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Cancer Cell Biology

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Stimuli that regulate cellular functions depend on pathways that detect signals at the cell surface and transmit them through the cytoplasm to nuclear and other intracellular targets. Mitogen activated protein kinase (MAPK) pathways are a prevalent mechanism for this intracellular signal transmission. The core of these pathways is comprised of three sequentially acting protein kinases that are members of the MEKK, MEK and MAPK families (Fig. 1A).

In humans, one cascade regulates cell proliferation and differentiation and several others regulate stress responses. The central importance of MAPK activation to cancer is reinforced by the finding that the proto-oncogenes Ras and Raf normally function in the MAPK cascade controlling proliferation and differentiation (Fig. 1B).

Organizational paradigms for MAPK activation cascades have come from studies on signal transduction in *S. cerevisiae* (Fig. 1C). The prototypes for the three kinase families of these conserved cascades were identified through their role in pheromone-induced mating differentiation in this organism. Subsequently, four additional yeast MAPK activation pathways were defined. Although reiteration of these cascades presents a potential for extensive crosstalk, it is generally observed that the MAPKs of a given pathway are activated only by the appropriate stimulus. Such fidelity is preserved even in circumstances where one of the enzymes functions in more than one pathway (e.g. Ste11). Pioneering studies on the yeast pathways revealed that specificity appears to be maintained because the enzymes of a given cascade are organized into functional modules. Two different modes for assembling these modules have emerged. In the mating differentiation pathway the Ste5 protein functions as a so called scaffold protein to organize the module. In the Sho1 branch of the stress survival pathway, it is a domain of one of the core enzymes (Pbs2) that serves this function. The likely generality of such signaling modules was revealed by the recent identification of potential scaffold proteins and domains that similarly organize mammalian MAPK cascades.

Our current research exploits the well-defined MAPK activation pathways of *S. cerevisiae* to uncover the molecular mechanisms that govern protein-protein associations within a given module and to learn how these associations influence the mechanics and specificity of signal transmission. We are also interested in defining the mechanisms that allow for coordination of signaling through different pathways within the context of these insular modules. To address these issues we rely on biochemical approaches including phosphoprotein analyses and *in vitro* phosphorylation assays. We also apply recombinant DNA technology and mutagenesis approaches that allow the generation and analysis of variants with altered regulation or specificity. Given the high degree of conservation that has already been documented for these cascades, it is likely that the regulatory principles uncovered through our studies will be generally applicable.

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Fig. 1. Schematic representation of MAPK dependent signaling pathways. A. Kinases families comprising a generic MAPK activation module. B. Mammalian pathway controlling proliferation and differentiation. C. Yeast pathways controlling mating differentiation and stress survival.