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Phenotypic Transformation of Liver Macrophages (Kupffer Cells): The Impact of Drug-Induced Immunosuppression on Innate Immunity

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Annotation: Liver macrophages, or Kupffer cells, are pivotal regulators of innate immunity, maintaining hepatic homeostasis and orchestrating inflammatory responses to pathogens, toxins, and cellular stress. Drug-induced immunosuppression, commonly employed in organ transplantation and treatment of autoimmune disorders, profoundly affects Kupffer cell phenotype, leading to altered cytokine production, impaired phagocytic activity, and dysregulation of innate immune responses. This article provides a detailed analysis of the phenotypic transformations of Kupffer cells under chronic immunosuppressive therapy, explores the molecular mechanisms underlying these changes, and evaluates the consequences for hepatic immunity and systemic inflammatory regulation. By examining shifts in macrophage polarization, functional activity, and interaction with other hepatic cell types, this review highlights the implications of immunosuppression on liver immunobiology and proposes potential strategies for mitigating immune dysfunction while preserving

therapeutic efficacy. Understanding Kupffer cell dynamics in this context is critical for optimizing patient outcomes, preventing infection, and reducing the risk of immunopathology during long-term pharmacological immunosuppression. Kupffer cells, as liver-resident macrophages, are central regulators of hepatic innate immunity, coordinating responses to pathogens, toxins, and tissue stress. Chronic drug-induced immunosuppression, a cornerstone of organ transplantation and autoimmune therapy, triggers phenotypic transformation of these cells, leading to altered polarization, diminished phagocytic function, and imbalanced cytokine production. This article presents a comprehensive analysis of the cellular and molecular mechanisms underlying Kupffer cell adaptation during prolonged immunosuppressive therapy, emphasizing the consequences for innate immune defense and systemic immune homeostasis. By evaluating shifts in M1/M2 polarization, functional impairment, and intercellular communication, the review highlights how immunosuppressive drugs reshape hepatic immune surveillance and identifies potential strategies to preserve immune competence. These insights provide a basis for optimizing therapeutic regimens, minimizing infection risk, and improving clinical outcomes in patients receiving long-term immunosuppressive treatment.

Keywords: Kupffer cells, liver macrophages, phenotypic transformation, immunosuppression, innate immunity, cytokine regulation, macrophage polarization, phagocytosis, hepatic inflammation, drug-induced immune modulation

Introduction

Kupffer cells, the resident macrophages of the liver, play a central role in innate immunity by surveilling the hepatic microenvironment, phagocytosing pathogens, clearing apoptotic cells, and producing immunomodulatory cytokines. They exhibit remarkable plasticity, adapting their phenotype in response to environmental signals, pathogen exposure, and pharmacological interventions. Drug-induced immunosuppression, including calcineurin inhibitors, corticosteroids, and antimetabolites, alters Kupffer cell phenotype, shifting the balance between

pro-inflammatory (M1) and anti-inflammatory (M2) polarization states. Such phenotypic transformation affects the liver's capacity to mount appropriate immune responses, potentially increasing susceptibility to infections, impairing tissue repair, and exacerbating drug- or disease-related hepatotoxicity. Chronic immunosuppressive therapy can reduce phagocytic activity, diminish the production of pro-inflammatory cytokines such as TNF-α and IL-1β, and enhance anti-inflammatory mediators including IL-10, ultimately modifying the immunological landscape of the liver. These shifts influence both local hepatic immunity and systemic immune homeostasis, underscoring the importance of understanding Kupffer cell adaptations during pharmacological intervention. The present study aims to elucidate the mechanisms of drug-induced phenotypic transformation of Kupffer cells, evaluate the functional consequences for innate immunity, and explore potential strategies to preserve immune competence while maintaining effective immunosuppressive therapy.

Liver macrophages, known as Kupffer cells, constitute a specialized population of innate immune cells tasked with maintaining hepatic homeostasis, clearing pathogens and apoptotic cells, and modulating inflammatory processes. These cells exhibit remarkable plasticity, dynamically adjusting their phenotype in response to environmental stimuli, pathogen exposure, and pharmacological interventions. Drug-induced immunosuppressive therapy—utilized extensively in organ transplantation and management of autoimmune disorders—profoundly influences Kupffer cell behavior, shifting the balance between pro-inflammatory M1 and anti-inflammatory M2 phenotypes. Such phenotypic transformation can reduce the liver's capacity to mount effective immune responses, impair pathogen clearance, and contribute to susceptibility to infections. Mechanistic studies suggest that chronic exposure to calcineurin inhibitors, corticosteroids, or antimetabolites suppresses NF-κB signaling and activates STAT6 pathways, facilitating anti-inflammatory polarization while dampening pro-inflammatory mediator expression such as TNF-α and iNOS. These changes not only impact local hepatic immunity but also affect systemic immune responses, highlighting the importance of understanding macrophage adaptations during prolonged pharmacological immunosuppression. The present study aims to examine the molecular, cellular, and functional alterations of Kupffer cells in this context, evaluating the impact on innate immunity and identifying strategies to mitigate immunological compromise while maintaining therapeutic efficacy.

Materials and Methods

The study included liver biopsy samples from patients receiving long-term immunosuppressive therapy following organ transplantation or for autoimmune disorder management. Kupffer cell populations were characterized using immunohistochemistry, flow cytometry, and molecular profiling. Markers of M1 polarization (CD86, iNOS, TNF-α) and M2 polarization (CD206, Arg1, IL-10) were analyzed to determine shifts in phenotypic expression. Phagocytic capacity was assessed using fluorescently labeled bacterial particles, and cytokine secretion profiles were evaluated by ELISA. Clinical parameters, including liver function tests, infection incidence, and duration and type of immunosuppressive therapy, were recorded. Statistical analyses included correlation and multivariate regression to determine associations between immunosuppressive exposure, Kupffer cell phenotype, and functional outcomes. Comparative analyses were performed between patients receiving different immunosuppressive regimens to identify differential effects on innate immunity.

Results

Immunohistochemical and flow cytometry analyses demonstrated significant phenotypic shifts in Kupffer cells under chronic immunosuppressive therapy. Patients treated with calcineurin inhibitors exhibited decreased M1 marker expression and attenuated pro-inflammatory cytokine production, accompanied by enhanced M2 polarization with elevated CD206 and IL-10 levels. Corticosteroid-treated patients showed similar trends, although to a lesser extent. Phagocytic activity of Kupffer cells was markedly reduced across all immunosuppressive regimens,

correlating with prolonged therapy duration and higher cumulative doses. Molecular profiling revealed altered expression of transcription factors governing macrophage polarization, including NF-κB suppression and STAT6 upregulation, corresponding to the observed phenotypic shift. Clinically, these changes were associated with increased susceptibility to bacterial infections, mild elevation of liver transaminases, and reduced inflammatory responsiveness to hepatocellular stress. Multivariate analysis confirmed that both type and duration of immunosuppressive therapy independently predicted phenotypic transformation and functional impairment of Kupffer cells. These results indicate that drug-induced immunosuppression induces a shift toward an anti-inflammatory M2-dominant phenotype, reducing innate immune competence while potentially limiting excessive hepatic inflammation.

Immunohistochemical analyses of liver tissue samples from patients under chronic immunosuppressive therapy revealed significant alterations in Kupffer cell phenotype. Markers of M1 polarization, including CD86 and iNOS, were markedly reduced, whereas M2 indicators, including CD206 and IL-10, were significantly elevated, reflecting a shift toward an anti-inflammatory state. Flow cytometry confirmed diminished phagocytic activity, evidenced by decreased uptake of fluorescently labeled bacterial particles. Molecular profiling demonstrated downregulation of NF-κB transcriptional activity alongside enhanced STAT6 and PPAR-γ signaling, indicating a mechanistic basis for the observed phenotypic shift. Clinically, these changes correlated with increased incidence of bacterial infections, mild hepatic enzyme elevation, and reduced inflammatory responsiveness. Comparative analyses revealed that calcineurin inhibitors induced the most pronounced M2 polarization, followed by corticosteroids, while antimetabolites exhibited a moderate effect. Statistical correlations indicated that both the type and duration of immunosuppressive therapy were independent predictors of Kupffer cell functional impairment, demonstrating a clear relationship between pharmacological exposure and innate immune compromise. These results underscore that prolonged immunosuppressive treatment reprograms Kupffer cell phenotype and function, favoring anti-inflammatory activity at the expense of effective pathogen clearance.

Discussion

The findings highlight the significant impact of chronic pharmacological immunosuppression on Kupffer cell biology, revealing a shift in phenotype toward an M2-dominant state characterized by anti-inflammatory activity, reduced phagocytosis, and impaired cytokine-mediated host defense. While this transformation may confer protection against hyperinflammatory liver injury, it compromises innate immunity and increases susceptibility to infection, particularly in the context of bacterial translocation or systemic microbial exposure. The differential effects of specific immunosuppressive agents underscore the need for personalized therapy to balance immunosuppression with preservation of hepatic immune competence. Mechanistically, suppression of NF-κB signaling and upregulation of STAT6-mediated pathways drive M2 polarization, while reduced iNOS and TNF-α production diminishes pro-inflammatory responses. Monitoring Kupffer cell phenotype and functional activity using immunohistochemical and molecular techniques can provide early indicators of immune dysregulation, guiding clinical decisions regarding infection prophylaxis, therapy modification, and supportive care. Future therapeutic approaches may include targeted modulation of macrophage polarization, cytokine supplementation, or adjunctive immunomodulatory interventions to maintain innate immune function without compromising the efficacy of immunosuppressive therapy. Understanding the interplay between pharmacological agents and Kupffer cell dynamics is essential for optimizing patient outcomes, preventing immunopathology, and maintaining hepatic homeostasis during long-term therapy.

The findings highlight the dual-edged impact of long-term immunosuppressive therapy on liver macrophages. Phenotypic reprogramming toward M2-dominant states reduces local inflammatory damage but concurrently compromises host defense, increasing susceptibility to infections. The suppression of NF-κB signaling and concomitant activation of STAT6 and

PPAR-γ pathways orchestrates this transformation, promoting anti-inflammatory cytokine production while limiting pro-inflammatory mediators. Such alterations have systemic implications, affecting the liver's ability to respond to microbial challenge and modulate immune homeostasis. Clinically, monitoring Kupffer cell phenotype and functional parameters can serve as a predictive tool for infection risk, guiding immunosuppressive dose adjustment and the implementation of prophylactic measures. Personalized therapeutic strategies may include selective modulation of macrophage polarization, cytokine supplementation, or adjunctive immune-supportive interventions to preserve innate immune capacity without compromising overall immunosuppressive efficacy. These approaches emphasize the importance of balancing pharmacological immunosuppression with maintenance of functional innate immunity to optimize patient outcomes and reduce complications associated with chronic therapy.

Conclusion

Drug-induced immunosuppression profoundly influences Kupffer cell phenotype, inducing a shift toward an anti-inflammatory M2-dominant state with diminished phagocytic capacity and reduced pro-inflammatory cytokine production. These alterations compromise innate hepatic immunity and increase vulnerability to infections while modulating inflammatory responses within the liver. Immunohistochemical and molecular assessment of Kupffer cells provides valuable prognostic information regarding immune function and potential hepatic complications. Personalized management strategies that consider the type and duration of immunosuppressive therapy, coupled with monitoring of macrophage phenotype and function, are critical for balancing effective immunosuppression with preservation of innate immunity. Therapeutic modulation of Kupffer cell polarization and function may offer innovative approaches to mitigate immune dysfunction, improve patient outcomes, and maintain liver homeostasis during long-term pharmacological immunosuppression.

Chronic drug-induced immunosuppression induces a pronounced phenotypic shift in Kupffer cells toward an anti-inflammatory M2-dominant state, characterized by reduced phagocytic function, diminished pro-inflammatory cytokine production, and altered transcriptional regulation. This reprogramming impairs innate hepatic immunity, increases infection susceptibility, and modifies systemic immune homeostasis. Immunohistochemical and molecular assessment of Kupffer cell phenotype provides critical prognostic insights, enabling clinicians to anticipate immune dysfunction and adjust therapeutic regimens accordingly. Personalized management strategies, integrating pharmacological choices with monitoring of macrophage function, are essential for preserving innate immunity, minimizing infection risk, and maintaining liver homeostasis during long-term immunosuppressive therapy. Optimizing Kupffer cell function represents a promising avenue for improving clinical outcomes and reducing complications in patients subjected to chronic immunosuppressive treatment.

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