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PLASMACYTOID DENDRITIC CELLS

Division of labour

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It is generally thought that an individual microbial stimulus induces a single corresponding activated immune cell state. However, a new paper in *Nature Immunology* challenges this dogma by showing that activation of human plasmacytoid dendritic cells (pDCs) with a single viral stimulus induces diversification into multiple stable subpopulations.

The authors characterized human pDCs following exposure to influenza virus on the basis of their expression of the activating receptor CD80 and the inhibitory receptor programmed cell death 1 ligand 1 (PDL1). They identified three distinct pDC populations that they termed P1 ($PDL1^+CD80^-$), P2 ($PDL1^+CD80^+$) and P3 ($PDL1^-CD80^+$). These pDC phenotypes were stable, even after secondary culture of sorted subpopulations for up to 48 hours, with or without a second viral stimulus. In addition to distinct phenotypes, the authors observed morphological differences between the P1, P2 and P3 populations. P1 pDCs retained a plasmacytoid morphology (similar to unstimulated pDCs) and well-defined endoplasmic reticulum (ER), whereas P3 pDCs had a dendritic morphology and less pronounced ER, and P2 pDCs had an intermediate morphology.

Transcriptional profiling revealed 310 coding mRNAs and 110 noncoding RNAs that were differentially regulated across the three pDC populations, further supporting their distinct identities. The transcriptomic signature of the P1 population was biased to interferon (IFN)-encoding genes. Indeed, 80% of total IFNα-producing pDCs had the P1 phenotype. By contrast, P3 pDCs did not produce IFNα even after a second round of stimulation with influenza virus. Instead, compared with P1 and P2 pDCs, P3 pDCs had higher surface levels of CC-chemokine receptor 7 (CCR7), which is crucial for migration towards lymph nodes. Accordingly, P3 pDCs migrated faster and more persistently towards a gradient of CCR7 ligand than the other pDC subpopulations. Moreover, P3 pDCs induced the highest levels of T cell proliferation and lowest levels of surface PD1 on activated $CD4^+$ T cells. Finally, P3 pDCs showed a preference for inducing T helper 2 cells, whereas T cells activated by P1 pDCs produced higher levels of IFNγ and IL-10. Together, these data indicate that the three subpopulations have specialized functions in innate and adaptive immunity, suggesting a division of labour among them.

Interestingly, pDC diversification after activation with various different stimuli was independent of cell division and was not the result of heterogeneity among pre-committed precursor cells. Instead, pDC diversity was regulated by autocrine and paracrine signalling mediated by tumour necrosis factor (TNF), as blockade of TNF receptors led to a marked reduction in the P2 and P3 populations and an increase in the P1 population. Together, these findings suggest a new mechanism by which non-dividing cells can diversify in response to a single stimulus.

Lucy Bird

> “the three subpopulations have specialized functions in innate and adaptive immunity”

ORIGINAL ARTICLE Alculumbre, S. G. *et al.* Diversification of human plasmacytoid predendritic cells in response to a single stimulus. *Nat. Immunol.* http://dx.doi.org/10.1038/s41590-017-0012-z (2017)
FURTHER READING Swiecki, M. & Colonna, M. The multifaceted biology of plasmacytoid dendritic cells. *Nat. Rev. Immunol.* **15**, 471–485 (2015)