Dynamics and heterogeneity of inflammatory signaling in cells and tissues

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Immune cells must accurately decode changing environmental signals to make fate decisions and coordinate tissue-level responses. Here we use a suite of single cell biology approaches including mathematical modelling, live-cell time-lapse microscopy and transcriptomics to understand signaling of the Nuclear Factor kappa B (NF-κB) system, a master regulator of inflammatory and immune responses. We show that this presumably noisy system, uses oscillatory „deterministic" refractory states to encode closely timed inflammatory cues [1], and operates in the cytokine consumption regime to restrict out-od-control propagation of the inflammation in the tissue [2]. We also demonstrate, that downstream of NF-κB activation, the stochastic expression of NF-κB-dependent genes is constrained by transcriptional bursting. Our analyses suggest that seemingly stochastic immune cells responses are defined by functional constrains.

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[2] Bagnall, J., Boddington, C., England, H., Brignall, R., Downton, P., Alsoufi, Z., Boyd, J., Rowe, W., Bennetts, A., Walker, C., Adamson, A., Patel, N., O'Cualain, R., Spiller, D., Jackson, D., Muller, W., Muldoon, M., White, M. & Paszek, P. "A quantitative analysis of competitive cytokine signaling predicts tissue thresholds for the propagation of macrophage activation", Science Signaling 2018 11:540