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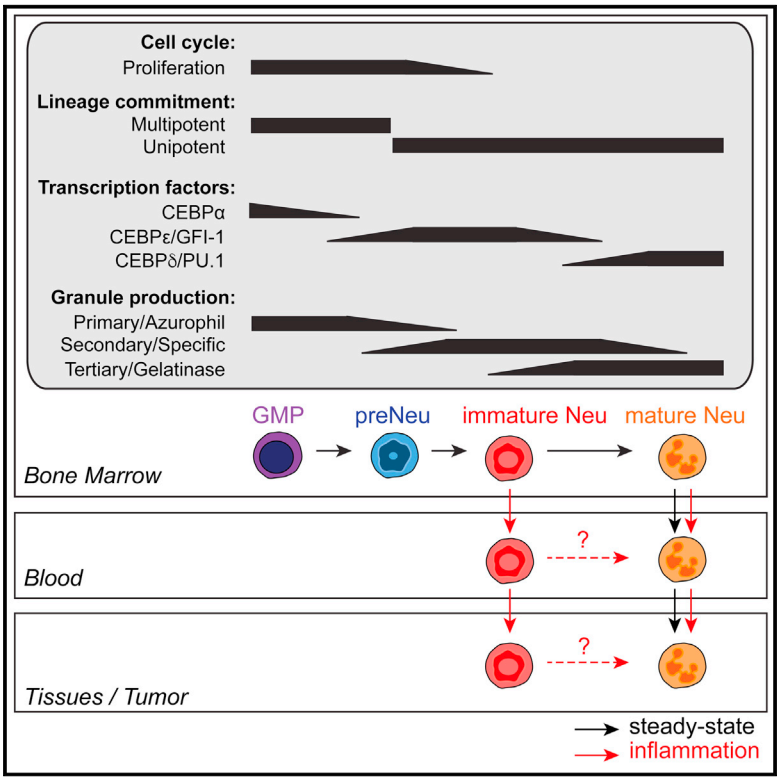
Developmental Analysis of Bone Marrow Neutrophils Reveals Populations Specialized in Expansion, Trafficking, and Effector Functions

Graphical Abstract



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In Brief

The neutrophil differentiation pathway is poorly defined. Evrard et. al. demonstrate a workflow of characterizing bone marrow neutrophil subsets on the basis of their proliferative capacity and molecular signatures and thereby define the developmental trajectory and functional properties of neutrophils.

Highlights

- Proliferation activity identifies committed neutrophil precursor in mice and humans
- Neutrophil subsets possess distinct transcriptomic and functional signatures
- Defect in neutrophil development leads to impaired neutrophil-mediated responses
- Increased circulating immature neutrophils are associated with cancer progression

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Developmental Analysis of Bone Marrow Neutrophils Reveals Populations Specialized in Expansion, Trafficking, and Effector Functions

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SUMMARY

Neutrophils are specialized innate cells that require constant replenishment from proliferative bone marrow (BM) precursors as a result of their short half-life. Although it is established that neutrophils are derived from the granulocyte-macrophage progenitor (GMP), the differentiation pathways from GMP to functional mature neutrophils are poorly defined. Using mass cytometry (CyTOF) and cell-cycle-based analysis, we identified three neutrophil subsets within the BM: a committed proliferative neutrophil precursor (preNeu) which differentiates into non-proliferating immature neutrophils and mature neutrophils. Transcriptomic profiling and functional analysis revealed that preNeu require the C/EBPε transcription factor for their generation from the GMP, and their proliferative program is substituted by a gain of migratory and effector function as they mature. preNeus expand under microbial and tumoral stress, and immature neutrophils are recruited to the periphery of tumor-bearing mice. In summary, our study identifies specialized BM granulocytic populations that ensure supply under homeostasis and stress responses.

INTRODUCTION

Neutrophils are the most abundant immune cell type in human peripheral blood and act as the first responders during sterile and microbial insults. They elicit powerful effector functions to eliminate foreign threats and play crucial roles in tissue remodeling (Borregaard, 2010; Kolaczkowska and Kubes, 2013). Neutrophils are short lived; they have an estimated half-life of 19 hr in humans (Lahoz-Beneytez et al., 2016; Tak et al., 2013). Therefore, neutrophils must be constantly replenished; an impairment in their production and migration leads to neutropenia and life-threatening conditions (Summers et al., 2010).

Historically, neutrophil development has been defined by histological staining and electron microscopy into stages based on neutrophil size, nucleus morphology, and cytosol coloration. After maturation, neutrophils are retained in the BM through CXCR4 chemokine receptor signaling, and CXCR2 signaling drives their release into the circulation (Devi et al., 2013). During inflammation, increased amounts of granulocyte-colony-stimulating factor (G-CSF) can potentiate mobilization of neutrophils from the BM by lowering the threshold of their release (Kim et al., 2006) and increasing the amounts of mobilizing signals (i.e., CXCL1) (Köhler et al., 2011).

It is believed that neutrophils consist of a homogeneous population. However, this view is rapidly evolving thanks to increasing reports of neutrophil heterogeneity (reviewed in (Silvestre-Roig et al., 2016)). Notably, these studies focused