Markus Covert
Stanford University
e-mail: mcovert@stanford.edu

Heterogeneous cellular responses via noisy paracrine signals

The mammalian immune response is a striking example of coordination between individual cells. We previously discovered that the response of wild-type murine embryonic fibroblasts (MEFs) to lipopolysaccharide (LPS) depends on paracrine secretion of tumor necrosis factor (TNF). We then demonstrated in single cells that the low concentration of the paracrine TNF signal results in two qualitatively different responses to LPS: roughly one-half of the cells exhibit a transient NF-kappaB response, while the other half exhibit a persistent response with NF-kappaB remaining in the nucleus for hours. Only cells that sense the low TNF concentration and therefore respond to the paracrine signal exhibit the persistent response. The ability of a low concentration signal to create qualitatively different subpopulations of cells in response to one stimulus led us to ask, how does a single cell respond to low concentrations of TNF? To answer this question, we measured NF-kappaB activity in thousands of living cells under TNF doses covering four orders of magnitude to determine the range of individual cell responses which occur in a population, and what effect these responses might have on NF-kappaB dependent gene expression.