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TACHYKININ-MEDIATED MODULATION OF THE IMMUNE RESPONSE

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1. ABSTRACT

Tachykinins represent a family of peptides which have significant effects on such diverse physiological responses as gut peristalsis, vascular permeability, and the transmission of pain. Traditionally, neurons have been identified as the major source of tachykinin peptides in peripheral tissues and in the central nervous system, resulting in their classification as neuropeptides or, more specifically, as neurokinins. The fact that a variety of cell types can express one or more members of the family of neurokinin receptors accounts for the remarkable ability of these tachykinin peptides to affect multiple organ systems and numerous biological responses.

Perhaps one of the most surprising findings during the last 15 years has been the understanding that expression of neurokinin receptors on leukocyte populations can be constitutive or inducible. This fact establishes a receptor-mediated mechanism by which tachykinin peptides can affect both innate and specific immune responses. Due to the numerous cytokines, chemokines, and other soluble mediators that can modulate leukocyte responses, the importance of tachykinin-mediated modulation of the immune response has met with some skepticism. The following reviews make a strong case for neurokinin receptor expression by leukocytes as a significant participant in host response. From hematopoiesis to antigen-specific T lymphocyte responses, tachykinins are present and can dramatically modulate maturation and responsiveness of these immune cells. Studies which document this surprising role for neurokinin receptor expression by leukocytes are detailed in the following reviews.

2. INTRODUCTION TO THE REVIEW: NON-NEURONAL MAMMALIAN TACHYKININ EXPRESSION

Drs. Nelson and Bost review the family of tachykinin peptides which have demonstrated effects on cells of the immune response (1). Perhaps the most surprising aspect of tachykinin expression is that there are non-neuronal sources of these peptides which are present at the site of immune responses. Thus, while tachykinins produced by peripheral neurons can influence immune responses, other cells, including leukocytes, can also be a source of such peptides. In fact, recent studies have identified a novel tachykinin, called hemokinin, which is preferentially expressed in peripheral tissues by leukocytes. This significant finding further emphasizes the potential for tachykinins to modulate the responses of leukocytes expressing neurokinin receptors.

3. INTRODUCTION TO THE REVIEW: TACHYKININS IN THE EMERGING IMMUNE RESPONSE: RELEVANCE TO BONE MARROW HOMEOSTASIS AND MAINTENANCE OF HEMATOPOIETIC STEM CELLS

From their beginning, the maturation of leukocyte precursors present in the bone marrow is influenced by the presence of tachykinins (2). Dr. Rameshwar and colleagues review the evidence demonstrating the importance of these peptides during hematopoiesis. Not only do hematopoietic cells express several types of neurokinin receptors, but there are also several potential sources of ligands, including the recently discovered hemokinin. Thus, the environment within the bone marrow that fosters leukocyte development is one which depends upon the presence of tachykinins. Perhaps the most striking evidence to date that demonstrates the importance of these peptides during hematopoiesis are the studies which document alterations in bone marrow homeostasis during disease states which alter tachykinin expression.

4. INTRODUCTION TO THE REVIEW: THE ROLE OF TACHYKININS ON BACTERIAL INFECTION

An optimal host response against bacterial pathogens depends upon expression of neurokinin

receptors. Dr. Pascual reviews the literature which supports this contention. In particular, it is clear that cells within both the innate and adaptive arms of the host response can respond to tachykinins by expressing neurokinin receptors. Therefore, tachykinin-mediated modulation of the response against bacterial pathogens is likely to occur at several steps during host immunity. This may be especially relevant for bacteria which invade at mucosal surfaces since these locations represent sites of high tachykinin content.

5. INTRODUCTION TO THE REVIEW: THE ROLE OF SUBSTANCE P, HEMOKININ AND THEIR RECEPTOR IN GOVERNING MUCOSAL INFLAMMATION AND GRANULOMATOUS RESPONSES

The host response against parasitic infections is also modulated by the presence of tachykinins and their receptors (3). Dr. Weinstock reviews the importance of the tachykinin, substance P, during the granulomatous inflammatory response to *Schistosoma mansoni* and other pathogens. It is especially important to note that responses mediated by neurokinin receptors can affect the nature of the T lymphocyte response. Thus, tachykinins act in concert with inflammatory cytokines to define the host response following infection. In fact, expression of neurokinin receptors by T lymphocytes governs IFN-gamma secretion and the T helper type 1 response.

6. INTRODUCTION TO THE REVIEW: SUBSTANCE P MODULATION OF THE ANTI-VIRAL RESPONSE

In addition to bacterial and parasitic infections, recent studies have demonstrated the importance of neurokinin receptor expression during the host response against viral infections. Despite the limited number of studies which have dealt with this subject, several important observations have been made. In particular the lack of neurokinin receptor expression can result in decreased cytotoxic T lymphocyte activity following infection with a gammaherpesvirus. Interestingly, this may represent alterations in the responsiveness of macrophages or dendritic cells which must support the development of cell mediated immunity. However it is also important to note that tachykinin expression during viral pathogenesis may also contribute to the pathophysiology associated with viral disease, especially during airway infections.

7. INTRODUCTION TO THE REVIEW: THE ROLE OF TACHYKININS IN CENTRAL NERVOUS SYSTEM INFLAMMATORY RESPONSES

Tachykinins have been designated neuropeptides due to their neuronal origin. Therefore it is surprising that so little attention has been given to the importance of neurokinin receptor signaling during inflammatory responses within the central nervous system. Dr. Marriott reviews our developing understanding of the contribution that tachykinins and their receptors might have during diseases of the central nervous system. Of particular importance is the finding that functional neurokinin receptors are present on microglia and astrocytes, demonstrating the potential for these cells to respond to tachykinins during infection or autoimmune diseases. Since tachykinins appear to augment inflammatory responses, this raises the possibility that neurokinin receptors may actually contribute to the pathophysiology within the central nervous system.

8. PERSPECTIVE

It is clear from this emerging body of evidence that expression of neurokinin receptors by leukocytes represents an important component of inflammatory responses. Most evidence demonstrates that tachykinins deliver pro-inflammatory signals, indicating that these peptides augment immune responses. This augmentation results in increased protective responses against pathogens, however it is also clear that the presence of tachykinins can contribute to the pathophysiology that can accompany inflammatory responses. The fact that effective agonists and antagonists of tachykinins exist suggests that pharmacological intervention might be possible to further augment immune responses or to limit tachykinin-mediated inflammation.

9. ACKNOWLEDGEMENT

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