Immune cell diversification in response to a single stimulus: from single cells to subsets and back

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Cells change state in response to environmental stimuli, a process called adjustment. When a seemingly homogeneous cell population receives a stimulus, it collectively and progressively switches to a different state. In a recent study of innate immune cells, i.e plasmacytoid pre-dendritic cells (pDC), we could show that primary human pDC diversify over 24h into three distinct subpopulations (P1, P2, P3) in response to a single microbial stimulus, such as influenza virus or CpG oligonucleotide (Alculumbre et al, Nat Immunol, 2018). This was revealed by single cell analysis using multicolor flow cytometry. P1-, P2-, and P3-pDC harbor distinct morphology, phenotype, transcriptional signatures for coding and non-coding RNA, as well as function. Subsequently, we turned back to single cell RNAseq analysis of pDC diversification in order to precisely quantify transcriptomic level diversity of pDC over time following stimulation, and search for putative molecular mechanisms underlying the stepwise diversification process, helped by pseudo time analysis. We propose that cell diversification may be a general mechanisms generating diversity following cellular adjustment to a single stimulus, driven by stochastic as well as deterministic events characterizing each specific cellular system.