

Safeguard function of PU.1 shapes the inflammatory epigenome of neutrophils.

Fischer J, Walter C, Tönges A, Aleth H, Jordão MJC, Leddin M, Gröning V, Erdmann T, Lenz G, Roth J, Vogl T, Prinz M, Dugas M, Jacobsen ID, Rosenbauer F (2019) Safeguard function of PU.1 shapes the inflammatory epigenome of neutrophils. *Nat Immunol* 20(5), 546-558.

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Abstract

Neutrophils are essential first-line defense cells against invading pathogens, yet when inappropriately activated, their strong immune response can cause collateral tissue damage and contributes to immunological diseases. However, whether neutrophils can intrinsically titrate their immune response remains unknown. Here we conditionally deleted the *Spi1* gene, which encodes the myeloid transcription factor PU.1, from neutrophils of mice undergoing fungal infection and then performed comprehensive epigenomic profiling. We found that as well as providing the transcriptional prerequisite for eradicating pathogens, the predominant function of PU.1 was to restrain the neutrophil defense by broadly inhibiting the accessibility of enhancers via the recruitment of histone deacetylase 1. Such epigenetic modifications impeded the immunostimulatory AP-1 transcription factor JUNB from entering chromatin and activating its

targets. Thus, neutrophils rely on a PU.1-installed inhibitor program to safeguard their epigenome from undergoing uncontrolled activation, protecting the host against an exorbitant innate immune response.

Involved units

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