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Review Article

Manipulating macrophage polarization through gene manipulation techniques in lung injury

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ARTICLE INFO

Article history:
Received 15-05-2023
Accepted 30-06-2023
Available online 27-07-2023

Keywords:
Macrophages play
Lung injury

ABSTRACT

Macrophages play a critical role in lung injury and repair processes. Their functions can be broadly classified into two polarized phenotypes. The M1 macrophages promote inflammation and defense against pathogens, while the M2 macrophages are involved in tissue repair and resolution of inflammation.
Gene manipulation techniques can be used to modulate macrophage polarization during lung injury. 1. Transcription factors: Transcription factors are proteins that regulate gene expression. Manipulating the expression or activity of specific transcription factors can influence macrophage polarization. 2. Cytokines and chemokines: Cytokines and chemokines are small signaling molecules that mediate immune responses. They can be used to manipulate macrophage polarization by inducing the expression of specific cytokines. 3. MicroRNAs (miRNAs): miRNAs are small non-coding RNA molecules that regulate gene expression at the post-transcriptional level. Certain miRNAs have been identified as regulators of macrophage polarization. 4. Genetic engineering: Genetic engineering techniques, such as CRISPR-Cas9, can be used to directly modify genes involved in macrophage polarization. By introducing specific genetic modifications, researchers can enhance or suppress the expression of genes associated with M1 or M2 polarization.
Manipulating macrophage polarization through gene manipulation techniques holds promise for modulating immune responses and promoting lung repair during injury.

1. Introduction

Lung injury, whether caused by infection, inflammation, or other factors, often involves a complex interplay between immune cells and the lung tissue.[1] Macrophages, as key players of the immune system, exhibit a remarkable phenotypic plasticity and can adopt different functional states, known as polarizations, to exert diverse roles in lung injury and repair.[2] In this review article, we delve into the significance of transcription factors, cytokines and chemokines, MicroRNAs and genes involved in macrophage polarization, discuss the specifics involved, and highlight their potential therapeutic applications in the context of lung injury.

2. Transcription Factors

Transcription factors serve as master regulators of gene expression, dictating the fate and functional properties of cells, including macrophages. Manipulating the expression or activity of specific transcription factors can influence macrophage polarization and consequently impact the immune response during lung injury.[3]

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https://doi.org/10.18231/j.achr.2023.019

2.1. Interferon regulatory factor 5 (IRF5)

IRF5 is a transcription factor that promotes M1 polarization and pro-inflammatory responses. Studies have shown that IRF5-deficient macrophages exhibit impaired M1 polarization, leading to reduced inflammation and tissue damage in models of lung injury. Conversely, overexpression of IRF5 enhances M1 polarization and exacerbates lung inflammation.[4]

2.2. Signal transducer and activator of transcription 6 (STAT6)

STAT6 is a transcription factor involved in promoting M2 polarization and anti-inflammatory responses. Activation of STAT6 by interleukin-4 (IL-4) or IL-13 leads to enhanced M2 polarization in macrophages. In lung injury models, STAT6-deficient mice display impaired M2 polarization, resulting in delayed tissue repair and resolution of inflammation.[5]

2.3. Nuclear factor-kappa B (NF-κB)

NF-κB is a transcription factor implicated in the regulation of various immune responses, including macrophage polarization. Activation of NF-κB signaling pathway promotes M1 polarization and pro-inflammatory cytokine production in macrophages. Inhibition of NF-κB signaling has been shown to shift macrophage polarization towards an anti-inflammatory M2 phenotype.[6]

2.4. Peroxisome proliferator-Activated receptors (PPARs)

PPARs, particularly PPAR-γ, have been identified as key transcription factors regulating macrophage polarization. PPAR-γ activation promotes M2 polarization and the expression of anti-inflammatory mediators. Pharmacological activation of PPAR-γ in lung injury models has shown beneficial effects, reducing inflammation and promoting tissue repair.[7]

The ability to manipulate transcription factors opens up exciting therapeutic opportunities for modulating macrophage polarization in lung injury. Targeting specific transcription factors may allow for fine-tuning the immune response, promoting tissue repair while preventing excessive inflammation and tissue damage. However, several challenges and future directions need to be considered. Efforts should focus on developing strategies that selectively target transcription factors in macrophages while minimizing off-target effects.[8] Novel delivery systems and gene-editing technologies, such as CRISPR-Cas9, may aid in achieving cell-specific modulation of transcription factors.[9] The timing of transcription factor manipulation is crucial, as the immune response during lung injury undergoes dynamic changes. Determining the optimal window for intervention, such as early during the pro-inflammatory phase or later during the resolution phase, will be essential for effective therapeutic strategies.[10] Considering the complexity of lung injury, combining strategies that target multiple transcription factors or utilize a combination of transcription factor manipulation with other immune-modulatory approaches may yield enhanced therapeutic outcomes.[11] Translating transcription factor manipulation strategies to clinical settings will require rigorous preclinical studies and safety assessments. Furthermore, exploring the feasibility of small molecule agonists or antagonists targeting transcription factors may offer alternative therapeutic avenues.[12] Given the heterogeneity of lung injury and varying responses among individuals, personalized approaches that consider patient-specific factors, such as genetic variations and disease subtypes, may optimize the efficacy of transcription factor-based therapies.

Transcription factors play a pivotal role in modulating macrophage polarization during lung injury. Manipulating the expression or activity of specific transcription factors holds significant therapeutic potential for precisely steering the immune response, promoting tissue repair, and minimizing collateral damage. Harnessing these transcriptional regulators may enable the development of novel therapeutic strategies for various lung injuries, including acute respiratory distress syndrome (ARDS), pneumonia, and chronic obstructive pulmonary disease (COPD).[13] However, further research is warranted to unravel the intricate regulatory networks governing macrophage polarization, optimize the delivery and specificity of transcription factor manipulation, and assess the long-term safety and efficacy of such interventions. By advancing our understanding and harnessing the power of transcription factors, we may pave the way for innovative immunotherapies that improve patient outcomes in lung injury scenarios.

3. Cytokines and Chemokines

Cytokines and chemokines, the small signaling molecules secreted by various cells, including macrophages themselves, have emerged as potent regulators of macrophage polarization. By inducing the expression of specific cytokines, these molecules can modulate macrophage polarization, promoting either pro-inflammatory M1 or anti-inflammatory M2 phenotypes.[14]

Cytokines are key mediators of intercellular communication, orchestrating immune responses.[15] Manipulating some of the following cytokines could allow for precise control over macrophage polarization in lung injury scenarios.

3.1. Interferon-gamma (IFN-γ)

IFN-γ is a potent cytokine that promotes M1 polarization. It stimulates macrophages to produce pro-inflammatory cytokines, such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α). IFN-γ also enhances antigen presentation and antimicrobial activity, critical for effective host defense during lung injury[16].

3.2. Interleukin-4 (IL-4 and Interleukin-13 (IL-13)

IL-4 and IL-13 are cytokines associated with M2 polarization. They induce macrophages to produce anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). IL-4 and IL-13 also promote tissue repair, extracellular matrix synthesis, and alternative activation of macrophages.[17]

3.3. Tumor Necrosis Factor-alpha (TNF-α)

TNF-α can exert diverse effects on macrophage polarization depending on the microenvironment. While it is generally associated with M1 polarization due to its pro-inflammatory properties, prolonged exposure to TNF-α can lead to alternative activation of macrophages and M2 polarization. The context-specific role of TNF-α in lung injury underscores the complexity of cytokine-mediated macrophage polarization.[18]

Chemokines, another class of small signaling molecules, regulate the recruitment and activation of immune cells, including macrophages, during lung injury.[19] Some of the chemokines that contribute to macrophage polarization by influencing their functional properties and migratory behavior include:

3.4. CCL2 (C-C motif ligand 2)

CCL2 is a chemokine involved in the recruitment of monocytes and their differentiation into macrophages. It is associated with M1 polarization and promotes the secretion of pro-inflammatory cytokines. Increased CCL2 levels in lung injury contribute to the recruitment of M1 macrophages, amplifying the inflammatory response.[20]

3.5. CCL17 and CCL22

CCL17 and CCL22 are chemokines associated with M2 polarization. They recruit regulatory T cells (Tregs) that secrete anti-inflammatory cytokines, shaping the local microenvironment towards an M2 phenotype.[21]

3.6. CXCL10 (C-X-C motif ligand 10)

CXCL10 is a chemokine involved in the recruitment of T cells and natural killer (NK) cells. It can promote M1 polarization by inducing the secretion of pro-inflammatory cytokines.[22]

Manipulating cytokines and chemokines holds significant therapeutic potential for modulating macrophage polarization in lung injury. Targeting specific cytokines and chemokines can help shift the balance between M1 and M2 phenotypes, promoting tissue repair while controlling excessive inflammation.[23] Therapeutic strategies could involve exogenous administration of cytokines or chemokines to promote a desired macrophage phenotype. For instance, administration of IFN-γ may boost M1 polarization for enhanced pathogen clearance, while IL-4 or IL-13 administration may promote M2 polarization for tissue repair and anti-inflammatory effects.[24] Developing small molecules that selectively target cytokine or chemokine receptors presents an alternative approach. These molecules could modulate macrophage polarization by influencing cytokine signaling pathways and downstream transcription factors. Considering the complex nature of lung injury, combining cytokine/chemokine-based therapies with other immunomodulatory approaches or cell-based therapies may yield synergistic effects for optimal macrophage polarization and tissue repair.[25] Individual variations in cytokine and chemokine profiles and response to therapy highlight the importance of personalized approaches. Identifying biomarkers that predict the patient's response to specific cytokine/chemokine interventions can guide treatment decisions and enhance therapeutic outcomes.[26]

Cytokines and chemokines serve as powerful regulators of macrophage polarization during lung injury. Manipulating their expression and activity can be harnessed to modulate the immune response, promoting tissue repair, and controlling inflammation. Understanding the intricate interplay between cytokines, chemokines, and macrophage polarization in lung injury will pave the way for innovative therapeutic strategies that harness the potential of these signaling molecules.[27] However, challenges such as achieving specificity, temporal regulation, and personalized approaches need to be addressed to maximize the efficacy of cytokine and chemokine-based interventions. With further research and advancements in targeted immunomodulatory approaches, cytokine and chemokine manipulation may offer promising avenues for future treatments aimed at promoting optimal macrophage polarization and improving outcomes in lung injury scenarios.[28]

4. MicroRNAs

MicroRNAs (miRNAs) are small non-coding RNA molecules that play crucial roles in post-transcriptional gene regulation. Emerging evidence indicates that miRNAs are involved in the regulation of macrophage polarization during lung injury. These tiny regulators can modulate the expression of specific genes and signaling pathways, thereby influencing macrophage phenotypes and the immune response. MiRNAs have emerged as crucial

regulators of macrophage polarization, orchestrating the fine-tuning of gene expression during lung injury.[29] Following miRNAs are identified to be able to influence macrophage polarization by targeting key genes and signaling pathways associated with M1 or M2 phenotypes.

4.1. MiR-155

MiR-155 is a well-studied miRNA that promotes M1 polarization in macrophages. It targets multiple genes involved in M2 polarization, such as suppressor of cytokine signaling 1 (SOCS1) and Krüppel-like factor 4 (KLF4), while enhancing the expression of M1-associated factors like TNF-α and IL-6.[30]

4.2. MiR-223

MiR-223 has been implicated in M2 polarization and tissue repair processes. It targets several genes associated with M1 polarization, including nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3), while promoting M2-associated factors like IL-10 and Arginase 1 (Arg1).[31]

4.3. MiR-146a

MiR-146a is known for its role in regulating the innate immune response. It attenuates M1 polarization by targeting interleukin-1 receptor-associated kinase 1 (IRAK1) and TNF receptor-associated factor 6 (TRAF6), both key components of Toll-like receptor (TLR) signaling pathways.[32]

4.4. Other MiRNAs

Several other miRNAs, including miR-21, miR-34a, and miR-125a, have been implicated in macrophage polarization during lung injury. These miRNAs target various genes and pathways involved in regulating M1 or M2 phenotypes, influencing the immune response and tissue repair processes.[33]

MiRNAs regulate macrophage polarization by binding to the 3' untranslated region (3'UTR) of target messenger RNAs (mRNAs), leading to mRNA degradation or translational repression.[34] The specific targets of miRNAs determine their impact on macrophage polarization and the resulting immune response. Some of the Mechanisms by which MiRNAs regulate macrophage polarization include: (i) Cross-Talk between MiRNAs and Transcription Factors: MiRNAs can indirectly influence macrophage polarization by targeting transcription factors involved in M1 or M2 activation. For example, miR-155 targets the transcription factor PU.1, which is critical for M2 polarization. By repressing PU.1, miR-155 enhances M1 polarization.[35] (ii) Autocrine and Paracrine Regulation: Macrophages themselves secrete miRNAs, which can be taken up by neighboring cells, including other macrophages. This autocrine and paracrine regulation through miRNAs contributes to the polarization and coordination of the immune response during lung injury.[36]

Targeting miRNAs holds promise as a therapeutic strategy to modulate macrophage polarization and alter the immune response in lung injury. However, several challenges and future directions need to be considered. Efficient and targeted delivery of miRNA-based therapies to specific lung tissues or macrophage populations remains a challenge. The development of nanoparticle-based delivery systems or viral vectors may facilitate the precise delivery of miRNAs to the desired cellular targets.[37] Combining miRNA-based therapies with other immunomodulatory approaches, such as cytokines or small molecule inhibitors, may offer synergistic effects and enhance therapeutic outcomes.[38] Further research is needed to identify novel miRNAs involved in macrophage polarization during lung injury. High-throughput sequencing technologies and functional screening methods can aid in the discovery of additional miRNAs and their specific roles in regulating macrophage phenotypes. Identifying miRNA signatures or biomarkers that correlate with specific macrophage phenotypes or disease progression may enable personalized treatment strategies and help monitor therapeutic efficacy.[39] With further research and technological advancements, miRNA-based therapies may contribute to the development of personalized treatments that promote optimal macrophage polarization and improve outcomes in lung injury.

5. Genetic Engineering Techniques

Genetic engineering techniques, particularly the revolutionary CRISPR-Cas9 system, offer unprecedented precision in modifying genes. In the context of lung injury, these techniques provide a powerful tool for directly manipulating genes involved in macrophage polarization. By targeting specific genes, researchers can gain insights into the intricate regulatory networks governing macrophage phenotypes and potentially develop novel therapeutic strategies.[40]

CRISPR-Cas9 is a versatile and widely adopted genetic engineering tool. It utilizes a guide RNA (gRNA) to target specific DNA sequences and the Cas9 nuclease to introduce precise modifications. CRISPR-Cas9 can be used for gene knockout, gene activation, or gene editing, allowing researchers to directly manipulate genes involved in macrophage polarization.[41] Numerous other genes have been identified as key regulators of macrophage polarization. For example, manipulating transcription factors such as STAT1, STAT6, or NF-κB can influence M1/M2 balance. Similarly, modifying genes involved in cytokine signaling, such as IFN-γ, IL-4, or IL-13 receptors, can impact macrophage polarization.[42]

Genetic engineering techniques offer valuable insights and potential therapeutic avenues for modulating macrophage polarization in lung injury. However, several challenges and considerations need to be addressed. Genetic engineering techniques allow for the precise manipulation of specific genes, enabling researchers to gain a deeper understanding of the molecular mechanisms underlying macrophage polarization. These insights can unveil novel targets for therapeutic intervention.[43] Modifying genes involved in macrophage polarization holds promise for developing targeted therapies in lung injury scenarios. By manipulating key regulators, it is possible to steer the immune response towards tissue repair and resolution of inflammation. Ensuring the specificity of genetic modifications is crucial. Genetic engineering techniques should be designed to minimize off-target effects, ensuring that only the intended genes are modified without unintended consequences. Efficient delivery of CRISPR-Cas9 components to target cells in the lung is essential. Developing safe and effective delivery systems, such as viral vectors or nanoparticles, is a critical aspect of translating genetic engineering approaches into therapeutic interventions. Modifying genes in vivo may elicit immune responses or have long-term effects on cell function and overall health. Thorough evaluation of safety and potential long-term consequences is essential for clinical translation. Future research directions, such as multigene editing and targeting non-coding RNA molecules, hold promise for further advancements in the field.[44] With continued progress and careful evaluation, genetic engineering approaches have the potential to revolutionize our ability to modulate macrophage polarization and improve outcomes in lung injury scenarios.

6. Conclusion

Future directions in understanding and manipulating genes involved in macrophage polarization during lung injury hold significant potential for advancing therapeutic strategies and improving patient outcomes. Here are some key areas of focus for future research:

6.1. Identification of novel gene targets

Continued exploration is needed to identify additional genes that play crucial roles in macrophage polarization during lung injury. High-throughput screening approaches, such as genome-wide association studies (GWAS) and transcriptomic analyses, can help uncover novel gene candidates and their specific functions in macrophage polarization. By expanding the repertoire of target genes, we can gain a more comprehensive understanding of the regulatory networks governing macrophage phenotypes.

6.2. Understanding gene interactions and signaling pathways

Further research is needed to elucidate the intricate interactions and signaling pathways among genes involved in macrophage polarization. By deciphering the complex molecular networks, we can identify critical nodes and potential therapeutic targets for modulating macrophage phenotypes. Integrated omics approaches, such as transcriptomics, proteomics, and network analyses, can provide valuable insights into these interactions and facilitate the development of targeted interventions.

6.3. Gene editing and delivery optimization

Improving the efficiency and specificity of gene editing techniques, such as CRISPR-Cas9, is essential for translating these approaches into clinical applications. Future research should focus on refining delivery systems, enhancing targeted delivery to lung tissues, and minimizing off-target effects. Advancements in nanoparticle-based delivery systems, viral vectors, and genome editing technologies will contribute to the development of safe and effective gene manipulation strategies in vivo.

6.4. Personalized approaches

Lung injury exhibits substantial heterogeneity across patients, necessitating personalized approaches to gene manipulation. Future research should aim to identify biomarkers or genetic signatures that correlate with specific macrophage phenotypes or disease progression. This information can guide treatment decisions, predict individual responses to gene manipulation therapies, and enable tailored interventions for optimal patient outcomes.

6.5. Combination therapies and immunomodulation

Exploring the potential of combination therapies that target multiple genes or signaling pathways holds promise for enhancing macrophage polarization modulation in lung injury. Integrating genetic manipulation techniques with other immunomodulatory approaches, such as cytokine administration, small molecule inhibitors, or cell-based therapies, may offer synergistic effects and improve therapeutic outcomes. Designing combinatorial strategies that balance pro-inflammatory and anti-inflammatory responses while promoting tissue repair will be a key focus for future investigations.

6.6. Preclinical and clinical validation

Translating gene manipulation strategies into clinical applications requires rigorous preclinical and clinical validation. Animal models that faithfully recapitulate lung injury scenarios, including relevant genetic backgrounds, should be used to evaluate the safety and efficacy of

gene manipulation approaches. Conducting well-designed clinical trials with appropriate patient selection criteria, outcome measures, and long-term follow-up will be crucial for assessing the therapeutic potential and establishing the clinical utility of gene manipulation in macrophage polarization during lung injury.

7. Conclusion

Future research on genes manipulating macrophage polarization during lung injury should focus on identifying novel gene targets, unraveling gene interactions and signaling pathways, optimizing gene editing and delivery systems, embracing personalized approaches, exploring combination therapies, and conducting comprehensive preclinical and clinical validation. These advancements will pave the way for more effective and targeted therapeutic interventions, ultimately improving outcomes for patients with lung injury.

8. Conflict of Interest

None.

9. Source of Funding

None.

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Cite this article: Jun L, Chakravarthi S, Karikalan B. Manipulating macrophage polarization through gene manipulation techniques in lung injury. *IP Arch Cytol Histopathology Res* 2023;8(2):76-82.