

STE20

Key References

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Overview

The Ste20 (Sterile 20) protein kinase family consists of enzymes with sequence homology to the yeast MAP4K Ste20p in the pheromone response pathway. Based on phylogenetic relationships, they can be divided into two subfamilies: PAK (p21-activated kinase) and GCK (germinal center kinase). The PAKs include six kinases that contain a C-terminal catalytic domain and an N-terminal regulatory domain with a small G protein binding motif. The GCKs include 24 kinases that contain an N-terminal catalytic domain and a C-terminal noncatalytic region with a wide variety of structures. Many Ste20 kinases activate mitogen-activated protein kinase (MAPK) pathways, among which the most studied are the ERK1/2, JNK and p38 cascades. These signal transduction pathways regulate gene transcription, cell cycle, apoptosis, proliferation, differentiation etc. Some Ste20 kinases phosphorylate and activate one or more MAP3Ks directly; thus they are MAP4Ks in MAPK pathways. Others activate MAPK pathways through protein-protein interactions, independent of their catalytic activities. Ste20 kinases have also been implicated in regulation of NF- κ B, cytoskeletal rearrangements, and cell polarity.

The PAK subfamily, which shares many characteristics with yeast Ste20p, can be further divided into two groups: PAK-I (PAK-1, 2 and 3) and PAK-II (PAK-4, 5 and 6). The group I PAKs are activated by GTP-bound small G proteins Cdc42 and Rac, but not by Ras or Rho. They can positively regulate the ERK1/2 MAPK pathway through at least two mechanisms. First, PAK2 phosphorylates Raf-1, a MAP3K, on Ser338. This phosphorylation is required for Ras activation of Raf-1 and is usually PI-3 kinase dependent. Second, PAK1 phosphorylates MEK1, a MAP2K, on Ser298, which is im-

portant for the interaction between Raf-1 and MEK1. In contrast, the group II PAKs contain higher basal kinase activity and are not further activated by small G proteins. However, binding of GTP-bound Cdc42 causes subcellular relocalization of PAK4 and 5. Both PAK groups regulate cytoskeletal rearrangements, although through different mechanisms. Several PAKs have also been implicated in anti-apoptotic processes.

The GCK subfamily can be divided into eight groups: GCK-I to GCK-VIII. Given the large number of these kinases, only a few representatives are discussed here. GCK in group I, plays an essential role in mediating the signal from TNF- α to the JNK MAPK pathway. The binding of TNF- α to its receptor induces the formation of a protein complex containing GCK, which binds to MEKK1, the MAP3K, leading to its activation. GCK activation of MEKK1 is apparently independent of its catalytic activity. MST1 in GCK-II group causes apoptosis when expressed in mammalian cells. MST1 first activates caspases and itself is cleaved by caspases to form a positive feedback loop. The resulting MST1 kinase domain then activates both JNK and p38 to promote apoptosis. GCK-IV contains four mammalian members including HGK (NIK) that binds to the SH3-containing protein Nck through its proline-rich motif. HGK is activated by the ephrin receptor family and its *Drosophila* ortholog Misshapen functions downstream of the fly Nck homolog. Misshapen is also involved in the Wnt pathway downstream of its receptor. GCK-VI contains OSR1 and SPAK, homologs of a *Drosophila* Ste20 kinase Fray. SPAK activates the p38 pathway, while OSR1 is unable to activate any known MAPK pathways. OSR1 phosphorylates PAK1 in the

N-terminal regulatory domain, which might reduce its activation by GTP-bound small G proteins. Both SPAK and OSR1 have been reported to interact with several cation chloride co-transporters including KCC3, NKCC1, and NKCC2. In contrast, TAOs in GCK-VIII, are genuine MAP3Ks in the p38 MAPK pathway. TAOs directly phosphorylate and activate MEK3/6, the MAP2Ks, and they are required for p38 activation by heterotrimeric G proteins.

STE20

FAMILY MEMBERS	PAK1	PAK4	GCK
OTHER NAMES	α -PAK; p21-activated kinase 1	p21-activated kinase 4	—
GROUP	PAK-I (A284)	PAK-II	GCK-I
MOLECULAR WEIGHT/ STRUCTURAL DATA	61 kDa 545 aa	64 kDa 591 aa	97 kDa 819 aa
ISOFORMS	PAK1-3 PAK4-6	GCK, HPK1, KHS1	
SPECIES	Human	Human	Human
DOMAIN ORGANIZATION	C-terminal kinase domain, PBD domain, AID domain	C-terminal kinase domain, PBD domain	N-terminal kinase domain, PEST motif
PHOSPHORYLATION SITES	Thr ⁴²³ Thr ⁸⁴	Ser ⁷⁴	Not known
TISSUE DISTRIBUTION	Brain, spleen	Ubiquitous	Ubiquitous
SUBCELLULAR LOCALIZATION	Focal adhesions	Golgi membrane	Cytosolic
BINDING PARTNERS/ ASSOCIATED PROTEINS	Rac, Cdc42, PIX, OSR1 GEF-H1	Cdc42, Integrin,	TRAF6
UPSTREAM ACTIVATORS	Cdc42-GTP, Rac-GTP, EGF (E9644), LPA (L7260)	HGF (H9661), Cdc42-GTP	TNF α (T6674), TNF β (T7799), poly(IC) LPS (L2630)
DOWNSTREAM ACTIVATION	MEK1 (M8568), MLCK, RhoGDI, DLC1	BAD (B1682), LIMK1, GEF-H1	MBP (M1891)
ACTIVATORS	Not known	Not known	Not known
INHIBITORS	NF2/merlin	Not known	Not known
SELECTIVE ACTIVATORS	Not known	Not known	Not known
PHYSIOLOGICAL FUNCTION	Cell motility, neurogenesis, angiogenesis	Cell survival, transformation filopodia formation, cell adhesion	Activation of JNK pathway
DISEASE RELEVANCE	Cancer metastasis, AIDS	Cancer	Not known

FOOTNOTES