regulating mitochondrial metabolism. Another key question will be to determine whether chronic IFN-1 signaling-mediated Bid mobilization switches metabolism in hematopoietic stem cells from glycolysis to oxidative phosphorylation and how this is accomplished. Indeed, IFN-1 signaling can enhance oxidative phosphorylation in plasmacytoid dendritic cell and non-hematopoietic cells in response to the Toll-like receptor-9 agonist CpGA (20). In addition, because Mll5 is expressed in human cells (21) and mutation in this gene has been implicated in acute myeloid leukemia (AML) and myeloproliferative disease (22) and positively associated with elevated ROS accumulation in (AML) cells, it would be clinically relevant to explore whether mutation in the Mll5 gene disrupts DNA repair machinery that leads to IFN-1 signaling, Bid mobilization and ROS accumulation in AML patients.

Acknowledgements

Funding: Supported by NIH grants HL096305, CA182947 and AG046246 to LM Pelus.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/sci.2017.02.06
Cite this article as: Singh P, Pelus LM. IFN-1 Bid crosstalk: foe or friend to stem cells. Stem Cell Investig 2017;4:18.

