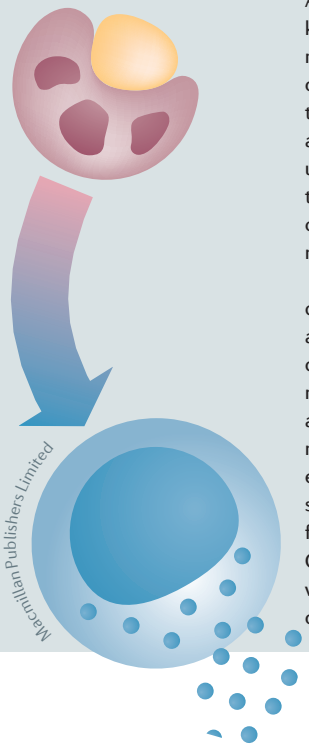
Nature Reviews Immunology | Published online 27 Oct 2017; doi:10.1038/nri.2017.122

NEUTROPHILS

Neutrophil differentiation is autophagy dependent



Autophagy-deficient neutrophils are known to have inadequate inflammatory responses that limit their cytotoxic capabilities; however, despite the rapid turnover of neutrophils, the role of autophagy in their differentiation is unclear. Now, Riffelmacher *et al.* report that the autophagy-mediated generation of free fatty acids (FFAs) is essential for neutrophil differentiation.

The authors first demonstrated dynamic regulation of autophagy at different stages of neutrophil differentiation *in vivo* using a transgenic mouse model. The highest levels of autophagic flux were observed in myeloblasts and promyelocytes in the early stages of differentiation, with a smaller re-engagement of autophagic flux observed at the final stage. Conditional targeted deletion of *Atg7*, which encodes an essential autophagy component, in haematopoietic stem cells (HSCs) and progenitor cells leads to the accumulation of immature neutrophils, thus confirming the importance of autophagy. The authors then generated a mouse model with a more-targeted deletion of *Atg7* in neutrophil progenitors, but not in HSCs. This model demonstrated a similar accumulation of immature neutrophils. Further evidence that this reflects deficient cell-intrinsic autophagy, and not other alterations during development, was provided by inducible deletion of *Atg5*, which is also critical to cell-intrinsic autophagy, in adult mice and in *in vitro* experiments.

The authors then examined alterations in metabolic requirements during neutrophil maturation. Metabolomic analysis of neutrophils undergoing granulocyte colony-stimulating factor-induced differentiation demonstrated a shift towards engagement of mitochondrial respiration, with downregulation of all glycolysis-associated genes. The same analysis of *Atg7*-deficient cells revealed upregulation of glycolysis at all stages of differentiation, suggesting that autophagy is required to engage mitochondrial respiration while also constraining glycolysis.

The authors also observed a depletion in FFA levels in *Atg7*-deficient myeloblasts *in vitro* relative to wild-type myeloblasts; similarly, *ex vivo Atg7*-deficient and *Atg5*-deficient neutrophils both showed signs of intracellular lipid accumulation, suggesting defective lipolysis.

Hypothesizing that oxidation of FFAs provides the necessary ATP for neutrophil differentiation, the authors were able to pharmacologically target this metabolic dependency to inhibit neutrophil maturation in wild-type myeloblasts. Furthermore, exposing *Atg7*-deficient neutrophil precursors to exogenous FFAs restored differentiation.

In summary, this research reveals the importance of cell-intrinsic autophagy in fulfilling the metabolic demands of neutrophil differentiation. These findings could guide the design of novel treatments for myeloid leukaemias or neutropenia.

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ORIGINAL ARTICLE Riffelmacher, T. *et al.* Autophagy-dependent generation of free fatty acids is critical for normal neutrophil differentiation. *Immunity* **47**, 466–480 (2017)