

P010 A growth factor receptor phospho-Tyr/phospho-Ser motif that acts as a binary switch to control PI3-kinase signalling is deregulated in leukemia.

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Previous work in our lab has identified a new mechanism by which PI 3-kinase can be recruited to growth factor and cytokine receptors. We have shown that phosphorylation of Ser585 of the β c subunit of the Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) receptor is essential for recruitment of the 14-3-3 phospho-serine binding proteins, the coupling of PI 3-kinase and the regulation of cell survival¹⁻³. We now show that the 14-3-3 binding site at Ser585 together with a Shc binding site at Tyr577 in the GM-CSF receptor represents a prototypic example of a novel phospho-Tyr/phospho-Ser binary switch that specifies two alternate signals to independently control cell survival and proliferation. The binary switch is regulated by cytokine concentrations and toggles between two mutually exclusive positions: Ser585 is phosphorylated in response to lower concentrations of cytokine (pM) to promote cell survival alone while Tyr577 is phosphorylated in response to higher concentrations of cytokine (fM) to promote cell proliferation as well as survival. Such a mechanism allows the GM-CSF receptor to convert an analogue input (GM-CSF concentration) to a binary output (either Ser585 or Tyr577 phosphorylation) thus permitting the independent regulation of cell survival and proliferation. Importantly, the phospho-Tyr/phospho-Ser binary switch allows two different modes of PI 3-kinase recruitment and activation: one that is phospho-Tyr-independent and occurs via Ser585 and the other that is dependent on the specific tyrosine phosphorylation of the 14-3-3 proteins. Furthermore, we have shown that this phospho-Tyr/phospho-Ser binary switch is deregulated in a panel of primary myeloid leukemias whereby constitutive Ser585 phosphorylation and PI 3-kinase signalling leads to autologous cell survival. We have identified transcriptional targets of this novel Ser585 signalling pathway and blocking one such target short-circuits the autologous survival of leukemic cells suggesting that this pathway may provide opportunities for the development of therapeutic strategies for the treatment of leukemia. Similar phospho-Tyr/phospho-Ser motifs in other cell surface receptors and signalling proteins have been identified suggesting that such signalling switches may play important roles for the independent regulation of cell survival and proliferation in other systems.