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Brief Commentary

There's no place like biome: Can helminths restore the body's ecosystem?



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Immunity is a proverbial double-edged sword. Whereas a competent immune system is crucial for maintaining a sufficiently high level of disease resistance, excessively heightened or over-reactive immune responses may be equally debilitating, leading to a host of allergies and autoimmune diseases. Of considerable concern to immunologists and non-immunologists alike is the dramatic rise in autoimmune and inflammatory disorders during the past decade. A study conducted by the National Center for Health and Statistics determined that the prevalence of asthma has increased from 2001 to 2010 and in 2012 was the highest in recorded history (Akinbami et al., 2012). Immune hyper-reactivity and dysbiosis have also been linked to autism spectrum disorders, anxiety, and obesity (Clarke et al., 2014). Recently, scientists have proffered the “biome depletion theory” to help make sense of these startling trends. According to this theory, marked increases in autoimmune and inflammatory diseases may be the result of a loss of critical components of our biome (e.g., microbes and multicellular organisms) that normally interact with our immune system. The loss of these microbial communities within modern societies can fuel potentially pathological immune over-reactions (Parker and Ollerton, 2013).

The paper by Williamson and colleagues (Williamson et al., 2016) in this issue of *Brain, Behavior, and Immunity* tests the idea that the loss of biome complexity contributes to hyperactive immune responses. Previous work by this group has demonstrated that neonatal rats infected with the gram negative bacterium *Escherichia coli* exhibited elevated brain cytokine levels and substantially impaired memory when subsequently exposed to a secondary immune challenge (i.e., lipopolysaccharide) in adulthood (Bilbo et al., 2005; Williamson et al., 2011). The results, while exciting, were also puzzling; why would the immune system have evolved to essentially overreact to exposures that surely must occur frequently in nature? The researchers speculated that perhaps the presence of commensal organisms, particularly gut worms, normally present in the wild (but lacking in most modern, aseptic laboratory rodent colonies), keep immune responses in check. Motivated by this intriguing idea, these researchers tested the effects of prenatal helminth colonization on brain cytokine

expression, microglial sensitization, and cognitive dysfunction in response to postnatal bacterial infection in rats (Williamson et al., 2016). Perhaps surprisingly, the results of their study showed that prenatal colonization influenced offspring gut microbiome and immune sensitivity. Critically, helminth exposure early in life prevented the exaggerated brain cytokine response they had previously reported following bacterial infection in adulthood and prevented memory impairment (Williamson et al., 2011). In other words, the presence of the helminths actually buffered the developing immune system of rats against hyper-responsiveness to subsequent immune challenges in adulthood.

While the exact relationships between helminths, the brain, and cognition have yet to be fully explored, these findings are exciting as they suggest that “biome restoration” can alter the immune system and microbial community in important ways that buffer against the adverse effects of neonatal infection. They also suggest the importance of considering inflammation within evolutionary and ecological contexts (Demas and Carlton, 2015). While there is no denying that excessive or unabated inflammation can be detrimental, inflammatory responses more commonly serve to clear individuals of potentially life-threatening infections (Bilbo and Schwarz, 2012). Within this context, the findings of Williamson and colleagues suggest that this “hyper-reactive” immune response, rather than being maladaptive, is likely an adaptive response to living in an evolutionarily unclean world. Under the artificially aseptic conditions found in most modern laboratories, however, this hyperactivity is most often detrimental to an animal's health. By creating these aseptic conditions, we are unable to investigate the natural relationships that exist among the different members of the biome. While these findings point to potential opportunities for therapeutic interventions, including the possibility of helminth colonization used to treat conditions like allergies, inflammatory bowel disease, and autism, they have equally important implications for animal welfare and husbandry (Wammes et al., 2014). Quite simply, they provide compelling support for the idea, long appreciated by farmers and their families (but perhaps less so by animal care and use committees) that there may indeed be such a thing as “too clean.”

Collectively, the results from this study clearly demonstrate that organisms, including ourselves, do not exist in a microbial vacuum. Rather, we evolved within complex biomes co-inhabited by a wide range of “neighbors” (both friend and foe alike),

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including bacteria, protozoans, and helminths (Parker and Ollerton, 2013). These organisms regularly interact with and thus have the potential to shape development of our own immune systems. Further, these data add to the growing evidence that suggests depletion of our biome diversity might very well contribute to the dramatic rise in autoimmune and inflammatory disorders. While additional studies will surely be needed to understand the precise mechanisms behind these important findings, one thing is increasingly clear; there's no place like biome.

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