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More evidence for a Gi-regulated ras exchanger.

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Editorial

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The MAP kinase pathway is a signal transduction module that is activated in many cell types by many agonists. Two apparently redundant MAP kinase isoforms $p42^{mapk}$/ERK 2 and $p44^{mapk}$/ERK1 are effectors in the pathway, targeting a number of substrates of regulatory significance prominently including transcription factors, two protein kinases, and cytoplasmic phospholipase A_2 (1). MAP kinase is regulated by dual tyrosine and threonine phosphorylation in a conserved TEY motif catalyzed by remarkably specific MAP kinase kinases (MKKs) or MEKs (see reference 2 and references therein). A family of mammalian protein kinases related to MAP kinase exists, all regulated by closely spaced tyrosine and threonine phosphorylations. The MAP kinase kinase/MAP kinase pairs are likely not to cross-activate. MEK 1 and MEK 2 do not activate the other MAP kinases examined.

In this issue of *The Journal,* Worthen and co-workers studied the mechanism of activation of the MAP kinase pathway by f-Met-Leu-Phe (FMLP). As a result of these studies, the authors have provided additional important evidence for a G_i regulated Ras exchanger. MEKs are activated in vitro by at least two protein kinases that are widely expressed in mammalian cells, the proto-oncogene Raf and the MEK kinase cloned and characterized in Dr. G. Johnson's laboratory (3). Lange-Carter and co-workers hypothesized that MEK kinase might account for MAP kinase activation by G proteins (3).

Surprisingly, several papers (4–5) including a previous paper from the Johnson lab (6) and now including the Worthen paper (6) have demonstrated that agonists that activate MAP kinase through a G_i pathway do so via a mechanism dependent on p21 Ras. Lysophosphatidic acid (4), adrenergic agonists via alpha 2A receptors (5), carbachol via muscarinic m2 receptors (6), and FMLP (7) have all now been shown to activate Ras and MAP kinase. In each case, GTP loading of Ras and MAP kinase activation are blocked by pertussis toxin which is not known to ADP ribosylate Ras. Ras GTP loading is required for activation of Raf. Thus several G proteins that were good candidates for participation in a Ras-independent pathway, possibly involving MEK kinase, appear instead to participate in a Ras/Raf pathway. MEK kinase is still looking for an activator. Identification of the mechanism of G_i-stimulated Ras activation promises to be an exciting arena for friendly competition among the signal transduction laboratories.

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