RESEARCH HIGHLIGHT

Run! White blood cells cued by a motor brain under stress

Hai Qi[1,2,3]✉ and Bo Liu[2,3]

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A recent study by Poller et al. published in *Nature* explores brain control of leukocyte distribution following acute stress and implicates motor circuits in promoting neutrophilia.

Startled with an unexpected danger, animals often freeze and then run away or fight it out. This fight-or-flight instinct is implemented partly through stress-processing circuits in the central autonomic network of the brain,[1] which also makes significant impacts on the immune system. The hypothalamus-pituitary-adrenal (HPA) axis stimulates secretion of glucocorticoids, which suppress immune functions via multiple mechanisms including induction of apoptosis.[2] Vagal activation attenuates inflammation partly by suppressing cytokine production from macrophages.[3] Sympathetic activation may enhance immune responses, particularly those mediated by antibodies.[4] In a recent study published in *Nature*, Poller et al. examined effects of stress on immune cell distribution and report an unexpected role for motor circuits.[5]

Building on previous observations that acute stress could alter the trafficking pattern of immune cells in rats,[6] Poller et al. kinetically characterized distribution of multiple immune cell types after body restraint of mouse models. This stress led to large numbers of lymphocytes and monocytes egressing from secondary lymphoid organs and homing to the bone marrow (BM), while at the same time neutrophils were mobilized from the BM into the blood. To explain the rapid re-distribution of immune cells, they systematically tested potential roles of the sympathetic nervous system and the HPA axis. They found that increased glucocorticoids were responsible for the depletion of lymphocytes and monocytes from the circulation but not responsible for the rapid increase of neutrophils in the blood. Glucocorticoids are known to modulate CXCR4 expression,[7] a chemokine receptor that directs homing to the BM. Accordingly, a CXCR4 antagonist could largely abrogate the acute stress-induced lymphopenia and monocytopenia. They further showed that lymphocyte- and monocyte-intrinsic responsiveness to glucocorticoids was required for their re-distribution following an episode of acute stress; corticotropin-releasing hormone (CRH) derived from CRH neurons in the paraventricular nucleus of the hypothalamus (PVH) drove the re-distribution. This set of observations, albeit to a large extent expected, nicely demonstrate that the HPA axis is indeed responsible for the re-distribution of lymphocytes and monocytes into the BM following acute stress.

Glucocorticoids have complex effects on neutrophils and cannot explain stress-induced neutrophilia.[5] The BM receives extensive sympathetic innervation, with cells of hematopoietic and stromal lineages expressing catecholamine receptors, and hematopoiesis is regulated by the sympathetic nervous system.[8] However, Poller et al. found that sympathetic activities did not promote neutrophilia. By examining a series of plasma cytokines that might regulate neutrophil trafficking, they found that CXCL1, a neutrophil-mobilizing chemokine that utilizes CXCR2 as its receptor,[9] was prominently elevated following acute stress. They then showed that CXCL1 was largely responsible for the neutrophilia. While CXCL1 can be expressed by a wide array of cell types and tissues,[10] it was most highly upregulated in skeletal muscles after restraining stress. On the other hand, CXCL1 was not upregulated in muscles during voluntary running. This distinction correlated with much higher intensities of muscle activation seen in the stress condition, although how much voluntary exercise that control animals conducted was not quantified. Poller et al. then worked their way up from the neuromuscular junctions to central motor circuits to show that skeletal muscles synthesize and release CXCL1 only when their motor neurons are excited to instruct contraction.

Finally, Poller et al. also explored effects of body-restraining stress on experimental autoimmune encephalomyelitis (EAE), infection models of SARS-CoV2 and influenza. Their results indicate that stress by body restraint inhibits adaptive immunity, ameliorating EAE while exacerbating viral infections, consistent with the well-established immunosuppressive effect of glucocorticoids, which are clinically approved for treatment of autoimmune and inflammatory diseases.

Overall the study is interesting in its revelation of the excessive motor activation as the root cause for stress-induced neutrophilia, while it also provides a nice set of data that systemically re-confirm the role of stress hormone glucocorticoids in immunosuppression. However, physiological functions of neutrophilia under stress have not been explored in details. Notably, intensive physical training causes neutrophil accumulation in target muscles under resistance exercise,[11,12] probably as an early step in the tissue repair response dealing with muscle damage. Therefore, it will be important to understand how the acute stress model studied by Poller et al. is related to voluntary resistance training. On the other hand, the fact that voluntary exercise model used in their study did not cause CXCL1 upregulation in muscles does not necessarily indicate that the intensity of muscle activities solely determines neutrophilia. It would be interesting to explore whether low levels of muscle activities, when combined with other effects of the stress or motor circuits, could promote muscular production of CXCL1 and/or neutrophilia. It would also be interesting to consider whether other types (e.g., psychological) or strengths of stress, with or without muscle involvement, could have different impacts on neutrophil

[1]Tsinghua-Peking Center for Life Sciences, Beijing, China. [2]Laboratory of Dynamic Immunobiology, Institute for Immunology, Tsinghua University, Beijing, China. [3]Department of Basic Medical Sciences, School of Medicine, Tsinghua University, Beijing, China. ✉email: qihai@tsinghua.edu.cn

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mobilization. In general, neutrophil mobilization could be a way the body prepares itself for defending against potential infections ensuing fight-or-fleeing response that causes the acute stress in the first place, which, in evolution, could be a frequent consequence of imminent dangers. The fact that CXCL1 can be rapidly produced in large amount by skeletal muscles under certain conditions might be exploited in the future for neutrophil-mobilizing treatment of acute bacterial infections. Fight or flight, neutrophils may now take orders from the motor brain.

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ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Hai Qi.