Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2026**; 31(1): 49480
https://doi.org/10.31083/FBL49480

Editorial

Cellular and Molecular Studies in Immunopharmacology

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Academic Editor: Graham Pawelec
Submitted: 26 December 2025 Accepted: 5 January 2026 Published: 20 January 2026

Immunopharmacology has evolved to a stage in which immune responses are no longer viewed as uniformly protective or harmful; instead, they are recognized as highly context-dependent processes shaped by tissue environments, cellular states, and interconnected signaling networks [1]. Efficient immune responses are essential for promoting wound healing, eliminating infections and cancer, and establishing durable vaccine-induced immunological memory [2]. Immunoprotection is characterized by active immune surveillance, rapid and robust immune activation, effective clearance of pathogens or danger signals, and timely resolution of inflammation, all of which are critical for the proliferative and remodeling phases of tissue repair [3]. Immune responses also contribute to tissue-intrinsic damage that arises during infection-driven immune activation, during which collateral tissue damage can occur [4,5]. Depending on the pathogen, its cellular niche, and the nature of the tissue injury, both innate and adaptive immune responses may confer protection or drive immunopathology (immune responses that cause tissue damage, chronic inflammation, or disease by targeting self or foreign antigens) [4,6]. In parallel, immunoregulation (immune mechanisms that restrain or resolve immune activation to maintain tissue homeostasis) plays a crucial role in limiting excessive inflammation, while paradoxically influencing outcomes in cancer and chronic disease [7,8].

These mechanisms were largely overlooked in early therapeutic strategies, which primarily focused on generalized immune activation or suppression. However, increasing mechanistic insight has revealed that such binary approaches often fail to achieve durable efficacy and may even exacerbate pathological immune responses [7]. This evolving understanding has important implications for a wide range of diseases driven by immune dysregulation, including cancer, stress-associated immune dysfunction, and sterile inflammatory injury [2–4,6,8]. The present Special Issue of "*Cellular and Molecular Studies in Immunopharmacology*" brings together four original contributions that exemplify this paradigm shift. These include psychological stress, solid tumor immunotherapy, acute lung injury, and drug-induced liver failure. These studies collectively demonstrate how immune pathways can exert either protective or deleterious effects depending on the biological context and immunopharmacological intervention. By interrogating immune regulation at cellular and molecular resolution, the studies featured in this issue underscore the necessity of precision immunopharmacology.

Stress, Neuroimmune Crosstalk, and Immune Homeostasis: Chronic psychological stress is a well-established but frequently underappreciated driver of immune dysfunction. Sustained activation of the hypothalamic-pituitary-adrenal axis leads to elevated glucocorticoid levels, thymic atrophy, impaired T-cell responses, and altered cytokine production, all of which increase susceptibility to inflammatory and infectious diseases. Zimecki *et al.* [9] provide compelling preclinical evidence that such stress-induced immune impairment is not irreversible and can be modulated using natural immunoregulatory agents. Using a murine immobilization stress model, the authors demonstrate marked suppression of contact hypersensitivity responses, reduced thymocyte levels, and diminished T-cell proliferation. Oral administration of yolkin, an immunoregulatory protein complex derived from egg yolk, significantly restored cellular immune parameters, including interferon-gamma (IFN-γ) and interleukin-6 (IL-6) production, splenocyte proliferation, and thymic architecture. Importantly, yolkin exerted regulatory rather than stimulatory effects, correlating with normalization of corticosterone levels and attenuation of stress-induced neutrophil infiltration and epidermal damage. These findings highlight the therapeutic potential of natural immunomodulators in restoring immune equilibrium under conditions of chronic stress.

Precision Immune Activation in Solid Tumors: In contrast to stress-induced immune suppression, cancer progression is often driven by immune evasion. While immune checkpoint inhibitors have transformed melanoma treatment, durable responses are not achieved in all patients, highlighting the need for additional immunotherapeutic strategies. Philippova *et al.* [10] address this challenge by exploring Disialoganglioside (GD2)-targeted chimeric antigen receptor (CAR) T-cell therapy in melanoma. GD2 is highly expressed on melanoma cells while exhibiting limited expression in normal tissues, making it an

attractive therapeutic target. The authors engineered GD2-specific CAR-T cells incorporating CD28/CD3ζ signaling domains together with glucocorticoid-induced tumor necrosis factor receptor (TNFR) family-related protein ligand (GITRL) costimulatory elements, resulting in a predominantly naïve, $CD8^+$ T-cell phenotype ($CD8^+CD40L^+CD69^-CD107a^+4\text{-}1BB^+FasL^+$) associated with enhanced persistence and anti-tumor efficacy. These CAR-T cells mediated potent and selective cytotoxicity against GD2-positive melanoma cells *in vitro* and significantly suppressed tumor growth following a single intratumoral administration in a murine xenograft model, without detectable toxicity. This study exemplifies how rational CAR design can overcome key barriers in solid tumor immunotherapy by achieving spatial and molecular restricted immune activation.

Notch1-CCR5 Signaling in Acute Lung Injury: Acute lung injury (ALI) and acute respiratory distress syndrome represent examples of immune-mediated tissue damage, in which excessive innate immune activation leads to vascular leakage, pulmonary edema, and respiratory failure. Zhang *et al*. [11] identify macrophage-specific Notch1-dependent Cysteine-cysteine chemokine receptor 5 (CCR5) signaling as a critical driver of inflammatory lung injury. In a lipopolysaccharide-induced murine model of ALI, the authors demonstrated robust activation of Notch signaling in lung macrophages accompanied by increased CCR5 expression. Genetic ablation of macrophage Notch1 or pharmacological inhibition of CCR5 significantly reduced macrophage recruitment, inflammatory cytokine production, and histopathological lung damage. Mechanistically, the Notch1-CCR5 axis regulated macrophage migration through Recombination Signal Binding Protein for Immunoglobulin Kappa J region (RBP-Jκ)-dependent transcription and intersected with Transforming Growth Factor-beta 1 (TGF-β1)/Mothers against decapentaplegic homolog 3 (Smad3) signaling pathways. These findings position CCR5 as a therapeutic downstream effector of Notch signaling in ALI and highlight the pathological potential of sustained innate immune activation.

Context-Dependent Protective Roles of Notch1 in Liver Injury: While Notch signaling promotes pathology in ALI, its role in sterile inflammation is context dependent. Yang *et al*. [12] reveal a protective function for Notch1 signaling in acetaminophen-induced liver injury, a leading cause of acute liver failure. Contrary to prevailing assumptions, pharmacological inhibition of Notch1 using the γ-secretase inhibitor DAPT (N-[N-(3,5-difluorophenacetyl)-L-alanyl]-S-phenylglycine tert-butyl ester) exacerbated hepatocellular damage, increased macrophage infiltration, and promoted polarization toward a pro-inflammatory M1 phenotype. Mechanistically, Notch1 inhibition suppressed β-catenin signaling, reinforcing Signal Transducer and Activator of Transcription (STAT)1 activation while decreasing STAT6-driven anti-inflammatory responses. Restoration of β-catenin signaling reversed these effects, identifying the Notch1-β-catenin axis as a critical regulator of macrophage functional states during acute liver injury. This study provides an important message against indiscriminate inhibition of immune signaling pathways and underscores the need to consider tissue- and injury-specific immune functions.

Collectively, the studies presented in this Special Issue highlight the central importance of contextual intelligence in immunopharmacology. Whether restoring immune competence during psychological stress, directing cytotoxic immunity against cancer cells, or fine-tuning innate immune responses in acute organ injury, therapeutic success depends on understanding when and how immune pathways should be modulated. Natural immunoregulatory agents such as yolkin demonstrate the feasibility of restoring immune homeostasis without excessive activation, while engineered cell therapies exemplify the power of molecular precision. The contrasting roles of Notch1 signaling in lung and liver injury caution against oversimplified therapeutic strategies. Together, these contributions advance immunopharmacology toward a future defined by targeted, adaptive, and biologically informed immune modulation.

Author Contributions

AR, SP, AP, and SRB contributed to conceptualization, writing, and critical revision of the editorial. All authors approved the final version and agree to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The authors thank all contributors to this Special Issue of *Cellular and Molecular Studies in Immunopharmacology* for their valuable scientific contributions. The authors acknowledge the Director, CSIR–IICT, Hyderabad, for continued institutional support of this collaborative work.

Funding

The SB laboratory is financially supported by the Anusandhan National Research Foundation (ANRF) through the Prime Minister Early Career Research Grant (Grant ID: ANRF/ECRG/2024/000505/LS), the Ignite Life Science Foundation (Acorn Grant ID: AMR3/RNATech/2024/01), and the Indian Council of Medical Research (ICMR) through a small extramural research grant (Grant ID: IIRPSG-2025-01-00183). This article is registered under the CSIR–IICT publication number IICT/Pubs./2025/467.

Conflict of Interest

The authors declare no conflict of interest. Given his role as the Guest Editor, Srinivasa Reddy Bonam had no involvement in the peer-review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Graham Pawelec.

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