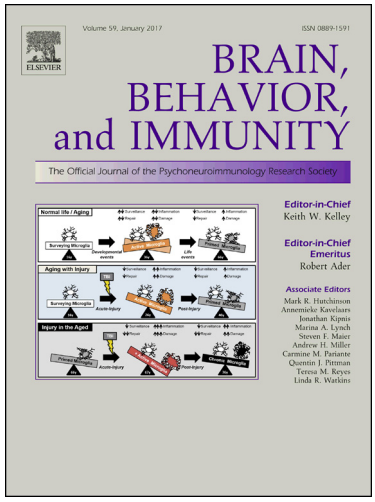
Accepted Manuscript



The contribution of microglia to "immunization against stress"

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PII: S0889-1591(18)30395-7
DOI: https://doi.org/10.1016/j.bbi.2018.08.002
Reference: YBRBI 3463

To appear in: *Brain, Behavior, and Immunity*

Received Date: 30 July 2018
Accepted Date: 1 August 2018

Please cite this article as: Herkenham, M., The contribution of microglia to "immunization against stress", *Brain, Behavior, and Immunity* (2018), doi: https://doi.org/10.1016/j.bbi.2018.08.002

The contribution of microglia to "immunization against stress"

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Graham Rook and Christopher Lowry have been studying *Mycobacterium vaccae (M. vaccae)* for quite some time. Let's say it all started with dirt, or more specifically, the benefits of some kinds of dirt as put forth in the "old friends" hypothesis. The hypothesis posits that early-life exposure to diverse macro- and microorganisms and microbiota that accompanied mammalian evolution tunes and primes our immune systems to withstand later insults [Rook et al. 2013]. One of the "old friends" is *M. vaccae*, a nonpathogenic species of the *Mycobacteriaceae* family of bacteria that lives naturally in soil. Research has shown that these bacteria may be beneficial by programming the adaptive immune system. Animals immunized (by spaced subcutaneous injections) with heat-killed *M. vaccae* showed altered immune responses, with a skewing of the T helper lymphocyte profile towards Th1 (IFNγ producing) [Janssen et al. 2001] and away from Th2 (IL-5 producing) [Wang and Rook 1998]. Consequently, *M. vaccae* immunization has been tested as an immunotherapy for a number of diseases such as allergic asthma, cancer, and tuberculosis. Now it is being considered as a treatment for depression. Lowry's team in 2016 found that immunization of mice with *M. vaccae* prior to exposure to chronic psychosocial housing stress reduced stress-induced development of both colitis and anxiety via skewing of the adaptive immune system towards regulatory T (Treg) cells. Treg cells in turn produce anti-inflammatory cytokines, specifically, IL-10 and TGFβ [Reber et al. 2016]. These striking findings attracted media attention for a potential therapeutic "immunization against stress" and made the top 10 list for breakthroughs by the Brain and Behavior Research Foundation that year.

The newest study by the Rook/Lowry team in collaboration with the Frank/Maier/Watkins team [Frank et al. 2018a] shows that immunization-induced changes in the peripheral immune system can translate to changes in the CNS via alterations in the microglial compartment. Their previous work indicated that following immunization, serotonin markers were elevated in the dorsal raphe nucleus and microglia in the medial prefrontal cortex were more densely immunostained with the antibody Iba1 [Reber et al. 2016]. However, little was known about how the peripheral immune signals were transmitted to brain and whether a central immune response was involved. Matthew Frank and colleagues [2018a] have now contributed important new insights to these mechanisms. In searching for suspects, the authors found that *M. vaccae* immunization elevated expression levels of Il4, Cd200r1, and Mrc1 mRNA and IL-4 protein while reducing levels of Nlrp3 (a key component of the inflammasome) and Nfkbia (IκBα, the rate-limiting molecule in NF-κB signaling) mRNA in the hippocampus. In general, the elevated transcripts are anti-inflammatory, and the reduced transcripts are pro-inflammatory. The cellular origin of these signals is not known, but microglia are a likely candidate.

The acute stressor used in this study—exposure to a single session of 100 inescapable footshocks—decreased levels of Cd200 and increased levels of high-mobility group box 1 (Hmgb1) mRNA. These two genes are candidates that might translate stress effects onto altered microglial activity [Deczkowska et al. 2018; Weber et al. 2015]. As predicted, prior *M. vaccae* immunization blunted those effects. The inescapable shock session primed the microglia as determined *ex vivo* by LPS challenge to isolated hippocampal microglia. Prior