IMMUNE RESPONSES

Variable neutrophils

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Neutrophils have always been classified as innate immune cells: cells that are the first to reach a site of inflammation and that recognize pathogens through invariant receptors. Now, new research shows that a subpopulation of mammalian neutrophils expresses a T-cell receptor (TCR)-based variable immunoreceptor, indicating that neutrophils might use both innate and adaptive immune mechanisms for pathogen recognition.

Immunohistochemical analysis of peripheral-blood neutrophils stained with antibodies specific for the α-chain and β-chain of the TCR showed that 5–8% of circulating neutrophils express both of these subunits. A similar percentage of $CD16^{hi}$ neutrophils were shown to express TCRα, using flow cytometry. Using electron microscopy, the authors showed that these subunits formed heterodimers and higher-order TCR complexes, similar to those seen at the surface of T cells. They also showed that neutrophils expressed the constant regions of TCRγ and TCRδ. Transcriptional profiling of the mRNA encoding the variable regions of TCRα and TCRβ showed great sequence variation, and the expression profile differed between individuals. Therefore, a subpopulation of neutrophils expresses TCR-based immunoreceptors that have complex variable regions and vary between individuals.

Interestingly, peripheral-blood neutrophils constitutively express recombination-activating gene 1 (RAG1) and RAG2 proteins, which initiate genomic V(D)J recombination, confirming that neutrophils express the specific proteins that are required for the generation of TCR diversity. Neutrophils also express components of the TCR-signalling complex, including the ζ-chain of CD3, ZAP70 (ζ-chain-associated protein kinase of 70 kDa) and linker for activation of T cells (LAT).

The authors isolated neutrophils from a patient with X-linked severe combined immunodeficiency (a disorder that results in markedly reduced numbers of T cells) and from nude mice (which are devoid of T cells) and showed that these neutrophils still expressed the constant regions of TCRα and TCRβ. Therefore, the expression of the TCR-based immunoreceptor by neutrophils is independent of TCR expression by T cells.

Expression of RAG1 and RAG2, as well as expression of the constant regions of the TCR chains, was shown to be regulated by granulocyte colony-stimulating factor, a factor that is important for the differentiation of neutrophil precursors. Stimulation of the neutrophil TCR-based immunoreceptor with CD3-specific antibody was found to increase expression of the anti-apoptotic factor B-cell lymphoma X_L ($BCL\text{-}X_L$), to protect neutrophils from apoptosis and to increase expression of the neutrophil-activating chemokine CXC-chemokine ligand 8 (CXCL8; also known as IL-8).

Taken together, these results provide evidence that a subpopulation of mammalian neutrophils expresses a TCR-based variable immunoreceptor. Although the exact role of the variable immunoreceptor of these cells is not known, this unique observation by Puellmann and colleagues could lead to a greater understanding of the role of neutrophils and the TCR in the immune system.

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ORIGINAL RESEARCH PAPER
Puellmann, K. *et al.* A variable immunoreceptor in a subpopulation of human neutrophils. *Proc. Natl Acad. Sci. USA* **103**, 14441–14446 (2006)
FURTHER READING Nathan, C. Neutrophils and immunity: challenges and opportunities. *Nature Rev. Immunol.* **6**, 173–182 (2006)