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Toll-like receptor 4 signalling pathway: a therapeutic target for multiple diseases

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ABSTRACT

The Toll-like receptor 4 (TLR4) signalling pathway is integral to the innate immune response and plays a pivotal role in numerous disease states, including infections, autoimmune disorders, metabolic conditions, and cancers. The activation of TLR4 initiates a cascade of signalling events that modulate key cellular processes and immune functions. The dysregulation of TLR4 signalling has been implicated in several pathophysiological conditions, particularly those involving chronic inflammation and immune dysfunction. This short review examines the mechanisms by which TLR4 signal transduction pathways influence cellular behaviour, highlights TLR4-mediated disease processes, and surveys current therapeutic strategies targeting TLR4. Evidence suggests that TLR4 inhibition can improve clinical outcomes in various settings, underscoring its therapeutic potential. We, herein, provide a succinct synthesis of recent advances in TLR4 research, emphasizing its viability as a clinical target. Finally, we consider the future implications of TLR4-focused therapies, and how such approaches might be integrated into routine practice in order to treat a broad spectrum of diseases.

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1. Introduction

The Toll-like receptor 4 (TLR4) is a critical component of the innate immune system, playing a central role in pathogen recognition and the coordination of immune responses. As a member of the Toll-like receptor family, TLR4 detects molecular patterns associated with microbial infections; most notably, lipopolysaccharides (LPS) found in the outer membranes of Gram-negative bacteria. Upon activation, TLR4

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initiates a cascade of intracellular signalling events that lead to the production of pro-inflammatory cytokines, thereby amplifying immune responses against invading pathogens[1].

Aberrant or dysregulated TLR4 signalling is increasingly implicated in the pathogenesis of various diseases, including chronic inflammatory disorders, autoimmune conditions, and certain malignancies. For example, TLR4-mediated signalling has been linked to heightened inflammatory responses and exacerbated tissue damage in diseases such as rheumatoid arthritis (RA) and type 2 diabetes. Emerging evidence also suggests that the modulation of TLR4 activity offers a promising avenue for therapeutic intervention across a wide range of pathological contexts. For example, preclinical studies indicate that TLR4 antagonists may attenuate inflammatory processes and improve clinical outcomes in chronic disease states, thereby reinforcing the receptor's appeal as a therapeutic target. Furthermore, deeper insight into the regulatory mechanisms governing TLR4 signalling could inform the development of novel therapeutic strategies, either to potentiate immune responses during infection or to dampen them in inflammatory disorders[2].

TLR4 is a membrane-associated protein with an estimated molecular weight of approximately 95 kDa. It features a leucine-rich extracellular domain and a cytoplasmic Toll/interleukin-1 receptor (TIR) domain, which enables interaction with a diverse range of ligands[3]. TLR4 primarily recognizes pathogen-associated molecular patterns (PAMPs), such as bacterial LPS, as well as damage-associated molecular patterns (DAMPs) released during tissue injury. Upon engagement, the receptor triggers signalling cascades that culminate in the production of pro-inflammatory cytokines; key mediators of the immune defence against pathogenic challenges[4].

TLR4-mediated signalling proceeds *via* two distinct pathways: the myeloid differentiation primary response 88 (MyD88)-dependent pathway and the TIR-domain-containing adapter-inducing interferon-beta (TRIF)-dependent pathway. The MyD88-dependent signalling cascade is initiated at the cell surface and involves the adaptor protein MyD88, ultimately leading to the production of cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). In contrast, the TRIF-dependent pathway is triggered following receptor internalization into endosomes, where TLR4 interacts with TRIF and the TRIF-related adaptor molecule (TRAM). This second pathway induces the production of type I interferons, which enhance antiviral immunity[5].

TLR4 is predominantly expressed in immune cells, including macrophages and dendritic cells, but it is also detectable in various non-immune cell types, such as epithelial and endothelial cells. Its expression is modulated by numerous environmental cues and inflammatory mediators, ultimately influencing the breadth and magnitude of immune responses[3]. This short review aims at examining the role of TLR4 in disease progression and to explore strategies for targeting this receptor in the context of diverse clinical conditions.

2. Role of TLR4 in disease progression

2.1. Cardiovascular diseases

TLR4 plays a significant role in inflammatory signalling pathways that aggravate heart failure. Experimental models deficient in TLR4 demonstrate improved cardiac function and reduced inflammatory marker expression, thereby suggesting that TLR4 inhibition holds promise as a therapeutic strategy for heart failure[6].

TLR4 is also centrally involved in mediating post-ischaemic inflammation following stroke. Its activation contributes to neurological deterioration *via* the upregulation of pro-inflammatory cytokines, including TNF-α and IL-6; key drivers in cardiovascular and cerebrovascular pathology. Accordingly, TLR4 is considered a viable therapeutic target in stroke management. Recent studies are increasingly focused on the development of targeted TLR4 inhibitors in order to attenuate inflammation and improve clinical outcomes in cardiovascular and cerebrovascular diseases. In fact, by blocking TLR4, one may yield protective effects by modulating the inflammatory cascade[3].

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2.2. Metabolic disorders; obesity

TLR4 activation has been linked to chronic low-grade inflammation in obesity. This inflammatory milieu promotes the release of cytokines that exacerbate insulin resistance and accelerate the progression of metabolic syndrome[5].

2.3. Autoimmune diseases; RA

RA is a chronic autoimmune condition characterized by persistent joint inflammation, progressive joint destruction, and functional impairment. TLR4 is increasingly recognized as a key factor in RA pathophysiology. As a pattern recognition receptor, TLR4 detects both PAMPs and DAMPs, with its activation being implicated in the initiation and perpetuation of inflammation in RA[7].

2.4. Infectious diseases and sepsis

TLR4 plays an essential role in initiating immune responses to bacterial infections. However, excessive stimulation can lead to a hyper-inflammatory state, thereby increasing the risk of sepsis and septic shock[8].

2.5. Neurological disorders and Alzheimer's disease

TLR4 is involved in neuroinflammatory mechanisms relevant to Alzheimer's disease. Its activation is associated with the deposition of amyloid-β plaques and subsequent neuronal degeneration[9].

2.6. Cancer / tumour progression

TLR4 contributes to tumour progression by amplifying inflammation within the tumour microenvironment. Its activation is correlated with enhanced tumour growth and metastasis across multiple cancer types. Chronic inflammation induced by TLR4 plays a documented role in oncogenesis. Cytokines released following TLR4 activation promote cell survival, proliferation, and angiogenesis. Moreover, neoplastic tissues may exploit TLR4 signalling in order to evade immune surveillance. The activation of this receptor can drive the production of immunosuppressive factors that hinder anti-tumour immunity and support unchecked tumour expansion[10]. Recent research has explored combination therapies involving TLR4 inhibitors alongside immunotherapeutic or chemotherapeutic agents; these synergistic approaches may increase treatment efficacy by re-sensitizing tumours to immune-mediated eradication.

3. Conclusion

The TLR4 signalling pathway presents a compelling target for therapeutic development across a wide range of diseases. Its involvement in the pathogenesis of infectious, autoimmune, metabolic, oncologic, and neurodegenerative conditions underscores its relevance to translational medicine. Continued investigation is required in order to unravel the complexity of TLR4-mediated pathways and to design precise interventions capable of modulating immune activity and improving clinical outcomes.

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Conflicts of interest

None exist.

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