

# The immune regulatory role of neutrophils

Daniel M. Altmann

Department of Medicine, Hammersmith  
Hospital, London, UK

doi:10.1111/imm.13049

Correspondence: Prof Daniel M. Altmann,  
Department of Medicine, Hammersmith  
Hospital, Du Cane Road, London W12  
0NN, UK.

Email: d.altmann@ic.ac.uk

## Summary

Neutrophils are appreciated to perform a wide range of pro- and anti-inflammatory effector functions in diverse settings. These go far beyond the response to acute infection, encompassing sterile injury, autoimmunity, allergy and tumours. There is growing appreciation of the nuances of their modes of action, especially elucidation of the nature and consequences of NETosis. New work suggests that it is time to give greater consideration to the anti-inflammatory role of neutrophils, such as in the control of cytokine release during sepsis.

It has been a truism of the march of molecular immunology that any cell-type once dismissed as performing a simple or limited function has turned out, when investigated with technologies that allow sufficient granularity, to encompass myriad, novel and fascinating receptors and functions. Consider the poor natural killer cell, marginalized for decades as a 'null-cell' – significant only for what it was not, neither B nor T, and killing targets with unrestricted abandon. Today, natural killer cell biology is among the most exciting branches of immunology, with ever more nuance apparent with respect to ligand recognition, the fine balance between inhibition and activation, and the wide range of transcriptional choices in terms of effector programmes.<sup>1</sup> Or, consider the humble neutrophil: in many textbooks, these were the Keystone Cops of innate immunity – the dumb, first line of attack of the acute inflammatory response, rushing into tissues by the million in response to infection or other insult, degranulating, often in a potentially damaging way, and then dying within the day.

Every aspect of this has had to be re-taught. There turn out to be subsets of neutrophils, produced in the bone marrow under regulated control so that, during infection, for example, synthesis can increase to 10 billion/kg human body weight.<sup>2</sup> Lifespan is now appreciated to be 7 days or more at the site of inflammation in tissue.<sup>3</sup> Among the most exciting updates has been the diversity and complexity of effector functions, including of course, NETosis, a weapon sometimes likened to the web used by Spiderman to catch crooks. 'NETs' are 'neutrophil extracellular traps', comprising expelled networks of extracellular fibres, histones, chromatin and DNA, used to trap bacteria and other microbial pathogens. Initially described as a suicidal event, it is now clear that NETosis may be either suicidal or 'vital' – that is, without cell death. Both protective and pathogenic functions of NETosis are under

investigation in diverse settings including in the tumour microenvironment, sterile injury, autoimmune disease, allergy and atherosclerosis.<sup>4–6</sup> There remain important questions about the activation signals for NETosis and the associated control, but there will clearly be important drug targets here. The observation that NETs promote tumour metastasis has encompassed initial experimental demonstration of therapeutic targeting of NETosis to block metastasis.<sup>5,6</sup>

One of the big unknowns in neutrophil biology is to characterize not just the pro-inflammatory functions, but also the regulatory ones. The possibility of regulatory neutrophil function was first raised a decade ago, in a model looking at control of lung inflammation.<sup>7</sup> An interesting new paper investigates the anti-inflammatory properties of neutrophils by comparing the lipopolysaccharide mouse challenge model in the presence or absence of neutrophils.<sup>8</sup> Surprisingly, it was found that a range of cytokines and chemokines were enhanced in the absence of neutrophil regulation, as was the release of exosomes. This finding opens the door to characterization of the precise functions and mechanisms of regulatory neutrophils – should they be called N-regs, by analogy to regulatory T cells, or Tregs? One recent study proposes that neutrophils may be able to regulate immunity through the modulation of dendritic cells.<sup>9</sup>

All of these issues will need to be considered in the context of the cross-talk between neutrophils and the adaptive immune system. Scapini and colleagues have comprehensively reviewed the intricate tango that is danced between neutrophils and lymphocytes at the interface between innate and adaptive immunity.<sup>10</sup> It is clear that neutrophils can engage in either positive or negative modulating interactions with T-cell subsets such as T helper type 1 (Th1), Th2, Th17, Treg, CD8 and  $\gamma\delta$  T cells.

All in all, busy times and challenges for neutrophil researchers: the Keystone Cops developed the skill set of Spiderman and were then found to have been in close contact with all the other Superheroes all along!

## References

- 1 Bastidas-Legarda LY, Khakoo SI. Conserved and variable natural killer cell receptors: diverse approaches to viral infections. *Immunology* 2018; <https://doi.org/10.1111/imm.13039>.
- 2 Ley K, Hoffman HM, Kubes P, Cassatella MA, Zychlinsky A, Hedrick CC *et al.* Neutrophils: new insights and open questions. *Sci Immunol* 2018; **3**(30). pii: eaat4579. <https://doi.org/10.1126/sciimmunol.aat4579>.
- 3 Summers C, Rankin SM, Condliffe AM, Singh N, Peters AM, Chilvers ER. Neutrophil kinetics in health and disease. *Trends Immunol* 2010; **31**:318–24.
- 4 Jorch SK, Kubes P. An emerging role for neutrophil extracellular traps in noninfectious disease. *Nat Med* 2017; **23**:279–87.
- 5 Albregues J, Shields MA, Ng D, Park CG, Ambrico A, Poindexter ME *et al.* Neutrophil extracellular traps produced during inflammation awaken dormant cancer cells in mice. *Science* 2018; **361**(6409). pii: eaao4227. <https://doi.org/10.1126/science.aao4227>.
- 6 Lee W, Ko SY, Mohamed MS, Kenny HA, Lengyel E, Naora H. Neutrophils facilitate ovarian cancer premetastatic niche formation in the omentum. *J Exp Med* 2019; **216**:176–94.
- 7 Zhang X, Majlessi L, Deriaud E, Leclerc C, Lo-Man R. Coactivation of Syk kinase and MyD88 adaptor protein pathways by bacteria promotes regulatory properties of neutrophils. *Immunity* 2009; **31**:761–71.
- 8 van der Meer AJ, Ding C, Hoogendijk AJ, deVos AF, Boon L, Zeerleder SS *et al.* Neutrophils mitigate the systemic host response during endotoxemia in mice. *Immunology* 2019; **156**:277–81.
- 9 Finlay TM, Palmer AL, Ousman SS. Murine neutrophils treated with zB-crystallin reduce IL-12p40 production by dendritic cells. *Immunology* 2018; **155**:72–84.
- 10 Costa S, Bevilacqua D, Cassatella MA, Scapini P. Recent advances on the crosstalk between neutrophils and B or T lymphocytes. *Immunology* 2019; **156**:23–32.