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Exploring the Causal Role of Immune Cells in Autoimmune Hepatitis: A Narrative review of Mendelian Randomization Insights

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Abstract

Autoimmune hepatitis (AIH) is a chronic, immune-mediated liver disease whose etiology remains incompletely defined. While observational studies have implicated dysregulated immunity in AIH, establishing causality has been challenging due to confounding and reverse causation. Mendelian randomization (MR) leverages genetic variants as instrumental variables to infer causal relationships.This narrative review aims to summarize and interpret findings from a recent bidirectional two-sample MR investigation that evaluated the causal effects of 731 immune cell traits on AIH risk. We contextualize these results within existing immunological knowledge of AIH.We focused on a key MR study that utilized genome-wide association study (GWAS) summary statistics for 731 immunophenotypes and AIH. Primary analyses employed inverse variance weighting, supplemented by sensitivity approaches (MR-Egger, weighted median) and reverse MR to assess robustness and directionality.Genetic evidence supports a causal contribution of specific innate and adaptive immune cell subsets to AIH pathogenesis. These findings underscore the therapeutic potential of targeting MDSCs, Tregs, dendritic cells, NKT cells, and the PD-1/PDL-1 pathway, and provide a foundation for future mechanistic and translational research.

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Introduction

Autoimmune hepatitis (AIH) is a progressive, immune-mediated liver condition characterized by interface hepatitis, hypergammaglobulinemia, and circulating autoantibodies [1]. Its global incidence is rising, with a notable female predominance, and untreated disease can advance to cirrhosis, liver failure, or necessitate transplantation [2,3]. First-line immunosuppressive regimens, typically corticosteroids and azathioprine, are effective for many patients but carry significant side-effect burdens, and a subset of individuals exhibit inadequate response [4,5]. The pathogenesis of AIH involves a breakdown of immune tolerance, influenced by genetic susceptibility, environmental factors, and immunoregulatory dysfunction [6,7].

Dysregulation of the adaptive immune system, particularly T lymphocytes, is considered central to AIH. An imbalance between regulatory T cells (Tregs) and pro-inflammatory T-helper 17 (Th17) cells represents a cornerstone of contemporary disease models [8,9]. Th17 cells secrete interleukin-17 (IL-17), which is elevated in AIH patients and experimental models, driving inflammatory responses and neutrophil recruitment [10,11]. Other immune populations, including NKT cells, dendritic cells (DCs), and myeloid-derived suppressor cells (MDSCs), are also implicated, though their precise roles are not fully elucidated [12,13].

Historically, evidence has largely stemmed from observational studies, which are inherently limited by confounding variables and an inability to definitively

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establish causality or temporal sequence [14]. For instance, it remains unclear whether alterations in immune cell phenotypes initiate the disease process or occur secondary to ongoing hepatic inflammation.

Mendelian randomization (MR) has emerged as a powerful method for causal inference in observational data [15]. By using genetic variants as proxies for exposures such as immune cell characteristics, MR can mitigate confounding and reverse causation, as genetic variants are randomly assorted at conception and generally fixed throughout life [16]. This review centers on a recent two-sample MR study that explored potential causal relationships between 731 immune cell traits and AIH risk [17]. We synthesize its principal findings, discuss the biological relevance of the implicated immune subsets, consider the strengths and limitations of the MR approach, and propose directions for future research and therapeutic development.

methods

The investigation adopted a bidirectional two-sample MR framework. Summary-level genetic data for AIH were derived from a GWAS meta-analysis [18]. Genetic associations for 731 immunophenotypes—encompassing absolute cell counts, median fluorescence intensities, morphological measures, and relative proportions—were obtained from the GWAS catalog, providing a comprehensive profile of immune cell features [19].

Findings

The MR analysis yielded robust genetic evidence for a causal influence of several immune cell traits on AIH susceptibility.

Causal Effects of Immunophenotypes on AIH

After FDR correction, six immunophenotypes demonstrated significant causal associations:

- **Risk-Increasing Traits (Odds Ratio > 1):**
  - CD45 expression on Mo MDSC (OR = 1.242)
  - Absolute count of $CD28^-$ $CD8^{br}$ T cells (OR = 1.486)
  - CD28 expression on $CD39^+$ secreting Tregs (OR = 1.194)
  - Absolute count of $CD62L^-$ myeloid DCs (OR = 1.252)
  - $CD16^-$ CD56 expression on NKT cells (OR = 1.182)
- **Protective Trait (Odds Ratio < 1):**
  - PDL-1 expression on $CD14^+$ $CD16^+$ monocytes (OR = 0.849)

Sensitivity analyses generally supported these associations, with minimal evidence of pleiotropy or heterogeneity.

Evaluation of Reverse Causality

Reverse MR analyses, testing the effect of AIH on the identified immunophenotypes, revealed no significant associations following multiple testing adjustment. This strengthens the conclusion that variation in these immune traits influences AIH risk rather than being a consequence of the disease.

Discussion

This MR study provides compelling genetic support for the causal involvement of specific immune cell phenotypes in AIH, advancing understanding beyond associative observations.

Biological Interpretation of Causal Immune Traits

The immunophenotypes identified align with and extend current immunological models of AIH.

Myeloid-Derived Suppressor Cells (MDSCs): The association between CD45 on Mo MDSC and increased AIH risk is intriguing. MDSCs typically expand in settings of chronic inflammation and malignancy, where they exert immunosuppressive functions [20,21]. In autoimmunity, their role appears more complex; they may accumulate as a compensatory regulatory response but might fail to adequately suppress pathogenic T cells or could acquire pro-inflammatory properties [22,23]. Their presence in AIH models has been documented [24,25]. The MR finding suggests that genetic predisposition to a particular MDSC phenotype may contribute causally to AIH development.

T Cell Dysregulation: The $CD28^-$ $CD8^{br}$ population represents senescent or terminally differentiated $CD8^+$ T cells, which accumulate in chronic viral infections and autoimmune conditions [26]. These cells exhibit reduced co-stimulatory capacity and heightened cytotoxic potential, possibly contributing to hepatocyte damage [27]. The association of CD28 on $CD39^+$ secreting Tregs with higher risk is nuanced. While CD28 signaling supports Treg function and stability [28], and $CD39^+$ Tregs suppress immunity via adenosine generation [29], the MR result may reflect an insufficient compensatory expansion of this regulatory subset in individuals genetically predisposed to autoimmunity. This interpretation is consistent with observed functional defects in Tregs from AIH patients [30,31].

Dendritic Cells (DCs): The causal role of $CD62L^-$ myeloid DCs highlights the importance of antigen presentation in AIH. Absence of CD62L may identify tissue-resident or inflammatory DC subsets that efficiently activate T cells locally [32]. Altered DC function is hypothesized to disrupt hepatic tolerance in AIH [33]; MR data now posit genetic variation influencing these DC subsets as an upstream causal factor.

NKT Cells: NKT cells, which are abundant in the liver, serve as a bridge between innate and adaptive immunity [34]. The $CD16^-$ CD56 on NKT trait likely marks a specific functional subset. CD56 (NCAM) is involved in cell adhesion and cytokine secretion, and NKT cell activation can promote Th1/Th17 responses relevant to AIH pathogenesis [35,36]. MR evidence solidifies their active contribution to disease.

PD-1/PDL-1 Pathway: The protective effect of PDL-1 on $CD14^+$ $CD16^+$ monocytes holds particular translational relevance. The PD-1/PDL-1 axis is a critical immune checkpoint that constrains T-cell activation and helps prevent autoimmunity [37]. In the liver, constitutive PDL-1 expression contributes to the maintenance of immune tolerance [38]. Reduced PDL-1 availability could lower the activation threshold for autoreactive T cells. This is supported by AIH models where PDL-1 deficiency exacerbates disease [39] and human studies correlating PDL-1 with disease biomarkers [40]. This finding suggests that therapeutic strategies aimed at enhancing this checkpoint may be beneficial.

Strengths, Limitations, and Future Directions

A primary strength of this MR study is its capacity to provide less confounded causal estimates. The use of large-scale GWAS data and comprehensive sensitivity analyses enhances the reliability of the findings.

Notable limitations include the restriction of genetic data to individuals of European ancestry, which may limit the generalizability of results to other populations [41]. Furthermore, MR estimates reflect the lifelong influence of genetic predisposition, which may differ from the effects of short-term pharmacological interventions. While MR can indicate causality, it does not elucidate the detailed molecular mechanisms involved.

Future research should prioritize:Functional Validation: Experimental studies to delineate the precise roles of the identified immune subsets in driving or modulating liver injury.

Multi-omics Integration: Combining genomic data with transcriptomic, epigenomic, and proteomic profiles from AIH patients to unravel downstream pathways.

Therapeutic Exploration: The PDL-1 finding suggests potential for checkpoint agonist therapies; modulation of MDSCs also represents a novel strategic avenue [42].

Trans-ancestry MR Studies: Replication in diverse genetic populations to ensure the broad applicability of the causal relationships identified.

Conclusion

Mendelian randomization marks a significant advance in the study of AIH, facilitating a shift from correlation toward causation. It offers genetic validation of immune dysregulation in the disease, pinpointing specific phenotypes of MDSCs, T cells, DCs, NKT cells, and the PDL-1 checkpoint. These insights refine the immunological framework of AIH and highlight promising targets for the development of more effective, immunologically precise treatments.

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Authors Contributions

The authors contributed to the data analysis. Drafting, revising and approving the article, responsible for all aspects of this work.

Conflict of Interest

None

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