

Neks

Key References

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Overview

The Nek protein kinase subfamily is named after the NIMA protein kinase of *Aspergillus nidulans*. Loss of NIMA function results in arrest at the G2/M boundary of the cell cycle despite activation of Cdc2. NIMA is necessary for the nuclear import of Cdc2 at the start of mitosis, and also for the construction of the mitotic spindle. Overexpression of NIMA results in chromatin condensation (possibly through direct histone H3 phosphorylation), and pseudomitotic arrest in both *Aspergillus* (where it also induces abnormal spindles) and in mammalian cells.

The latter suggested that a NIMA-like signaling pathway exists in higher eukaryotes. A single NIMA-family member has been described in both budding and fission yeast, named KIN3 and fin-1, respectively; the latter has been shown to be involved in the control of late mitotic events. The human genome encodes 11 protein kinases whose catalytic domains are approximately 40% identical to NIMA, and 40-85% identical to each other. Research in the past 10 years indicates that the expansion of the Nek family may reflect both an enlargement and a subdivision of the functions of NIMA among a divergent array of related kinases.

The Nek protein kinase domains are all located near the protein aminoterminal (except for a central location in Nek10). Neks differ primarily in their noncatalytic carboxyterminal tails, which presumably specify different cellular localizations, substrate selection and/or modes of regulation. A feature common to the noncatalytic regions of almost all Neks is the presence of one or more coiled-coil motifs, that in at least two cases (Nek2 and Ncrcc1/Nek9) confer a homo-oligomerization that is essential to the activation of their catalytic function. In addition, Nek8 and Ncrcc1

contain a domain homologous to RCC1, the guanyl nucleotide exchange factor for the small GTPase Ran. In the case of Ncrcc1 the RCC1 domain acts as an autoinhibitory domain that is capable of binding both the Ncrcc1 catalytic domain and Ran.

Little is known as to the regulation or functions of Nek3, Nek4, Nek5 and Nek10. Nek2 is predominantly a centrosomal protein whose kinase activity is high in S and G2, wherein it is involved in centrosome separation, and low in M and G1. Ncrcc1/Nek9 is activated in mitosis, and is necessary for proper organization of the mitotic spindle. Microinjection of anti-Ncrcc1 antibodies during prophase induces arrest in prometaphase with disorganized spindle structures or abnormal mitosis with resultant aneuploidy. Nek6 and Nek7, 85% identical, lack appreciable noncatalytic segments; Nek6 and Nek7 bind to the carboxyterminal tail of Ncrcc1 and can be phosphorylated and activated by the latter both *in vivo* and *in vitro*, likely forming a signaling cassette that is activated during mitosis. Interference with, or RNAi-induced depletion of Nek 6, impedes mitotic progression.

Nek1 and Nek8 are unrelated in their carboxyterminal noncatalytic tails, however mutations in the genes encoding these polypeptides have been identified as the causative lesion in two mouse models of autosomal recessive polycystic kidney disease (PKD). All gene products identified thus far whose mutation results in PKD have been shown to be localized to the non-motile cilia of renal epithelia. Fa2p, a Nek ortholog in *Chlamydomonas* is important for ciliary function and Nek1 and Nek8 are localized to some extent to the primary cilia of different cell types. It is likely there-

fore that Nek1 and Nek8 are also involved in the formation or function of cilia. In addition Nek1, Nek2 and Nek11 have been suggested to be involved in the response to DNA damage.

Neks differ in size, expression pattern, subcellular localization and protein kinase activity regulation. Nevertheless, the pattern emerging from recent reports indicates that one important, common function of several Neks is in the control of the centrosomal and cellular microtubule machinery. Thus, some Neks may retain important roles related to those of NIMA in the regulation of centrosome and/or spindle structure and function and perhaps other cell cycle-related processes (such the response to DNA damage), while other Neks may have evolved to participate in the regulation of other highly specialized microtubule structures such as cilia.

Neks

FAMILY MEMBERS	Nek1	Nek2 (N4787)	Nek3
OTHER NAMES	NY-REN-55	—	—
MOLECULAR WEIGHT/ STRUCTURAL DATA ^b	180 kDa 1258 ^c aa; Oligomer	50 kDa 445 aa (A), 384 aa (B); oligomer	55 kDa 459 aa
ISOFORMS	Nek1A, Nek1B	Nek2A, Nek2B	Not known
SPECIES	Human, mouse, fruit fly	Human, mouse, <i>Xenopus</i> , fruit fly	Human, mouse
DOMAIN ORGANIZATION	PK domain, NLS domain, CC domain	PK domain, CC domain, KEN domain, box domain, D-box domain	PK domain, NLS domain
PHOSPHORYLATION SITES	Thr ¹⁶² , other	Not known	Not known
TISSUE DISTRIBUTION ^d	Testis, ovary, nervous system	Testis	Small intestine, testis, ovary
SUBCELLULAR LOCALIZATION	Cytoplasmic, centrosomal	Cytoplasmic, centrosomal	Cytoplasmic
BINDING PARTNERS/ ASSOCIATED PROTEINS	KIF3A, tuberin, α -catulin	cNap1, Hec1, PP1, HMGA2, Nek11, MAD1, Erk2 (M3172)	Not known
UPSTREAM ACTIVATORS	Not known	Not known	Not known
POSSIBLE PHYSIOLOGICAL SUBSTRATES	Not known	cNap1, Hec1, PP1, HMGA2, Nek11	Not known
ACTIVATORS	Not known	Not known	Not known
INHIBITORS	Not known	Not known	Not known
SELECTIVE ACTIVATORS	Not known	Not known	Not known
DISEASE RELEVANCE	Knockout causes cystic kidney disease	Overexpressed in human breast cancer	Not known

FOOTNOTES

a Nercc1 was also designated as Nek8. As a different NIMA-family member had already been assigned that name, it was later renamed as Nek9. We favor the Nercc1 designation to avoid any confusion.

b Number of residues corresponds to the human form.

c Originally described as a partial (774 aa) clone from mouse.

d Only a partial list of expression is shown; most of Neks are detected in all tissues at minor levels.

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Neks

FAMILY MEMBERS	Nek4	Nek5	Nek6 (N4662)
OTHER NAMES	STK2	—	SID6-1512
MOLECULAR WEIGHT/ STRUCTURAL DATA^b	90 kDa 841 aa	889 aa	35 kDa 313 aa Monomer
ISOFORMS	Not known	Not known	Not known
SPECIES	Human, mouse	Human, mouse	Human, mouse, <i>Xenopus</i>
DOMAIN ORGANIZATION	PK domain, NLS domain	PK domain, CC domain	PK domain
PHOSPHORYLATION SITES	Not known	Not known	Thr ²⁰² , Ser ²⁰⁶ , other
TISSUE DISTRIBUTION	Testis	Not known	Liver, placenta, brain, intestine, ovary
SUBCELLULAR LOCALIZATION	Not known	Not known	Cytoplasmic
BINDING PARTNERS/ ASSOCIATED PROTEINS	Not known	Not known	Nercc1
UPSTREAM ACTIVATORS	Not known	Not known	Nercc1
POSSIBLE PHYSIOLOGICAL SUBSTRATES	Not known	Not known	Cdc16
ACTIVATORS	Not known	Not known	Not known
INHIBITORS	Not known	Not known	Not known
SELECTIVE ACTIVATORS	Not known	Not known	Not known
DISEASE RELEVANCE	Not known	Not known	Not known

FOOTNOTES

- a** Nercc1 was also designated as Nek8. As a different NIMA-family member had already been assigned that name, it was later renamed as Nek9. We favor the Nercc1 designation to avoid any confusion.
- b** Number of residues corresponds to the human form
- c** Originally described as a partial (774 aa) clone from mouse.
- d** Only major sites of expression is shown; most Neks are detected in all tissues at minor levels.

Neks

FAMILY MEMBERS	Nek7 (N4537)	Nek8	Nercc1
OTHER NAMES	—	—	Nek9, (Nek8) ^a
MOLECULAR WEIGHT/ STRUCTURAL DATA^b	35 kDa 302 aa; Monomer	75 kDa 703 aa	120 kDa 979 aa
ISOFORMS	Not known	Not known	Not known
SPECIES	Human, mouse, <i>Xenopus</i>	Human, mouse, zebrafish	Human, mouse, <i>Xenopus</i>
DOMAIN ORGANIZATION	PK domain	PK domain, RCC1 domain	PK domain, NLS domain, RCC1 domain, CC domain
PHOSPHORYLATION SITES	Thr ¹⁹¹ , Ser ¹⁹⁵ , other	Not known	Ser ²⁰⁶ , Thr ²¹⁰ , other
TISSUE DISTRIBUTION	Liver, kidney, ovary	Testis, kidney, liver	Testis, heart, skeletal muscle, kidney, brain
SUBCELLULAR LOCALIZATION	Cytoplasmic	Cytoplasmic	Cytoplasmic
BINDING PARTNERS/ ASSOCIATED PROTEINS	Nercc1	Not known	Nek6 (N4662), Nek7 (N4537), Ran
UPSTREAM ACTIVATORS	Nercc1	Not known	Not known
POSSIBLE PHYSIOLOGICAL SUBSTRATES	Cdc16	Not known	Nek6 (N4662), Nek7 (N4537), Bicd2
ACTIVATORS	Not known	Not known	Not known
INHIBITORS	Not known	Not known	Not known
SELECTIVE ACTIVATORS	Not known	Not known	Not known
DISEASE RELEVANCE	Not known	Knockout causes cystic kidney; overexpressed in primary human breast tumors	Not known

FOOTNOTES

a Nercc1 was also designated as Nek8. As a different NIMA-family member had already been assigned that name, it was later renamed as Nek9. We favor the Nercc1 designation to avoid any confusion.

b Number of residues corresponds to the human form.

c Originally described as a partial (774 aa) clone from mouse.

d Only a few sites of expression is shown; most Neks are detected in all tissues at minor levels.

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Neks

FAMILY MEMBERS	Nek10	Nek11
OTHER NAMES	—	—
MOLECULAR WEIGHT/ STRUCTURAL DATA^b	1125 aa	75 kDa (L) 645 aa (L), 470 (S); aa
ISOFORMS	Not known	Nek11L, Nek11S
SPECIES	Human, mouse	Human, mouse
DOMAIN ORGANIZATION	CC domain, PK domain	PK domain, CC domain
PHOSPHORYLATION SITES	Not known	Not known
TISSUE DISTRIBUTION	Not known	Not known
SUBCELLULAR LOCALIZATION	Not known	Nuclear, nucleolar
BINDING PARTNERS/ ASSOCIATED PROTEINS	Not known	Nek2A
UPSTREAM ACTIVATORS	Not known	Not known
POSSIBLE PHYSIOLOGICAL SUBSTRATES	Not known	Not known
ACTIVATORS	Not known	Not known
INHIBITORS	Not known	Not known
SELECTIVE ACTIVATORS	Not known	Not known
PHYSIOLOGICAL FUNCTION	Not known	Not known
DISEASE RELEVANCE	Not known	Not known

FOOTNOTES

- ¹ Nercc1 was also designated as Nek8. As a different NIMA-family member had already been assigned that name, it was later renamed as Nek9. We favor the Nercc1 designation to avoid any confusion.
- ² Number of residues corresponds to the human form
- ³ Originally described as a partial (774 aa) clone from mouse.
- ⁴ Only major sites of expression is shown; most of Neks are detected in all tissues at minor levels.