Unneutral neutrophils in patients with late-phase allergic reactions

David P. Huston, MD  Houston, Tex

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Neutrophils are the most abundant leukocyte in the body, and their role in both innate and adaptive immunity continues to unfold. In the context of immediate hypersensitivity allergic reactions, neutrophils have been observed in patients with cutaneous, nasal, and asthmatic late-phase allergic reactions (LPARs). However, as the complexities of immediate hypersensitivity reactions and LPARs have been elucidated over the past 30 years, the role of neutrophils in these reactions remains poorly understood.

The clinical and histologic evolution of LPARs after allergen challenge is usually evident over 4 to 12 hours but might persist longer and is characterized by a mixed cellular influx of neutrophils, eosinophils, basophils, monocytes, and CD4\(^+\) and CD8\(^+\) T cells. However, what promotes the LPAR in some subjects and not others after an immediate hypersensitivity reaction, as manifested by mast cell activation and degranulation, remains unknown.

Recently, Polak et al\(^2\) provided evidence that neutrophils activated by GM-CSF, IL-3, and IFN-\(\gamma\) have the potential to endocytose the prototypic birch pollen allergen Bet v 1, which was then rapidly degraded in endolysosomes into peptide fragments that were loaded into HLA-DR molecules. These molecules were transported to the cell surface and efficiently stimulated Bet v 1–specific T\(_{H}2\) cell clones in an epitope-specific manner to proliferate and produce IL-4, IL-5, and IL-13 but little IFN-\(\gamma\). A characteristic of the activated neutrophils was the absence of CD80 or CD86 expression, suggesting that their capacity to stimulate T cells was limited to memory T cells and not naive T cells. Neutrophils that were not cytokine activated were unable to stimulate the T-cell clones.

Comparison of cytokine-activated neutrophils with cytokine-activated monocytes revealed that cytokine-activated neutrophils had accelerated kinetics of antigen processing, whereas monocytes were more potent stimulators of the T-cell clones and had accelerated kinetics of antigen processing, whereas monocytes. Neutrophils could stimulate T-cell activation and proliferation and provided evidence that neutrophil CD58 engagement of CD2 on T cells provided signal 2 after TCR engagement of allergen peptide presented by the neutrophil HLA-DR.

Although the authors confirmed and extended previous studies demonstrating the capacity of GM-CSF–, IL-3–, and IFN-\(\gamma\)–stimulated neutrophils to upregulate HLA-DR expression and serve as antigen-presenting cells to memory CD4\(^+\) T cells, their conclusion regarding the role of activated neutrophils in the pathobiology of LPARs deserves additional consideration. Because the LPAR usually evolves over 4 to 12 hours and the cytokine-stimulated neutrophils used in the in vitro studies were cultured for 48 hours before coculture with the birch allergen–specific T-cell clones that were also expanded in vitro, extrapolation of in vitro results to in vivo events must be cautiously considered. Because the LPAR influx of leukocytes after mast cell degranulation usually peaks by 12 hours, the in vivo kinetics of cytokine activation of neutrophils becomes important. Equally relevant is that the in vitro studies were done with purified neutrophils and birch pollen–specific T-cell clones in the absence of the complex milieu of the in vivo mixed cellular, chemokine, and cytokine response that occurs during the immediate allergic response and the evolution of the LPAR. A key aspect of their studies was the detailed analysis of the ability of cytokine-activated neutrophils to endocytose and degrade Bet v 1 into peptides that could be loaded into HLA-DR molecules and expressed as a broad spectrum of epitopes recognized by Bet v 1–specific CD4\(^+\) T-cell clones.

The dynamics of neutrophil participation in the LPAR might also extend beyond serving as antigen-presenting cells. IL-4 has been shown in mice to antagonize neutrophil expansion and migration by signaling through the type 2 IL-4 receptor to decrease responsiveness to granulocyte colony-stimulating factor and downregulate expression of chemokine receptors. In this issue, Impellizzeri et al\(^6\) demonstrate that engagement of the human neutrophil type 1 or type 2 IL-4 receptor by either IL-4 or IL-13, respectively, can downregulate neutrophil CXCR1 and CXCR2 expression and thereby impairs their chemotaxis to CXCL8. Hence in the LPAR, cytokine-activated neutrophils...
can serve as antigen-presenting cells capable of stimulating the proliferation of influxing CD4$^+$ T-cells and their production of TH2 cytokines (IL-4, IL-5, and IL-13), which serve as an agonist for promotion of TH2 immunity. Furthermore, the induced IL-4 and IL-13 can act in a negative feedback loop to neutrophils to antagonize their further migration, thereby limiting the local immune reaction. This model is consistent with the minor presence of neutrophils in TH2/TH22 axis lesions of patients with atopic dermatitis versus an abundance of neutrophils in TH1/TH17-driven lesions of patients with psoriasis. Such a negative feedback loop is also consistent with the ability of anti–IL-4 mAb to increase lung neutrophil counts in a dust mite sensitization model of airway inflammation.

An additional consideration in the role of neutrophils in the LPAR is the emerging appreciation of phenotypic diversity and plasticity among neutrophil subpopulations. Precise identification of the various functional subpopulations is not yet clearly established, but the demonstration by Polak et al$^2$ that less than 25% of the cytokine-stimulated neutrophils expressed HLA-DR raises the possibility of neutrophil heterogeneity within the LPAR. The concept of proatopic neutrophil subsets has been suggested by association of CD49d$^+$ cysteinyi leukotriene receptor 1–positive neutrophils in patients with acute viral respiratory tract infections and postviral atopic airway disease.$^7$ Further evidence for neutrophil heterogeneity is suggested in patients with allergic rhinitis, in whom activated neutrophils in atopic nasal tissue were predominantly CD16$^{high}$CD62L$^{dim}$ in comparison with normal nasal mucosal neutrophils that were CD16$^{high}$CD62L$^{high}$, with the activated neutrophils capable of stimulating T cells.$^9$

Both neutrophil and eosinophil extracellular DNA traps have been described in atopic patients with neutrophilic and eosinophilic inflammation, respectively, of the respiratory and nasal sinus tracts and have been implicated in exacerbation of the inflammatory response as a mechanism of host defense against microbes.$^{10}$ Herein, Impellizzieri et al$^5$ extended their studies to demonstrate that IL-4 or IL-13 stimulation of neutrophils decreased neutrophil extracellular DNA trap formation. In aggregate, the recent studies by Polak et al$^{2,3}$ and Impellizzieri et al$^5$ implicate the neutrophil as a dynamic player in LPARs (Fig 1).

There is still much to learn regarding the role of neutrophils in the initiation and promotion of immune responses for both host defense and atopy. Since the early descriptions of neutrophils as part of the cutaneous LPAR, neutrophils took a backseat to atopy mechanistic studies focused on TH2 responses. However, the recent literature is replete with evidence that the neutrophil is far more than a short-lived innate cell relegated to antimicrobial activity. Insight into the partisan role of activated neutrophils for promoting TH2 immunity and the potential for TH2 immunity to modulate neutrophil function might provide the mechanistic basis for therapeutic manipulation of neutrophils.

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REFERENCES


