

EDITORIAL | OPEN ACCESS

Role of the immune system for conditioning in cerebrovascular diseases

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The philosopher Friedrich Nietzsche wrote “what doesn’t kill me, makes me stronger” (Wohns 2020), a fact that is hard for any of us to ignore at work, with trauma, or following an illness. How many times in life has a new reality been reached – achieved through struggle and stress and previously difficult to imagine but nonetheless manageable. This adaptation to stress underlies the concept of conditioning, and specifically the studies by which resistance phenotypes can be achieved in cells, organs, tissues, or organisms. Thus, conditioning is integral to life- it is the response to stress and the subsequent change by an organism that drives adaptation and resilience. Often overlooked in the concept of conditioning are the pleiotropic effects of responses within an organism. Effects from a single systemic conditioning stimulus can induce changes to multiple organ systems and/or confer resilience to many types of injury or disease.

A series of articles in this issue of *Conditioning Medicine* takes these pleiotropic effects into consideration, as we look at the immune system’s response to conditioning. Decades of research have focused on protective effects of conditioning in various organ systems, including heart, lung, liver, and brain, and includes conditioning in all forms: pre-, per-, and post-conditioning (Leak et al. 2018, Zhou et al. 2018). In one prominent and practical methodological form, hypoxic conditioning is achieved by cycles of inflation and deflation of a blood pressure cuff on an arm. What links the various organs that have been studied for protective conditioning effects are both the cardiovascular and immune systems. And while specific cardiovascular effects secondary to conditioning are well known (e.g. angiogenesis, improved vasoreactivity), our mechanistic understanding of conditioning effects on the immune system are less studied and will be the focus of this series of articles.

One review article by Dr. Richard Milner et al. from the San Diego Biomedical Research Institute in San Diego,

CA, USA (Halder and Milner, 2021) focuses on the effects of hypoxic conditioning on multiple sclerosis (MS), the prototypical autoimmune disease of the CNS. This article links and comprehensively discusses the cardiovascular and immune system responses to hypoxia, highlighting the multiple protective effects on vascular integrity and induction of anti-inflammatory mechanisms, as well as effects on immune cell phenotype even with conditioning initiated during the course of disease. Dr. Milner concludes with the potential for hypoxic conditioning to treat MS patients, with a call for preclinical studies to confirm efficacy. This translational potential is also a major focus of a second review article by Dr. Tony Parker and colleagues from the Queensland University of Technology in Brisbane, Australia, with an emphasis on potential neuroprotective effects during stroke using two forms of conditioning: remote ischemic conditioning (for example achieved by the above-mentioned blood pressure cuff technique) and blood flow restriction (Schmidt et al., 2021). Both of these conditioning paradigms rely on pleiotropic conditioning effects on the cardiovascular system to influence the immune response to brain injury after stroke. Major biochemical and molecular mechanisms are reviewed, with an emphasis of the ease of use and therapeutic potential of blood flow restriction conditioning, given further research. An original research article by Dr. Jeff Gidday, Dr. Ann Stowe, and colleagues from the Louisiana State University School of Medicine and the University of Kentucky in New Orleans, LA, and Lexington, KY, USA, respectively, combines topics from the above discussed review articles to focus on the cerebral microvascular response to systemic hypoxia using conditioning paradigms shown to protect from ischemic stroke (Harman et al., 2021). This article uses bioinformatics to show how the transcriptional response following one exposure to systemic hypoxia differs from the transcriptional response following multiple exposures to hypoxia. They identify inflammatory pathways that are directly

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upregulated in cerebral microvessels, critically linking the cardiovascular and immune system responses to conditioning. Another review article by Dr. Jürgen Bernhagen and colleagues from the Institute for Stroke and Dementia Research at LMU University Hospital, Munich, Germany (Wang et al., 2021), follows up on the discussion in Dr. Parker's article on mechanisms of remote ischemic conditioning in stroke, but lays a special emphasis on the role of cytokines with a focus on both classical chemokines and atypical chemokines including MIF proteins. Owing to their key role as orchestrators of leukocyte recruitment responses, chemokines have been amply implicated in microglia activation and leukocyte infiltration in the post-stroke inflammatory response. The article summarizes the evidence on classical chemokines such as CXCL12 and CCL5 and discusses the emerging evidence on danger-associated molecular patterns (DAMPs) and atypical chemokines such as HMGB1, peroxiredoxins, and MIF proteins. Their roles in ischemic stroke pathogenesis are compiled and reviewed, discussing involved subclasses, relevant receptors, and available therapeutic evidence. Moreover, highlighting initial evidence for CXCL12, CCL2, or MIF, the article discusses opportunities to target such mediators in ischemic conditioning paradigms in stroke or cardiac ischemia. Finally, we end with a review by Dr. Corinne Benakis from the Institute for Stroke and Dementia Research in Munich, Germany, on gut microbial metabolites as potential circulating immunomodulators to mediate protection from brain injury (Fink et al., 2021). Immune function and the gut microbiome are highly integrated systems that play critical roles in health and disease. Unfortunately, few studies have even identified potential gut metabolites that may mediate pleiotropic conditioning effects. We hope that this review will spur our colleagues to consider including quantification of gut microbial metabolites in future conditioning studies to confirm a mechanistic role, as well as to identify potential biomarkers and therapeutic targets.

In summary, this series of articles highlights the role of important mechanisms and arms of our immune system in mediating conditioning-induced protection. This is done in light of the intricate balance of the cardiovascular and immune systems as vital mediators of pleiotropic effects of protection in the whole organism. While there is much work to be accomplished in better characterizing the conditioned immune response to injury and disease, we hope that these articles are a launching point for future studies that could ultimately result in translation to clinical interventions.

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