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Review Article

Regulation of polarization of lung macrophages by Nur77/Nr4a1

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ABSTRACT

Nur77, also known as NR4A1 (nuclear receptor subfamily 4 group A member 1), is a transcription factor belonging to the NR4A subfamily of nuclear receptors. Emerging evidence suggests its involvement in modulating macrophage polarization states.

Macrophages are versatile immune cells that can adopt distinct functional states depending on the signals they receive from their microenvironment. Two main polarization states are commonly recognized: the classically activated (M1) phenotype, associated with pro-inflammatory responses, and the alternatively activated (M2) phenotype, linked to tissue repair and immunoregulation. The balance between M1 and M2 polarization is critical for maintaining immune homeostasis in the lung.

Several studies have indicated that Nur77/NR4A1 may influence macrophage polarization towards the M1 phenotype. Also, other studies have also indicated a potential role for Nur77 in regulating M2 polarization of macrophages. Research findings suggest a dual role for Nur77 in modulating macrophage polarization, potentially promoting both M1 and M2 phenotypes depending on the context and specific signaling cues.

It's important to note that the exact mechanisms underlying Nur77's regulation of macrophage polarization in the lung are still being elucidated. Further research is needed to fully understand the complex interplay between Nur77, other transcription factors, and the signaling pathways involved in lung macrophage polarization. Nonetheless, the current evidence suggests that Nur77/NR4A1 is a key player in orchestrating the immune responses of lung macrophages and may have a role in regulating their polarization towards both M1 and M2 phenotypes.

1. Introduction

Nur77, also known as NR4A1, is a nuclear receptor belonging to the NR4A subfamily, which includes Nur77 (NR4A1), Nurr1 (NR4A2), and NOR-1 (NR4A3). These receptors are considered orphan receptors because their endogenous ligands are still largely unknown.[1] Nur77 is a transcription factor that can translocate to the nucleus and directly bind to DNA, regulating the expression of target genes involved in various biological processes.[2] Nur77 is widely expressed in different tissues and cell types, including immune cells such as macrophages, T cells, and dendritic cells. It is involved in diverse physiological and pathological processes, including apoptosis, inflammation, metabolism, and cell differentiation. Nur77 can function as both a transcriptional activator and repressor, depending on the cellular context and interacting co-factors.[3]

In the context of immune responses, Nur77 has been implicated in regulating the function of immune cells, including macrophages. Its role in modulating macrophage polarization and function has gained considerable attention.[4] By binding to specific DNA sequences called

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Nur response elements (NurREs), Nur77 can influence the expression of target genes involved in macrophage activation and polarization.[5] The activity of Nur77 in macrophages is tightly regulated by various signaling pathways and stimuli. For instance, pro-inflammatory stimuli such as lipopolysaccharide (LPS) can induce the expression and activation of Nur77 in macrophages. Nur77 has been shown to promote the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), in response to LPS stimulation.[6]

Furthermore, Nur77 has been implicated in regulating the metabolic and phagocytic functions of macrophages. It has been reported to play a role in lipid metabolism and cholesterol efflux in macrophages, which are essential processes for foam cell formation and atherosclerosis development.[7] Additionally, Nur77 has been shown to promote phagocytosis and clearance of apoptotic cells by macrophages, contributing to tissue homeostasis and resolution of inflammation[8]. Overall, Nur77/NR4A1 is a versatile transcription factor that plays a role in regulating immune responses, including macrophage function and polarization. Its precise mechanisms of action and specific target genes in the context of lung macrophage polarization are still an active area of research. In this brief review article, we explore distinct functional states of macrophages depending on the signals they receive from their microenvironment with special emphasis on lung injury.

2. Influence of Nur77/NR4A1 on Macrophage Polarization Towards the M1 Phenotype

The M1 phenotype macrophages represents a classically activated state associated with pro-inflammatory responses, pathogen clearance, and antigen presentation. The transcription factor Nur77, also known as NR4A1, has emerged as a potential regulator of macrophage polarization. Researchers have given insights on some of the mechanisms by which Nur77/NR4A1 may influence macrophage polarization towards the M1 phenotype. The expression and activity of Nur77/NR4A1 have been linked to the promotion of M1 polarization in macrophages.[7] Studies have demonstrated that Nur77/NR4A1 expression is upregulated in response to pro-inflammatory stimuli, such as lipopolysaccharide (LPS) or interferon-gamma (IFN-γ). Nur77/NR4A1 has been shown to enhance the production of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-12 (IL-12), which are characteristic of the M1 phenotype.[9]

Nur77/NR4A1 exerts its effects on M1 polarization through various mechanisms. It can directly bind to the promoter regions of pro-inflammatory genes, such as IL-6 and TNF-α, leading to their upregulation. Furthermore, Nur77/NR4A1 can interact with other transcription factors, such as nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1), to enhance their transcriptional activity, thereby amplifying the inflammatory response.[10] Additionally, Nur77/NR4A1 has been implicated in promoting the expression of inducible nitric oxide synthase (iNOS), a key enzyme involved in the production of nitric oxide (NO) and the antimicrobial response[11]. Apart from its role in cytokine production, Nur77/NR4A1 can influence the metabolic rewiring of macrophages towards an M1 phenotype. It has been reported to enhance glycolysis, a metabolic pathway associated with M1 polarization and increased energy production. By regulating the expression of genes involved in glucose metabolism, such as glucose transporter 1 (GLUT1) and hexokinase 2 (HK2), Nur77/NR4A1 promotes glycolysis and supports the energy demands of M1 macrophages.[12]

Understanding the implications of Nur77/NR4A1 in M1 polarization is crucial for uncovering the underlying mechanisms and potential therapeutic targets. Dysregulated M1 polarization can contribute to chronic inflammation, autoimmune diseases, and certain cancers. Therefore, modulation of Nur77/NR4A1 activity may hold therapeutic potential for managing these conditions.[13] The activity of Nur77/NR4A1 in macrophages is tightly regulated by various signaling pathways and co-factors. In addition to pro-inflammatory stimuli, other factors, such as Toll-like receptors (TLRs) and interferon regulatory factors (IRFs), can also influence the expression and activation of Nur77/NR4A1. Moreover, epigenetic modifications, including DNA methylation and histone acetylation, can modulate Nur77/NR4A1 expression, thereby affecting macrophage polarization.[14]

While the current understanding of Nur77/NR4A1's role in M1 polarization has provided valuable insights, several aspects remain to be explored. Further studies are needed to elucidate the specific signaling pathways and co-factors that regulate Nur77/NR4A1-mediated M1 polarization. Additionally, identifying the precise target genes and understanding their functional consequences will enhance our understanding of the underlying mechanisms. Nur77/NR4A1 has emerged as a key regulator of macrophage polarization towards the M1 phenotype. Its ability to promote the production of pro-inflammatory cytokines, enhance metabolic rewiring, and influence the expression of critical M1-associated genes underscores its significance in orchestrating the inflammatory response. Elucidating the intricate molecular mechanisms and regulatory networks associated with Nur77/NR4A1-mediated M1 polarization will pave the way for potential therapeutic interventions in various inflammatory diseases and immunological disorders.[15]

3. Influence of Nur77/NR4A1 on Macrophage Polarization Towards the M2 Phenotype

The M2 phenotype represents an alternatively activated state associated with tissue repair, immunoregulation, and anti-inflammatory responses. In recent years, the transcription factor Nur77, also known as NR4A1, has garnered attention for its potential role in modulating macrophage polarization towards the M2 phenotype.[7] Researchers have given insights on some of the mechanisms by which Nur77/NR4A1 may influence macrophage polarization towards the M2 phenotype. Emerging evidence suggests that Nur77/NR4A1 can play a role in promoting M2 polarization of macrophages. Several studies have demonstrated that Nur77/NR4A1 expression is upregulated during M2 polarization in response to specific stimuli, such as interleukin-4 (IL-4) and interleukin-13 (IL-13), which are known inducers of M2 polarization. Activation of Nur77/NR4A1 has been associated with the upregulation of M2 markers, including arginase-1 (Arg1), mannose receptor (CD206), and chitinase-like proteins (Ym1 and Fizz1). These markers are indicative of the M2 phenotype and are involved in tissue repair, extracellular matrix remodeling, and immune modulation.[16]

Nur77/NR4A1 exerts its effects on M2 polarization through various mechanisms. It can directly bind to the promoter regions of M2-associated genes and enhance their expression. For instance, Nur77/NR4A1 has been shown to bind to the promoter region of Arg1, a key enzyme involved in M2 macrophage-mediated tissue repair and immunoregulation, leading to its upregulation.[17] Moreover, Nur77/NR4A1 can interact with other transcription factors, such as peroxisome proliferator-activated receptor gamma (PPARγ) and Kruppel-like factor 4 (KLF4), to promote their transcriptional activity and amplify the M2 polarization response.[18] Additionally, Nur77/NR4A1 has been implicated in enhancing the phagocytic activity of M2 macrophages. It has been shown to regulate the expression of scavenger receptors, such as CD36 and CD163, which are involved in the recognition and uptake of apoptotic cells and debris. This enhanced phagocytic capacity of M2 macrophages contributes to tissue homeostasis and resolution of inflammation.[7]

The activity of Nur77/NR4A1 in macrophages is tightly regulated by various signaling pathways and co-factors. Several factors, including IL-4/IL-13-induced signaling cascades and activation of the STAT6 transcription factor, have been implicated in Nur77/NR4A1 upregulation during M2 polarization.[19] Additionally, epigenetic modifications, such as DNA methylation and histone acetylation, can influence Nur77/NR4A1 expression and subsequently impact M2 polarization. Understanding the implications of Nur77/NR4A1 in M2 polarization has significant therapeutic potential. Dysregulated M2 polarization has been implicated in various diseases, including fibrosis, chronic inflammation, and cancer. Modulation of Nur77/NR4A1 activity may offer a promising approach to promote beneficial M2 responses and mitigate pathological conditions associated with dysregulated macrophage polarization.[7]

While our understanding of the influence of Nur77/NR4A1 on M2 polarization has advanced, further investigations are needed to unravel the intricate molecular mechanisms and specific target genes involved. Elucidating the precise signaling pathways, co-factors, and epigenetic modifications that regulate Nur77/NR4A1-mediated M2 polarization will deepen our understanding of macrophage biology and pave the way for potential therapeutic interventions in diseases associated with dysregulated polarization. Nur77/NR4A1 emerges as a potential regulator of macrophage polarization towards the M2 phenotype. Its ability to enhance the expression of M2-associated markers, promote phagocytic activity, and influence key transcription factors highlights its significance in modulating the tissue repair and immunoregulatory functions of M2 macrophages. Unraveling the underlying mechanisms and identifying specific target genes will shed light on the therapeutic potential of Nur77/NR4A1 modulation in conditions where promoting M2 polarization is beneficial.[18]

4. Role of Nur77/NR4A1 in Orchestrating Immune Responses and Macrophage Polarization in Lung Injury

Lung injury, whether caused by infections, pollutants, or other insults, triggers a complex immune response aimed at restoring tissue homeostasis. Macrophages, as key immune cells in the lung, play a critical role in this process.[19] The transcription factor Nur77, also known as NR4A1, has emerged as a significant regulator of immune responses and macrophage polarization in lung injury. Researchers have explored the role of Nur77/NR4A1 in orchestrating immune responses and its potential involvement in regulating macrophage polarization towards both M1 and M2 phenotypes in the context of lung injury.[20]

Nur77/NR4A1 has been identified as a key player in lung injury, as its expression and activity are modulated in response to various insults. Studies have demonstrated that Nur77/NR4A1 levels are upregulated in lung macrophages upon injury, indicating its potential involvement in the immune response. In lung injury models, Nur77/NR4A1 has been associated with the regulation of inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), suggesting its role in promoting M1 polarization.[7,18]

Furthermore, Nur77/NR4A1 has been implicated in the resolution phase of lung injury, where the immune response shifts towards tissue repair and anti-inflammatory processes. During this phase, macrophages adopt an M2-like phenotype to facilitate tissue healing and remodeling.

Nur77/NR4A1 has been shown to enhance M2 polarization in macrophages, promoting the expression of M2 markers, such as arginase-1 (Arg1) and mannose receptor (CD206). This suggests that Nur77/NR4A1 may play a role in regulating both M1 and M2 phenotypes in lung injury, depending on the stage and context of the immune response.[21]

The regulation of Nur77/NR4A1 in lung injury is complex and involves various signaling pathways and co-factors. Several factors, including pro-inflammatory cytokines, Toll-like receptor (TLR) ligands, and oxidative stress, have been shown to induce Nur77/NR4A1 expression in lung macrophages. Moreover, downstream signaling molecules, such as mitogen-activated protein kinases (MAPKs) and nuclear factor-kappa B (NF-κB), are implicated in mediating Nur77/NR4A1 activation and its effects on macrophage polarization.[11,22]

Understanding the implications of Nur77/NR4A1 in lung injury has significant clinical relevance. Dysregulated immune responses and macrophage polarization can contribute to the pathogenesis of lung diseases, including acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), and asthma. Modulation of Nur77/NR4A1 activity may offer therapeutic opportunities to regulate macrophage polarization and control the inflammatory and reparative processes in these conditions.[23]

5. Conclusion

While our understanding of the role of Nur77/NR4A1 in orchestrating immune responses and macrophage polarization in lung injury has advanced, further investigations are necessary to elucidate the precise mechanisms and signaling pathways involved. Future studies should focus on deciphering the context-dependent regulation of Nur77/NR4A1 in lung macrophages during different phases of lung injury. Additionally, identifying specific target genes and downstream signaling pathways influenced by Nur77/NR4 A1 will enhance our understanding of its functional implications in lung immunity and disease. In conclusion, Nur77/NR4A1 emerges as a key player in orchestrating immune responses and regulating macrophage polarization in lung injury. Its potential involvement in both M1 and M2 phenotypes highlights its context-dependent role in the immune response and tissue repair processes. Further investigations into the regulation and functional consequences of Nur77/NR4A1 in lung injury will deepen our understanding of lung immunology and potentially lead to therapeutic strategies aimed at modulating macrophage polarization for better clinical outcomes.

6. Conflicts of interest

There are no conflicts of interest.

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