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REVIEW

Gene-specific control of the TLR-induced inflammatory response

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Abstract Toll-like receptors (TLRs) induce a complex inflammatory response that functions to alert the body to infection, neutralize pathogens, and repair damaged tissues. An excessive or persistent inflammatory response can be fatal, so multiple regulatory mechanisms have evolved to control the extent and duration of inflammation. Our current understanding of the control of inflammation is based on negative regulation of TLR signaling. However, TLR-induced genes have diverse functions, and control of signaling pathways does not allow for groups of genes with distinct functions to be differentially regulated. Recent evidence suggests that many inflammatory genes are instead regulated by epigenetic modifications to individual promoters. This level of control allows a single gene to be expressed or silenced according to its function, irrespective of other genes induced by the same receptor, and therefore is "gene-specific." Gene-specific control of the TLR-induced inflammatory response is an emerging paradigm in the study of inflammation, and may provide the basis for selective modulation of the inflammatory response.

Contents

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Overview

Inflammation is a complex response to infection, trauma, and other conditions of homeostatic imbalance [1]. Because this response can cause dramatic changes in host physiology, dysregulated inflammation leads to tissue pathology and underlies many human diseases [2]. Current treatments for the diseases caused by persistent or unchecked inflammation often don't work, have systemic side effects, or leave patients susceptible to infection. Therefore, it is essential to find ways to safely modulate the inflammatory response. This review will discuss the concept of gene-specific control of the inflammatory response, specifically in the context of the phenomenon of lipopolysaccharide (LPS) tolerance—the altered responsiveness of cells or organisms to repeated doses of bacterial LPS. We suggest that epigenetic modifications are the basis for selective control of different aspects of inflammation.

Inflammation: a complex response initiated by the innate immune system

The inflammatory response to infection consists of multiple components with distinct functions, including proinflammatory mediators, which coordinate the immune response, and antimicrobial effectors, which directly target pathogens. Toll-like receptors (TLRs) are the most well-studied of a growing group of innate immune receptors responsible for initiating inflammation [3]. These receptors are expressed by multiple cell-types in the immune system, and recognize structures present on microbes that are not found in the host [3]. Almost immediately after microbes invade, microbial products signal through TLRs on tissue-resident mast cells and macrophages, activating these cells to produce histamine and proinflammatory cytokines. The proinflammatory mediators activate endothelial cells, which then recruit leukocytes, and leak plasma proteins, clotting factors, and complement into the infected tissue. Complement factors both directly target microbes and further activate leukocytes and endothelial cells. Clotting factors stop bleeding and section off the infected area, preventing microbes from spreading. Antimicrobial peptides and proteins (AMP) are also secreted at the site of infection. In contrast to the inflammatory mediators mentioned above, these antimicrobial factors recognize components of bacterial cell walls that are not present in mammalian cell membranes, and therefore target pathogens specifically while having minimal, if any, affect on host tissue physiology [4].

If the pathogen cannot be contained by the initial local response, a systemic response is activated. IL-1 and TNFα produced by macrophages induce fever, presumably making the body temperature inhospitable to pathogens. Macrophages also produce IL-6, which activates the acute phase response (APR) of the liver. The APR induces multiple metabolic and neuroendocrine changes in the body [5]. APR effector proteins include metabolic modulators, additional coagulation factors, anti-inflammatory factors, and opsonins [5]. In addition, peptide hormones, steroid hormones, and endorphins are suppressed or increased, depending on the hormone [5]. Thus, the body undergoes profound alterations in systemic homeostasis to support host defense.

Consequences of dysregulated inflammation

Because the inflammatory response causes dramatic changes in tissue physiology, dysregulated inflammation can lead to a variety of pathological conditions, including septic shock, autoimmunity, atherosclerosis and metabolic syndrome [2]. Recently, many diseases have become linked to a low-grade, chronic inflammatory response. Some of these diseases have been definitively tied to chronic infection. For example, infection with Helicobacter pylori can lead to gastric cancer [2]. Other inflammatory etiologies are more cryptic in nature: no infectious cause has been found for the excessive production of SAA (serum amyloid A) in systemic amyloidoses [6]. Chronic inflammation is characterized by an escalating cycle of tissue damage followed by unproductive tissue repair, leading to breaks in self-tolerance (autoimmunity), malignant transformation (tumors), or deleterious changes in tissue morphology and function (fibrotic change) [2].

In contrast to the "smoldering" diseases of chronic inflammation, excessive acute inflammation can quickly be lethal. One of the most dramatic consequences of overwhelming acute inflammation is septic shock due to bacterial LPS, the most potent inducer of the inflammatory response. Too much LPS in the blood leads to excessive production of proinflammatory cytokines including IL-1, TNFα, and IL-6 [7]. These cytokines activate endothelium systemically, leading to vascular instability and leakiness [8]. At the same time, clotting factors are induced and anti-clotting factors suppressed, leading to an enhanced production of fibrin clots in small blood vessels [9]. Together with the leakage of fluid from capillaries, this excessive clotting stops blood supply to tissues, and eventually leads to multiple organ dysfunction and death; up to 50% of patients diagnosed with septic shock die, even when given the best supportive care and antibiotics [9].

Patients who survive the acute phase of septic shock often become immunocompromised and susceptible to superinfections [7]. This state is known as immunoparalysis, and is thought to be caused by an overproduction of anti-inflammatory mediators compensating for the initial overproduction of proinflammatory mediators [7]. This compensatory anti-inflammatory state may account for some of the lethality of septic shock [7]. Thus proinflammatory cytokines and coagulation factors are essential for initiating host defense, but their persistent production is not necessary for protection. Furthermore, when their production is prolonged or excessive, they can cause systemic host damage.

Regulation of the TLR-induced inflammatory response

Accordingly, to avoid host damage, the inflammatory response must be highly regulated at multiple levels. However, the current understanding of the regulatory mechanisms of inflammation is limited primarily to the control of TLR signaling pathways. Toll-like receptor 4 (TLR4), the prototypical member of the TLR family, is the receptor for LPS [3]. TLR4 activates several distinct signaling modules, including the MAP kinases, NFκB, and IRFs (Fig. 1A) [3]. This occurs through two pathways: one that depends on the adaptor protein MyD88, and one that is MyD88