Correspondence

Platelet-macrophage cross talk in IL-33–driven type 2 lung inflammation: Advances, gaps, and future directions

To the Editor:

The recent study by Hayashi et al provides compelling mechanistic insight into how platelet-macrophage cooperation drives IL-33–dependent type 2 lung immunopathology in a sex-biased manner.[1] Building on a growing body of literature recognizing platelets as active immune modulators rather than passive hemostatic elements, this work advances our understanding of how innate immune circuits amplify type 2 inflammation (T2I) in the lung.

A major strength of the study by Hayashi et al[1] is its demonstration that platelets act as upstream orchestrators of macrophage-driven IL-33 responses rather than by merely amplifying downstream inflammation.[1] The authors show that platelet activation promotes the recruitment and activation of IL-33–expressing macrophages and enhances leukotriene C_4 synthesis.[1] Platelet-derived leukotriene C_4, in turn, sustains expansion of alveolar type 2 epithelial cells and group 2 innate lymphoid cells (ILC2s), establishing a feedforward inflammatory loop that reinforces T2I.[1]

Importantly, these pathways are integrated within a sex-biased immunologic framework, with females exhibiting heightened susceptibility. These findings are consistent with prior observations that IL-33–driven responses and asthma severity differ by sex, particularly in adulthood. By directly linking platelet-macrophage interactions to sex-dependent immune amplification, the study by Hayashi et al[1] offers a mechanistic explanation for clinical patterns that have largely remained phenomenological.

The work by Hayashi et al[1] extends earlier studies demonstrating that platelets contribute to leukocyte recruitment and generation of inflammatory mediators, including IL-33 and cysteinyl leukotrienes, in allergic airway disease.[2] Although some reports have suggested that platelets can store and release IL-33,[3] Hayashi et al[1] refine this paradigm by showing that although platelets are central regulators of the IL-33 axis, macrophages represent the dominant rapidly inducible source of IL-33 in this context.

Conceptually, the delineation of a platelet-macrophage/alveolar type 2/ILC2 axis represents a significant advance, integrating lipid mediators, epithelial alarmins, and innate lymphoid responses into a cohesive inflammatory circuit. This framework extends existing models of T2I by positioning platelets at the apex of immune coordination rather than as accessory cells, reinforcing the fact that immune cell cooperation rather than isolated cell-intrinsic signaling underlies the severity and persistence of allergic lung disease.

Despite these advances, several limitations warrant consideration. First, the specificity of the genetic models used by Hayashi et al[1] remains an inherent challenge. Cre-loxP strategies (*Pf4* [platelet factor 4]-Cre, *Cx3cr1* [C-X3-C motif chemokine receptor 1]-Cre, and *Sftpc* [surfactant protein C]-Cre), although powerful, are not absolutely cell restricted; notably, Cx3cr1 expression extends beyond macrophages to other $CD45^+$ populations.[4] Second, the inability to achieve platelet-specific IL-33 deletion leaves uncertainty regarding the quantitative contribution of platelet-derived IL-33 to early inflammatory responses. Third, although early (at 6 hours) and delayed (at 24 hours) time points are examined, the temporal resolution may not fully capture rapid platelet-macrophage interactions or macrophage heterogeneity revealed by single-cell studies,[5] including evidence that ILC2 can reprogram alveolar macrophage inflammatory states.[6] Fourth, although interactions among sex hormones, IL-33, and epidermal growth factor receptor are implicated in shaping T2I,[7] the molecular mechanisms by which estrogen and androgens modulate platelet-macrophage signaling remain incompletely understood.[8] Finally, altered circadian clock genes have been linked to time-of-day– and sex-dependent variation in allergen-induced T2I[9,10]; whether circadian regulation directly modulates IL-33 release in this context remains an important open question.

In summary, Hayashi et al[1] identify platelet-macrophage cooperation as a central driver of IL-33–dependent, sex-biased T2I.[1] Although key questions remain regarding cell specificity, temporal dynamics, hormonal regulation, circadian regulation, and translational relevance, the work by Hayashi et al[1] provides a robust framework to guide future investigations and highlights platelets as critical regulators of innate immune coordination in allergic airway disease.

DISCLOSURE STATEMENT

Supported in part by the National Institutes of Health (grant R01HL142543 and R21 ES038641 [to I.K.S.]), as well as by the University of Kansas Medical Center, School of Medicine, Internal Medicine Start-Up Funds (to I.K.S.). The scientific content described in this correspondence is solely the author's responsibility and does not necessarily represent the official views of the National Institutes of Health.

Disclosure of potential conflict of interest: The author declares that he has no relevant conflicts of interest.

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https://doi.org/10.1016/j.jaci.2026.06.022