A is for ...

Scaffold Protein

scaffold protein In signal transduction, a nonenzymatic component of a pathway, essential for efficient and specific signaling.

Environmental signals, if they are to induce a cellular response, must activate a system of intracellular processes that are collectively known as signal transduction. In a eukaryotic cell, transduction pathways lead from the cell membrane to nuclear transcription factors or to other effectors, so that the cell responds appropriately to the signals.

Principal components of these pathways are mitogen-activated protein kinases (MAP kinases or MAPK's), which add phosphate groups to specific amino acids on other proteins and thereby activate them. The MAP kinases are themselves activated by MAP kinase kinases (MAPKK's), which in turn are activated by membrane-associated MAPKK kinases. The three sequentially activated kinases form a MAP kinase module, and a module can be activated by different signals initially received by different receptors.

So far, six MAP kinases, seven MAPK kinases, and seven MAPKK kinases have been identified in mammalian cells. Each is able to function in more than one pathway, so the question is how a signal traverses a specific pathway to reliably activate a particular target.

Kinases can be restricted in terms of their sites of action in two ways. First, after being activated they can be recruited into multiprotein complexes. Formation of signaling complexes requires that one protein include one or more specialized amino acid sequences, called domains, each of which recognizes a specific sequence on another protein. A single protein containing two such domains can simultaneously associate with two binding partners.

Second, several kinases may be bound to a common protein. An anchoring protein is one that holds inactive kinases close to their respective substrates until separate signals activate them. A docking protein contains several potential binding sites for signaling proteins that bind once the docking protein is phosphorylated. Finally, a scaffold protein simultaneously binds the three elements of a MAP kinase module.

Found first in yeast and recently in mammalian cells, scaffold proteins enable the tight control of signaling pathways by clustering the successive members of a MAP kinase cascade. The quick passage of signals from one kinase to the next prevents activation of functionally unrelated kinases not bound to the scaffold. Because different scaffold proteins may bind the same kinase, their existence helps explain how signal specificity is maintained even though different pathways require some of the same kinases.

Hans J. Schaeffer et al., *Science* 281:1668-1671, September 11, 1998. [MP-1.]

Alan J. Whitmarsh et al., *Science* 281:1671-1674, September 11, 1998. [JIP-1.]

Mitogen-activated protein kinase (MAPK) cascades in mammalian cells are known by the designations of the MAP kinases with which they end: extracellular signal related kinase (ERK), c-Jun NH_2-terminal kinase (JNK), and the more prosaic p38. Within these groups, two particular pathways have been shown to require scaffold proteins for efficient signal transduction. The proteins are called MEK partner 1 (MP-1) and JNK interacting protein 1 (JIP-1).