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RESEARCH NEWS

Phosphorylation, CREB, and Mental Retardation

A review of: Harum KH, Alemi L, Johnston MV 2001 Cognitive impairment in Coffin-Lowry syndrome correlates with reduced RSK2 activation. Neurology 56:207–214

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OVER THE PAST decade, our understanding of the molecular biology of learning and memory has expanded dramatically. The identification of critical receptors, signal transduction components, transcription factors, and RNA binding proteins has painted an ever more detailed picture of how memories are formed. Despite these advances, the connection between basic science findings and developmental disabilities in patients has been slow to emerge. With a few exceptions (notably Fragile X syndrome and Rett syndrome), we still do not understand how the majority of cases of mental retardation are mediated at a molecular level.

Yet, this too is now changing. One example of such progress is research on Coffin-Lowry Syndrome (CLS), an X-linked disorder characterized by mental retardation, facial dysmorphisms, and progressive bony abnormalities. CLS is associated with mutations in the gene for the p90 Ribosomal S6 kinase isoform RSK-2 (1). RSK-2 is a serine/threonine protein kinase that is activated by a number of signal transduction pathways, most notably the Ras/MAP kinase pathway and protein kinase C (PKC) mediated signaling. Although it has a number of different enzymatic targets, perhaps the most intriguing is the cyclic AMP response element binding protein, CREB. CREB is a transcription factor that is implicated as a necessary component for the formation and storage of long-term memories in a variety of species, including *Drosophila*, *Aplysia*, and mice (for review, see ref. 2). Activation of CREB requires phosphorylation at a specific residue (serine 133) and this event in turn leads to the transcriptional activation of a number of genes, including c-Fos.

A recent study by Harum and colleagues has now demonstrated a solid link between Coffin-Lowry syndrome and CREB activation. First, in confirmation of previous studies by other groups (1, 3), they show that fibroblasts derived from a patient with a severe form of CLS lack the ability to phosphorylate CREB in response to stimulation with either epidermal growth factor (EGF) or the phorbol ester PMA, activators of the Ras/MAP kinase and PKC pathways, respectively. This loss of activation is specific to CREB phosphorylation induced by EGF or PMA, as forskolin, which activates CREB through a protein kinase A dependent mechanism, still leads to CREB phosphorylation in these cells. Next, using lymphoblasts derived from a series of seven unrelated cases of CLS, they demonstrate that different mutations in RSK-2 lead to variable levels of expression and inactivation of RSK-2's ability to phosphorylate a CREB-like peptide *in vitro*. Moreover, they show that the degree to which these mutant RSK-2 proteins can phosphorylate this CREB-like target in response to PKC activation directly correlates with the IQs of the patients from which they were derived.

This last finding is especially exciting because of the importance it implies for CREB phosphorylation via this pathway in a human disease. Although other targets of RSK-2 phosphorylation likely play a role in CLS, this marks the most direct connection to date between CREB activation and cognitive impairments in humans. Hopefully it will also be a sign of things to come, whereby the gains made in basic molecular neurobiology will begin to explain the black box that still surrounds many forms of human mental retardation.

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2. Yin JC, Tully T 1996 CREB and the formation of long-term memory. Curr Opin Neurobiol 6:264–268
3. De Cesare D, Jaquot S, Pannetier S, Hanauer A, Sassone-Corsi P 1998 Rsk-2 activity is necessary for epidermal growth factor induced phosphorylation of CREB protein and transcription of c-fos gene Proc Natl Acad Sci USA 95:12202–12207

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