ANTI-INFLAMMATORY/ANALGESICS: AN IN-DEPTH LOOK AT P38 MAP KINASES

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1 INTRODUCTION

1.1 Inflammatory Response and Inflammatory Pain

Inflammation in mammals is a complex biological response to the endogenous or exogenous products of injury or infection (danger signals), for example, pathogens, damaged cells, and inflammatory mediators. Cells in the immune system are equipped with receptors for these stimuli; notable examples are the interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), and Toll-like receptors. The cells in the innate branch of the immune response such as neutrophils, epithelial cells, and monocytes/macrophages are the first responders to such danger signals. Receptor ligation on these cells induces an acute cellular response that is characterized by the expression of a repertoire of early-response genes including genes that encode for pro-inflammatory cytokines (TNF-α, IL-6), chemokines (IL-8, Gro-α/CXCL1) and antibacterial agents (antimicrobial peptides, reactive oxygen/nitrogen species). The mediators that are produced from early-response gene transcription will prompt additional cellular and physiological events that collectively facilitate eradication of the irritant that initiated the response [1]. In doing so, however, the inflammatory mediators inescabably cause collateral damage to host tissues and can stimulate inflammatory and neuropathic pain [2]. Inflammatory pain is associated with swelling and damage in the inflected tissue via the natural influx of immune cells and subsequent release of proteases and toxic agents. Neuropathic pain results from the activation and sensitization of primary sensory nociceptors in the peripheral nervous system (PNS) and/or via dorsal horn and brain neurons in the central nervous system (CNS). Mediators of both peripheral and central sensitization to pain include prostaglandins, nitric oxide (NO), and cytokines (TNF-α and IL-1β). To minimize the negative effects that can be incurred during an inflammatory response, the process is designed to be inherently self-limiting. Receptor ligation inevitably induces an active anti-inflammatory response through the production of anti-inflammatory mediators [e.g., IL-10, transforming growth factor-β (TGFβ)] and the expression and/or activation of cellular proteins that calm the cellular response to stimuli. This culminates in physiological processes such as wound healing and a reversion to basal levels of cellular activity in which pro-inflammatory responses are constrained by negative regulation. As both inflammatory and neuropathic pain are linked to the inflammatory episode, sensations of pain should cease with the resolution of the inflammatory response.

The coordinated induction and resolution of the inflammatory response is a complex system that depends on the balanced expression and management of numerous positive and negative regulatory molecules. The family of mitogen-activated protein (MAP) kinases are key signaling molecules broadly expressed in cells and tissues of the immune system. MAP kinases profoundly influence many aspects of cellular physiology via regulation of gene transcription, protein synthesis, cell-cycle

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