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Design principles for information processing through signalling networks

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Cells have to respond to changes in their environment. Alterations in extracellular signals are perceived by cell surface receptors and trigger the activation of complex intracellular signalling networks. Currently rather little is known regarding design principles that link pathway activation with cellular responses.

The erythropoieting receptor (EpoR) is a cytokine receptor and the key regulator of erythropoiesis regulating proliferation, differentiation and survival of erythroid progenitor cells. A major signaling pathway activated by the EpoR is the extracellular signal regulated kinase (ERK) cascade. By combining quantitative data with mathematical modelling, we predicted and experimentally confirmed a distributive ERK phosphorylation mechanism in response to EpoR activation. Model analysis revealed that increasing one ERK isoform reduces activation of the other isoform, which was verified by protein overexpression. Furthermore we showed by statistical modelling that double-phosphorylated ERK1 attenuates proliferation beyond a certain activation level, while activated ERK2 enhances proliferation with saturation kinetics. Thus, we provide a quantitative link between previously unobservable signalling dynamics and cellular responses.

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