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CELL SIGNALLING

PRMT5 restricts ERK activity

> a PRMT5-induced methylation event can decrease the amplitude of ERK phosphorylation.

Growth factors can activate the RAS–RAF–MEK–ERK (RAS–RAF–MAPK/ERK kinase (also known as MAPKK)–extracellular signal-regulated kinase) pathway with different kinetics to result in distinct biological outcomes. For example, ERK activation in PC12 cells is high and sustained in response to nerve growth factor (NGF), resulting in cell differentiation, but low and transient in response to epidermal growth factor (EGF), resulting in cell proliferation. Andreu-Pérez *et al*. have identified the mechanism behind this phenomenon, revealing that, in response to certain growth factors, protein Arg *N*-methyltransferase 5 (PRMT5) methylates RAF isoforms to enhance their degradation and reduce the amplitude of ERK activation.

The authors observed that cellular ERK1 and ERK2 phosphorylation increase in response to several growth factors in the presence of the methylation inhibitor 5′-methylthioadenosine (MTA). Depletion of the methyltransferase PRMT5 also increased growth factor-induced ERK phosphorylation, suggesting that a PRMT5-induced methylation event can decrease the amplitude of ERK phosphorylation.

So, what does PRMT5 methylate to regulate ERK phosphorylation?

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The authors found that CRAF (also known as RAF1) and BRAF interacted with PRMT5, and that their kinase activity in response to growth factors was increased in the presence of MTA or in the absence of PRMT5. Moreover, CRAF was methylated at Arg563 in response to EGF, and mutation of this site or of the equivalent site in BRAF increased the stability and catalytic activity of these proteins. Thus, methylation of BRAF and CRAF, in response to specific growth factors, decreases their stability and activity to reduce ERK1 and ERK2 phosphorylation.

Finally, the authors determined whether this methylation regulates the difference in the biological response of PC12 cells to EGF and NGF. Indeed, treatment of PC12 cells with EGF and MTA, or expression of CRAF or BRAF mutants that cannot be methylated, increased EGF-induced ERK phosphorylation in PC12 cells. This led to the cellular differentiation that is usually seen in response to NGF. Importantly, as PRMT5 activity was increased in response to EGF but decreased in response to NGF, RAF methylation is likely to explain the difference in ERK signal amplitude and biological outcome in response to these ligands.

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ORIGINAL RESEARCH PAPER Andreu-Pérez, P. *et al*. Protein arginine methyltransferase 5 regulates ERK1/2 signal transduction amplitude and cell fate through CRAF. *Sci. Signal.* **4**, ra58 (2011)