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INTRODUCTION

Neuro-immune interactions

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The immune system harbors immense potential energy, which must be harnessed even in the face of the most egregious assaults by pathogenic organisms. From the outside, it may seem that immunity operates on a binary ON/OFF switch. In the absence of infection, the immune system seems invisible. Challenge it with even a single danger signal, and the kinetic energy of immune cells appears to be released in full force. In reality, there are intrinsic checks and balances that control the magnitude of immune responsiveness, such as central tolerance, suppressive cytokines, Treg cells, and checkpoint inhibitors, to name a few. Collectively, these control mechanisms effectively stabilize the immune system so that self/non-self discrimination acts as the main switch to engage a response. While these intrinsic regulatory pathways control major immune processes such as antigen recognition, immune homeostasis is an important facet of immune regulation that is often under appreciated.

Both immune intrinsic and extrinsic mechanisms contribute to immune homeostasis, and in this issue of Seminars in Immunopathology, we will explore recent advances in our understanding of how the nervous system participates in immune homeostasis and how its dysregulation leads to inappropriate responses. Historically, the role of the nervous system in regulating immunity was marginalized until multiple neurotransmitter receptors were discovered to be expressed by immune cells, clearly indicating that the immune system responds to neural cues. Further proof of this interaction came with the description of sympathetic nerve fibers that innervate primary and secondary immune tissues, creating intimate interactions with immune cells. Here, we will explore some of those neuro-immune interactions that shape both the nature and magnitude of the immune response as well as immune surveillance activities under homeostasis.

Perhaps the most well-studied pathway of neurological control involves glucocorticoids, which have been used therapeutically for decades to treat inflammation and to mitigate the overwhelming cytokine storm that occurs in response to systemic infections. While expressed on many cells, the glucocorticoid receptor in immune cells, particularly innate cells, represents perhaps one of the most fundamental neuro-immune regulators that acutely blocks inflammatory cytokine secretion. Ikuta and colleagues provide an overview of glucocorticoids, the GC receptor, molecular interactions, and clinical interventions of this powerful primary immunomodulator [1]. Both sympathetic and parasympathetic neurotransmitters regulate physiological processes, and their neurotransmitter ligands, such as chatecholamines, play a significant role in regulating inflammation. Campos and Pacheco highlight the interaction between the dopaminergic and renin-angiotensin systems in modulating inflammatory processes in the context of inflammatory diseases [2]. Regulation of the autonomic nervous system and its associated neurotransmitters is under tight control of circadian rhythms. Virtually all organisms on earth's surface have evolved a molecular clock to time physiological processes to a light/dark cycle. The immune system is no exception, and recent studies have highlighted the significant impact of circadian rhythms on immunity. Brooks and Hooper review these studies, and place this burgeoning field in the context of how immunity operates at epithelial barriers [3]. One of the main oscillating neurotransmitters, norepinephrine, is component to perhaps one of the most widely studied neuro-immune pathways to date. We review the historical perspective on research into the adrenergic system and delve into new studies that highlight the adrenergic receptor as a key immunosuppressive cytokine and its involvement in controlling circadian behavior in immune cells [4]. Finally, neurological stress is an important neuro-regulatory pathway that has a major impact on diseases ranging from autoimmunity to cancer. Focusing on the adrenergic system in the context of external stress, Repasky and colleagues highlight

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recent advances in our understanding of this complex pathway in cancer biology and cancer immunotherapy [5].

I hope that you will gain a new appreciation and perspective on how external stimuli, sensed neurologically, directly impact immune responses. As we move further in our understanding of this complex interaction, we will no doubt uncover new avenues for therapeutic intervention, both pharmacologically and behaviorally.

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