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Platelets Give a Running Start to Adult Hippocampal Neurogenesis

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Exercise boosts neural stem and progenitor cell proliferation and differentiation in the dentate gyrus region of the hippocampus. In this issue of *Stem Cell Reports*, Leiter et al. (2019) identify acute exercise-induced platelet activation and platelet factor-4 as novel systemic mediators of adult hippocampal neurogenesis.

Adult neurogenesis, the generation of new neurons in the adult brain, occurs in two distinct brain regions: the dentate gyrus (DG) of the hippocampus and the subventricular zone (SVZ) of the lateral ventricles. In the hippocampus, neural stem cells proliferate and differentiate into nascent neurons. These newborn neurons have a lower threshold for induction of synaptic plasticity and are preferentially incorporated into learning and memory circuits (Schmidt-Hieber et al., 2004), suggesting that adult hippocampal neurogenesis (AHN) supports hippocampal-dependent cognition. Systemic-based interventions, such as dietary manipulation and exercise, promote brain health in a number of functional ways, including enhanced AHN (Horowitz and Villeda, 2017). In particular, aerobic exercise training robustly enhances AHN in rodents, independent of paradigm (treadmill or voluntary running) and age of the animal (van Praag et al., 2005). An emerging area of research has begun to identify a blood-brain axis, where circulating factors mediate some of the beneficial effects of these systemic interventions (Horowitz and Villeda, 2017). For example, several circulating factors (i.e., insulin-like growth factor-1, vascular endothelial growth factor, and Cathepsin B) have been identified as potential systemic mediators of exercise-training-induced AHN (Tari et al., 2019). To date, however, no study has identified media-

tors of increased AHN in the context of short-term exercise. In this issue of *Stem Cell Reports*, Leiter and colleagues present work implicating platelets, an anuclear cellular component of blood traditionally known to be involved in hemostasis, as a novel systemic mediator of the neurogenic response to acute voluntary running (Figure 1).

To evaluate if the pro-neurogenic effects of acute running are mediated by circulating factors, Leiter et al. (2019) cultured hippocampal neural progenitor cells (NPCs) with serum collected from mice following a short period of voluntary wheel running (4 days). Serum from runners increased the number of neurospheres formed *in vitro* relative to NPCs cultured with serum from sedentary mice, indicating that acute-exercise-induced factors in the blood can promote NPC proliferation. Using a mass spectrometry approach, Leiter et al. (2019) identified an increase in platelet-activation-related proteins in the plasma of mice following running (4 days). Notably, while previous experiments in the field identified secreted factors through exercise-mimetic experiments *in vitro* and prolonged exercise training *in vivo* (Tari et al., 2019), this article evaluates protein level changes *in vivo* following acute exercise. Furthermore, flow cytometry confirmed that platelets were activated following 1 and 4 days of running, but they returned to baseline after 7 days, indicating that exercise-

induced platelet activation is a transient response. Platelets are dynamic cells with complex signaling machinery capable of responding to various stimuli to release soluble factors stored in granules. This canonical platelet activation response is critical for hemostasis by mediating thrombus formation in response to vascular damage. However, emerging studies have begun to identify context-dependent release of factors from platelets (Italiano et al., 2008), raising the possibility that platelet activation, in the context of acute exercise, enhances AHN.

To investigate the effects of platelets following acute exercise, the authors treated isolated hippocampal NPCs with platelet-rich-plasma (PRP) or platelet-poor-plasma (PPP). Interestingly, neither PRP nor PPP freshly isolated from exercised mice enhanced hippocampal NPC proliferation, as assessed by neurosphere number, obfuscating the efficacy of exercise-induced activation of platelets on NPC proliferation. Nonetheless, artificial freeze-thaw-cycle-induced activation of PRP samples from both sedentary and acutely exercised mice enhanced both NPC proliferation and neuronal differentiation. This pro-neurogenic effect did not extend to NPCs isolated from the SVZ, suggesting distinct brain-region-specific responses to platelet activation. It should be noted that while results by Leiter and colleagues posit activated platelets as enhancers



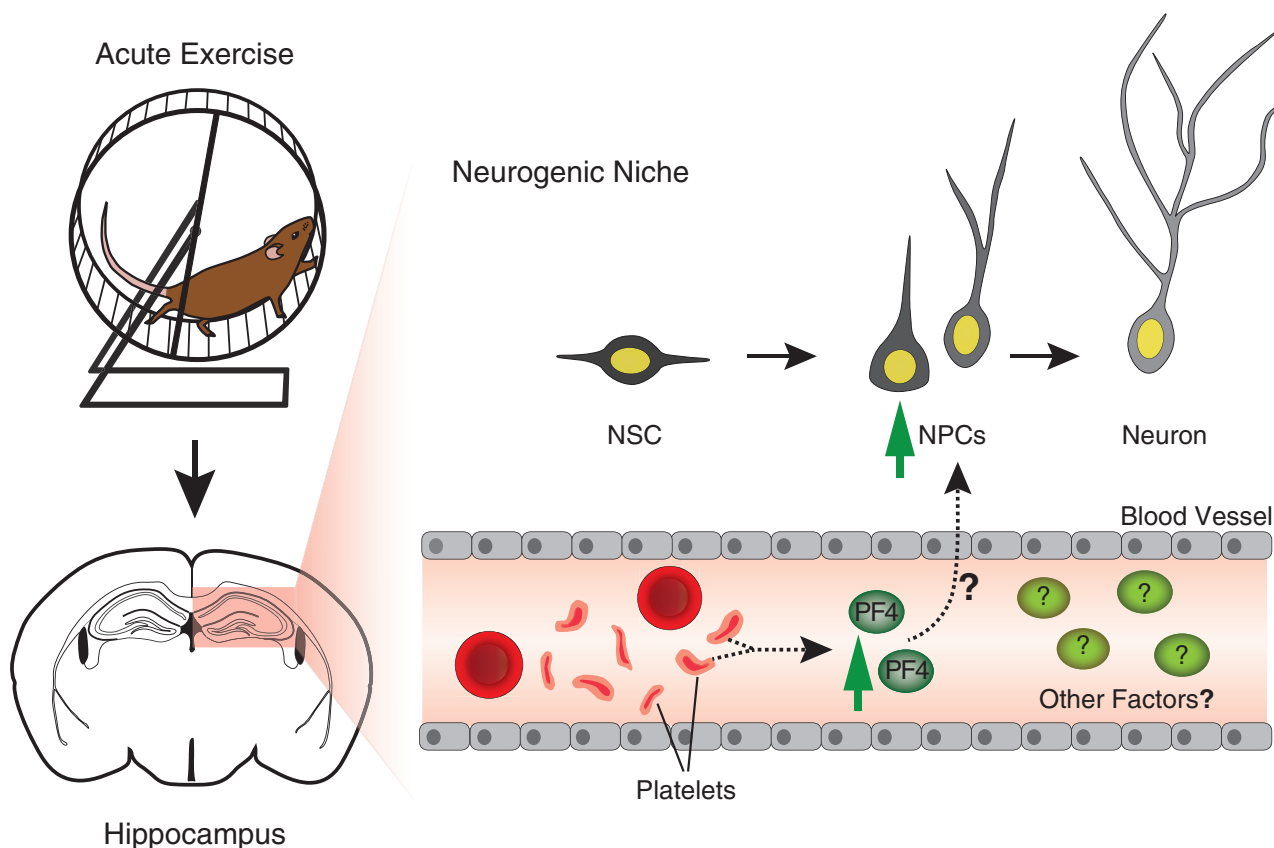


Figure 1. Plates Mediate Acute-Exercise-Induced Adult Hippocampal Neurogenesis

Acute aerobic exercise enhances proliferation of neural stem cells (NSCs) and differentiation of neural progenitor cells (NPCs) in the hippocampus. Leiter et al. (2019) identified a necessary role for platelets in the pro-neurogenic response to acute exercise in mice. Platelet factor-4 (PF4) was identified as one potential platelet-derived factor regulating the pro-neurogenic effect of activated platelets locally within the hippocampal neurogenic niche.

of AHN, they fail to demonstrate the sufficiency of exercise-induced platelet activation in this process, at least *in vitro*.

To elucidate the necessity of platelet activation in acute-exercise-induced AHN, Leiter et al. (2019) sought to determine whether antibody-mediated depletion of platelets alters exercise-induced NPC proliferation *in vivo*. Consistent with previous reports (Tari et al., 2019), 10 days of exercise elevated the number of proliferating cells in the DG relative to that in sedentary control mice; however, platelet depletion abolished this effect. These findings identify platelets as a critical mediator of short-term exercise-induced AHN *in vivo*.

Previously, work interrogating the blood-brain axis has focused on identifying soluble protein factors within plasma, independent of the cellular components of blood, that may influence hippocampal function. The identification of platelets as mediators of acute-exercise-induced AHN provides an extra dimension to research studying the role of peripheral regulators of hippocampal function. Cellular components, such as platelets, are capable of both releasing soluble factors systemically into the bloodstream and releasing them in a controlled manner at discreet sites (e.g., hippocampus). Leiter and colleagues identify platelet factor-4 (PF4)—a cytokine released from alpha granules of activated plate-

lets involved in blood coagulation, wound repair, inflammation, and megakaryocyte maturation (Eisman et al., 1990)—as one such potential factor. The authors detect PF4 as being elevated in the plasma of mice following 4 days of running. Functionally, Leiter and colleagues demonstrate that hippocampal NPC proliferation and differentiation are enhanced by PF4 *in vitro*. Interestingly, when delivered locally to the hippocampus via mini-osmotic pumps, PF4 did not alter NPC proliferation *in vivo*; however, an increase in the neuroblast population was observed, suggesting that PF4 promotes neurogenesis.

In contrast to the acute exercise paradigm employed by Leiter et al.



(2019), previous reports assessing the systemic mediators of exercise-induced AHN have focused on longer durations of exercise training, ranging from weeks to months (Tari et al., 2019). While hippocampal cell proliferation can increase as early as 24 h post-running in rodents, the pro-neurogenic efficacy of aerobic exercise training continues throughout 6 months of training (Marlatt et al., 2012). However, running-induced activation of platelets, as shown by Leiter et al. (2019), returns to baseline levels 7 days after running, indicating that running-induced platelet activation likely serves an acute, transient role in exercise-induced AHN. Indeed, the authors demonstrate that platelets are likely key to initiating the neurogenic response, but perhaps not to maintaining it. Identifying other mediators of AHN after the acute exercise phase will be important to further elucidate the mechanisms by which exercise promotes AHN. Additionally, discovering systemic blood-borne mediators in the prolonged response to exercise may allow the identification of therapeutic targets for not only the initiation of AHN, but also the maintenance of a pro-neurogenic environment and promotion of hippocampal function. Importantly, aerobic exercise training promotes hippocampal function through not only AHN, but via elevated synaptic plasticity, neovascularization, attenuated neuroinflammation, and reduced protein aggregation (Horowitz and Villeda, 2017). Each of these neurological changes has the potential to influence hippocampal-dependent cognitive function. How exercise produces such dramatic long-term changes remains elusive.

From a therapeutic standpoint, the findings by Leiter et al. (2019) raise a number of exciting questions: first, does the systemic administration of activated platelets or PF4 promote AHN *in vivo*? While depletion of platelets mitigates acute-running-induced

AHN, whether systemic administration of activated platelets is sufficient to induce AHN should be explored. Likewise, the authors determined that local administration of a single platelet-derived factor, PF4, to the hippocampus can promote survival of immature neurons, but the effect of peripherally delivered PF4 has not been assessed. Elucidating whether peripheral PF4 can enter the brain or how it may otherwise send a pro-neurogenic signal specifically to the hippocampus is necessary to adequately establish its therapeutic potential. Functionally, it will be crucial to determine if systemic administration of activated platelets or PF4 can promote hippocampal-dependent learning and memory. Indeed, many interventions that enhance AHN in mice, such as exercise or exposure to young blood, also enhance hippocampal-dependent cognitive processes (van Praag et al., 2005; Villeda et al., 2014). Directly assessing the capacity of activated platelets and PF4 to improve cognitive function will greatly strengthen the case for these factors as potential therapeutic targets.

While Leiter et al. (2019) highlight a novel, beneficial role for platelet activation in exercise, recent work has also found a deleterious function of platelet activation in neurodegenerative pathology. Specifically, platelets derived from an Alzheimer's disease mouse model have been implicated in cerebrovascular dysfunction and neuroinflammation (Kniewallner et al., 2018), potentially linking disease progression to platelet dysfunction. The combination of these two findings highlights the importance of proper platelet function and further illustrates the importance of context-dependent release of factors from platelets in response to different stimuli (Italiano et al., 2008). These studies now prompt future investigations into the effects of platelets across different neurological contexts. For example,

do age-related changes to platelets influence age-related hippocampal dysfunction? Further elucidation of the effects of platelets, and platelet-derived factors, on hippocampal function in such conditions will provide an exciting new vista for developing therapeutic strategies to promote cognitive function in health and disease.

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