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Commentary

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Loss of P2Y14 results in an arresting response to hematological stress

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The regenerative capacity of tissues to recover from injury or stress is dependent on stem cell competence, yet the underlying mechanisms that govern how stem cells detect stress and initiate appropriate responses are poorly understood. In this issue of the JCI, Cho and Yusuf et al. demonstrate that the purinergic receptor P2Y14 may mediate the hematopoietic stem and progenitor cell regenerative response.

Senescence and stem cell decline

Cellular senescence, a state of permanent irreversible growth arrest, was initially described over half a century ago by Leonard Hayflick and Paul Moorhead, who observed that normal human fibroblasts cease to replicate after 50 to 60 cellular divisions (1). This barrier to everlasting cellular proliferation later became termed the “Hayflick limit,” denoting the loss of proliferative potential even though the cell remains viable and metabolically active. While this phenomenon was originally connected to long-term in vitro cell propagation, cellular senescence is now understood to be a complex mechanism that may limit cell growth as well as prevent cancer in vivo and that can be initiated in response to a variety of cellular stresses, including oxidative damage, telomere shortening, DNA damage, and gene deregulation (2–4).

As with the majority of tissues, the hematopoietic system exhibits signs of age-related decline, including immune dysfunction, decreased red blood cell production, increased incidence of malignancies, and impaired recovery from injury, much of which appears to arise through cell autonomous changes in the HSC compartment (5–8). These age-related changes in the HSC compartment appear to be

Conflict of interest: Derrick Rossi has an ownership stake and provides consultation for Moderna Therapeutics.

Citation for this article: J Clin Invest. 2014;124(7):2846–2848. doi:10.1172/JCI76626.
Loss of P2Y14 leads to reduced HSC potential in response to stress

In this issue, Cho, Yusuf, and colleagues provide evidence that stress-induced senescence in hematopoietic stem progenitor cells (HSPCs) is regulated through the G-coupled cell-surface receptor P2Y14 (17). HSCs give rise to all blood effector cells for the life of an individual, and the capacity to constantly replenish the hematopoietic compartment requires a careful balance among HSC fate decisions, including self-renewal, quiescence, apoptosis, and multilineage differentiation. In contrast with HSCs, differentiated effector populations frequently have a short life span, measured in days, resulting in a huge daily cell turnover that necessitates tight homeostatic control of the upstream HSPC populations, where transit amplification occurs.

Under situations of stress, such as irradiation or chemotherapy, a portion of the HSPC pool may be lost, leading to myelosuppression (decreased red cell, white cell, and platelet numbers), and in such cases, the surviving HSPCs must increase self-renewal and differentiation to repopulate required cell populations. How HSPCs integrate stress signals to invoke the appropriate stress responses remains unclear. Cho, Yusuf, and colleagues have revealed that P2Y14 regulates the HSPC response to stress. Specifically, the authors demonstrate that HSPCs lacking P2Y14 are not at a disadvantage for restoring hematopoietic populations when cotransplanted with equivalent WT HSPCs in lethally irradiated mice under steady state conditions; however, under various stress conditions, including serial transplantation, radiation, and chemotherapy, cells lacking P2Y14 were less competitive than WT cells. As a result of the stress-induced loss of competitiveness, there was a decline in P2Y14-deficient HSPCs and total peripheral blood chimerism (Figure 1). Interestingly, the loss of functionality in P2Y14-deficient cells occurred concurrently with increased detection of several classical senescence biomarkers, including p16INK4A, greater β-gal (SA-β-gal) activity, and increased ROS, implicating cellular senescence as a possible consequence of P2Y14 deficiency during stress. Furthermore, Cho, Yusuf, and colleagues demonstrated that the enhanced susceptibility to irradiation stress in P2Y14-deficient HSPCs could be alleviated through administration of the ROS scavenger N-acetyl-cysteine (NAC) or inhibition of p38 MAPK, an important mediator of the ROS-response pathway, indicating that dysfunctional ROS management may be a significant underlying contributor (17).

HSC function has previously been shown to diminish as a consequence of ROS dysregulation, leading to premature exhaustion and shortened lifespan. For example, mice deficient in ataxia telangiectasia mutated (ATM) experience hematopoietic failure, which is largely abrogated by NAC treatment (18). Similarly, deletion of genes encoding forkhead box transcription factors (FoxOs) has been shown to negatively affect HSC function and numbers through increased ROS production and subsequent HSC apoptosis (19–21). Together, these results indicate that increased ROS levels diminish HSC function; therefore, it is likely that the increased ROS detected in P2Y14-deficient HSPCs is playing an integral role in the observed phenotypes through cellular oxidative damage and perhaps apoptosis, although future work will be needed to elucidate the exact connection between the P2Y14 receptor and ROS management.

Conclusions and future directions

Cho, Yusuf, and colleagues have shown that HSPCs lacking the P2Y14 receptor are compromised in their ability to withstand and recover from several types of stress. The authors make a strong biochemical case for a senescence-based mechanism explaining the diminished function of P2Y14-deficient HSPCs during stress, though the development of functional assays that uncouple senescence from other processes that diminish HSC potential, such as apoptosis,
will likely be required to definitively elucidate how P2Y14 mediates the HSCP stress response (10, 22). If P2Y14-deficient HSCs within the animal model system developed by Cho, Yusuf, and colleagues do indeed prove to be functionally senescent, then this could be an exciting model system for studying the onset of stress-induced senescence within the HSC compartment. A better understanding of the regulators of HSC stress response has important implications for regenerative medicine.

Acknowledgments
D.J. Rossi is a New York Stem Cell Foundation Robertson Investigator.

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Twisting mice move the dystonia field forward
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A common form of the hyperkinetic movement disorder dystonia is caused by mutations in the gene TOR1A (located within the DYT1 locus), which encodes the ATPase torsinA. The underlying neurobiological mechanisms that result in dystonia are poorly understood, and progress in the field has been hampered by the absence of a dystonia-like phenotype in animal models with genetic modification of Tor1a. In this issue of the JCI, Liang et al. establish the first animal model with a dystonic motor phenotype and link torsinA hypofunction to the development of early neurodegenerative changes in distinct sensorimotor regions. The findings of this study will likely play an important role in elucidating the neural substrate for dystonia and should stimulate systematic neuroepidemiological and imaging studies in carriers of TOR1A mutations.

Neurological disorders and the need for animal models
For many brain disorders, identification and characterization of the underlying neurobiological mechanisms remains a challenge for clinicians and scientists. Lack of defined neural substrates and an understanding of the pathways responsible for neurological and psychiatric symptoms has limited the development of novel therapies, which are urgently needed to improve the care and quality of life of affected individuals. In this issue, Liang and colleagues present animal models that recapitulate the major clinical symptomatology of dystonia (1). The study by Liang and colleagues represents an important leap forward for the dystonia research field.

Dystonia: the twists and turns
Dystonia is characterized by sustained or intermittent muscle contractions that cause abnormal, often repetitive, twisting movements and postures and is now recognized as a heterogeneous group of hyperkinetic movement disorders. The term dystonia was coined in 1911 by Herman Oppenheim, who used “dystonia musculorum deformans” to describe a childhood-onset form of generalized dystonia (2). These disorders have traditionally been classified as either primary or secondary dystonias. Primary dystonia is considered to only present with tremor or myoclonus as an additional neurological symptom.