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means of recognizing bacterial and viral components to accelerate immunity, but if or how these cells directly sense fungal products, such as Zymosan, is still an open area of investigation.

This study also raises intriguing questions with regards to NET formation in mouse and human cavity tissues. As the authors note in their discussion, what is the role of CitH3+ DNA on the fluid-facing surface of FALCs during inflammation? Is this structural, or does it serve as a signal for other immune cells? Indeed, peritoneal macrophages infiltrate wounded tissues, where they promote tissue-regeneration by triggering release of necrotic cell DNA (Wang and Kubes, 2016). Perhaps the omental CitH3+ DNA that is exposed to the cavity space enables repair of FALCs in addition to limiting pathogen spread? It is also interesting to speculate as to whether the phenomena described here are specific to omentum or if FALC in other cavity spaces, like the mediastinal FALC in the pleural cavity, exhibit similar stromal-neutrophil crosstalk during inflammation.

The field of immunology is revealing how stromal cells regulate multiple aspects of immune responses within diverse tissue microenvironments. This study extends stromal control of immunity to neutrophils, a cell type that undergoes a seemingly supernatural form of death in NETosis. Fittingly, the authors characterize a non-classical form of this process in the omentum, a tissue whose function McLachlin and Denton whimsically speculate has been obfuscated by the taint of the occult (McLachlin and Denton, 1973).

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Something Else to Stress about: Perinatal Stress Attenuates CD8+ T Cell Activity in Adults

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Early-life stress has adverse health effects, but the underlying mechanisms are unclear. Hong et al. demonstrate that perinatal exposure to glucocorticoids in mice reprograms the neuroendocrine stress pathway. This results in reduced glucocorticoid levels in adults, leading to attenuated anti-tumor and anti-bacterial CD8+ T cell responses.

These crazy days of the COVID-19 pandemic expose us to new lifestyles, new emotional experiences, and obviously, new challenges to our immune systems. It is almost surprising how fast organisms adapt to changes in their environment. In part, this remarkable capacity can be attributed to the plasticity of the primary systems that mediate our interactions with the external world: the nervous and the immune systems. The maturation of these systems is sculpted by experience and thus unique to each individual. As these systems also interact with each other, the adaptation of one system is expected to affect the other. This is especially relevant in the context of the stress response, a central process of communication between the brain and the periphery known to affect immune activity (Dantzer, 2018).
To maintain homeostasis, the stress response must be tightly regulated. While a balanced and timely stress response prepares the body to deal with challenges and is vital for health, overwhelming and chronic stress is associated with the emergence of disease ranging from cardiovascular pathologies (Rosengren et al., 2004) to cancer (Armaiz-Pena et al., 2009). As organisms vary in their experiences, their stress mechanisms have to be adapted individually. Many of these adaptation processes take place during development. Indeed, early-life stress, which potentially predicts adverse life conditions, alters the activity of the neuroendocrine stress pathway, the hypothalamic-pituitary-adrenal (HPA) axis (van Bodegom et al., 2017). Stress-regulating pathways, and specifically the products of the HPA axis, glucocorticoids (GCs), are known to affect immune activity (Dantzer, 2018). Thus, it is expected that early-life stress, via HPA axis activation, will also have major implications on the adult immune system. Surprisingly, in spite of extensive epidemiological data indicating that stress in early life is associated with increased risk of disease, especially cancer, at adulthood, underlying mechanisms are relatively poorly understood (Kelly-Irving et al., 2013). In their paper in Cell, Hong et al. (2020) provide molecular, cellular, and functional evidence for changes in the activity of adult CD8+ T cells in mice that experienced early-life stress (Figure 1). The study offers a rare integrated perspective regarding the stress-induced changes in the HPA axis and their implications to the immune system’s capacity to cope with bacteria and cancer at adulthood.

To induce perinatal stress, the authors used dexamethasone (DEX), a synthetic analog of cortisol, in the drinking water of pregnant dams and tested long-term effects of this perinatal exposure to GCs. They found that perinatal DEX exposure reprogrammed the HPA axis manifested in the adult hippocampus by increased expression levels of one of the corticosterone (CORT) receptors, the mineralocorticoid receptor (MR). This adaptation enhanced the negative feedback of the HPA axis and decreased CORT levels under both basal and stressful conditions in adult mice. The authors then analyzed the effects of this attenuation in CORT levels on the immune system. They found that perinatal DEX exposure and the subsequent reduction in CORT levels specifically attenuated CD8+ T cell function and activation, partially due to alterations in the transcription factor T-bet. Functionally, the reduction in CD8+ T cell activation results in impaired anti-tumor and anti-bacterial responses. Thus, early-life stress modifies adult immunity through reprogramming of the HPA axis.

**Figure 1. Perinatal Stress Reprograms the HPA Axis and Attenuates Anti-bacterial and Anti-tumor CD8 T Cell Activity**
Perinatal glucocorticoids (GCs) exposure results in long-term reprogramming of the hypothalamic-pituitary-adrenal (HPA) axis. This is manifested by an increased mineralocorticoid receptor (MR) expression in the hippocampus of the adult offspring, thereby lowering the threshold for HPA negative feedback. The new set point of the HPA axis results in diminished levels of basal and stress induce GCs. Reduction in GCs signaling leads to attenuated CD8+ T cell function and activation, partially due to alterations in the transcription factor T-bet. Functionally, the reduction in CD8+ T cell activation results in impaired anti-tumor and antibacterial responses. Thus, early-life stress modifies adult immunity through reprogramming of the HPA axis.

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reduced inside the tumors as well as in tumor-draining lymph nodes in perinatal DEX-treated mice. Even at the early stage of tumor development, their CD8+ T cells showed reduced interleukin 2 (IL-2) and granzyme B expression. To directly test the role of CD8+ T cells in anti-tumor responses, they utilized OT-I mice and the E.G7-OVA lymphoma, which expresses OVA antigen, and adaptively transferred OT-I CD8+ T cells from mice with or without perinatal DEX exposure. Mice that received OT-I cells from control animals effectively suppressed E.G7-OVA tumor growth, while mice that received OT-I cells from perinatally DEX-exposed mice failed to control tumor growth. Such attenuated suppression of the anti-tumor and anti-bacterial immune response is consistent with the evolving understanding that prolonged exposure to GCs enhances immune activation, although GCs are classically known for their anti-inflammatory effects (Dantzer, 2018). These findings are also consistent with epidemiological data indicating that exposure to stressful events in early life increases the risk of cancer (Kelly-Irving et al., 2013). Furthermore, studies show that maternal exposure to a stressful life event during pregnancy increases the offspring’s risk of infectious disease in childhood (Henriksen and Thuen, 2015). Now, the findings by Hong et al. suggest that this increased risk persists to adulthood.

The authors found that perinatal stress results in long-term epigenetic changes in naive CD8+ T cells. ATAC sequencing (ATAC-seq) analysis revealed that naive CD8+ T cells have reduced chromatin accessibility to the Tbx21 locus, which encodes T-bet, a transcription factor that regulates naive T lymphocyte development. Interestingly, they also identified consensus GR binding sites in the affected sites of Tbx21 locus. Given that the epigenetic effects of stress were shown to be passed across multiple generations (Bohacek and Mansuy, 2013), these findings suggest that their immune outcomes may stretch beyond the lifetime of the individual.

The changes induced by perinatal GCs exposure affected the site at which immune cells develop: the bone marrow. The authors show that the effect is evident both in immune cells and within the bone marrow niche. By using bone marrow transplantation, Hong et al. demonstrate that alterations to the non-hematopoietic compartment of the bone marrow induced by perinatal stress contribute to the decreased activation of CD8+ T cells. This is in line with other studies indicating that the bone marrow is a niche sensitive to stress, although these studies mainly focused on the effects of another stress-regulating pathway, the sympathetic nervous system and its secretion of noradrenaline (Heidt et al., 2014).

The effects of early-life stress on the adult’s immune system and capacity to cope with diseases is supported by extensive epidemiological data. However, stress is a very complex phenomenon. As the authors indicate, early-life stress models have been reported to result in hyperactive or hypoactive HPA axis, accompanied by increased or decreased GCs levels (van Bodegom et al., 2017). These discrepancies depend on the properties of the stressful stimulus, such as the duration of the stimulus and developmental time window (van Bodegom et al., 2017). Hong et al. identified a critical time point after birth at which a single GCs application was sufficient to reduce GCs levels in adulthood. They also show that different stress models have distinct effects on the long-term activity of the HPA axis, and thus, their implications to the immune system vary. Moreover, even stress at adulthood appears to have inconsistent effects on the immune system. Some suggest that stress suppresses immunity, while others provide evidence that stress can induce inflammation and autoimmune conditions (Dhabhar, 2014). The current study characterized the cellular and functional effects of stress on a specific immune subset. However, not only is stress a complex system with numerous pathways and outcomes, it also affects most systems of the organism, including metabolism and blood pressure, each of which can themselves affect immunity; such interactions highlight the need to examine the effects of stress at the level of the physiology of the entire organism. The current study takes an important step toward the fulfillment of the emerging need for a systematic yet detailed characterization of the stress response, and its implications on immunity and physiology in general. Stress is evident in our daily lives, especially as the world is facing the COVID-19 pandemic. Given the prominent effects of stress on immunity, it is essential that we understand the underlying mechanisms of this interaction, as such an understanding can be crucial for the capacity to maintain our health during these trying times.

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