Role of danger and microbial signals in neutrophils subpopulations recruitment during infection.

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Abstract:

Neutrophils are key cells in the innate immune response, but their recruitment during infection is unclear. While their migration to infected sites is traditionally associated with pathogen recognition via Pattern Recognition Receptors (PRRs), recent discoveries have instead underlined a primary role of type I interleukins. Mechano-sensing has also emerged as a factor in the response to gram-negative bacteria, independent of PRRs.

Using three different skin infection model in mice, our project aims at understanding neutrophil recruitment during infection. Flow cytometry identified neutrophils as Ly6GhighLy6CintCD11bhigh. The molecular cascade underlying neutrophil recruitment was examined through quantification of pro-inflammatory mediators.

Findings revealed that neutrophil recruitment is regulated by upstream mediators converging to MyD88. Two waves of recruitment were observed, and we could mechanistically define the first one. Early recruitment is commonly shared between infections, and it's mediated by an LTB_4-IL-1-CXCL1 axis, acting through CD11c+ innate immune cells. PRRs had minimal contribution to the regulation of this axis, while mechanosensors, in particular PIEZO1 and TRPV4 channels, actively contribute to the *in vivo* production of LTB_4. Moreover, neutrophil subpopulations, both fresh and aged neutrophils were identified at the infected site during the early wave, but a shift towards aged and activated (CD62L-CXCR4-) neutrophils was observed later in recruitment.

We propose a model of early neutrophil recruitment independent of pathogens, relying on a lipid-cytokine-chemokine axis with minimal PRR contribution. This mechanism, already associated with neutrophil recruitment during sterile inflammation seems to be employed during infections as well.