1. Phylogeny  
   Serine/threonine‐protein kinase Nek5 belongs to the NIMA‐related kinase (NEK) family, a conserved group of serine/threonine kinases found throughout eukaryotes that can be traced back to ancient kinase lineages as described by Manning et al. in their seminal analyses of the human kinome (Manning et al. 2002). Nek5 orthologs have been identified in several mammalian species, placing it within a core set of cell cycle regulators that include related NEK family members such as NEK1, NEK3, NEK4, and NEK8, which have been classified by evolutionary studies as part of the extended mitotic regulatory network (Manning et al. 2002). In addition, comparative substrate‐specificity profiling indicates that Nek5 and NEK8 share similar phosphorylation motifs, suggesting that they occupy a distinct subgroup within the NEK family; however, detailed subgroup assignment based on substrate motifs derives largely from studies that are not included here, so only the broad familial relationships are emphasized (Pavan et al. 2021, pages 3-5).
2. Reaction Catalyzed  
   Nek5 catalyzes the transfer of a phosphate moiety from ATP to the hydroxyl group of serine or threonine residues on target substrate proteins, thereby converting ATP to ADP and producing a phosphorylated protein, following the canonical reaction mechanism of serine/threonine kinases (Manning et al. 2002).
3. Cofactor Requirements  
   As with most serine/threonine kinases, the catalytic activity of Nek5 depends on the presence of divalent metal ions, with Mg²⁺ serving as an essential cofactor that coordinates ATP binding and facilitates catalysis (Manning et al. 2002).
4. Substrate Specificity  
   Limited peer‐reviewed data are available regarding the intrinsic substrate specificity of Nek5; one study employing structural dynamics and phosphopeptide profiling reported that phosphopeptide regions derived from Nek5 can interact with the polo‐box domain of Plk1, indicating that Nek5 harbors specific phosphorylation site motifs that support such interactions (Bibi et al. 2013, pages 12-13). Despite the lack of a comprehensively defined consensus motif in the peer‐reviewed literature, this observation implies that Nek5 may preferentially recognize and phosphorylate substrates that contain features compatible with docking and phosphorylation by cell cycle–associated kinases.
5. Structure  
   Nek5 is encoded on chromosome 13q14.3 and comprises 708 amino acids, conferring an approximate molecular weight of 81 kDa (Pavan et al. 2021, pages 3-5). Its domain organization includes an N‐terminal catalytic kinase domain, which is responsible for phosphoryl transfer and contains the conserved ATP‐binding lysine residue (Lys33), a central DEAD‐box helicase–like domain that is unique among NEK family members and may mediate interactions with RNA or ribonucleoprotein complexes, and a C‐terminal coiled‐coil region that likely facilitates regulatory protein–protein interactions (Pavan et al. 2021, pages 3-5). Although high‐resolution experimental structural data such as X‐ray crystallography or definitive AlphaFold predictions have not yet been reported in the literature for Nek5, its overall structural organization is inferred from these conserved domain features and by analogy with other kinases in the NEK family (Pavan et al. 2021, pages 3-5).
6. Regulation  
   The activity of Nek5 is regulated in part through post‐translational modification; for example, it has been shown to serve as a substrate of caspase‐3, with a caspase‐3 cleavage site located between amino acids 456 and 498, a modification that is implicated in its functional role during myogenesis (Bibi et al. 2013, pages 12-13). In addition, Nek5’s regulation appears to involve its integration into cell cycle control mechanisms, whereby its interaction with proteins at the centrosome and with mitochondrial factors may influence its activation state during mitosis and responses to DNA damage (Bachus et al. 2022, pages 13-14; Pavan et al. 2021, pages 3-5). Although the precise phosphorylation sites and additional regulatory inputs remain to be fully elucidated in peer‐reviewed studies, the available data underscore the contribution of proteolytic processing and protein–protein interactions to the regulation of Nek5 activity.
7. Function  
   Functionally, Nek5 plays a role in several critical cellular processes. It has been implicated in the regulation of centrosomal integrity and mitotic spindle formation, thereby contributing to proper centrosome disjunction and accurate chromosomal segregation during mitosis (Pavan et al. 2021, pages 3-5; Bachus et al. 2022, pages 13-14). In addition to its mitotic functions, Nek5 localizes to mitochondria and has been associated with the regulation of mitochondrial respiration and mitochondrial DNA maintenance, indicating a role in preserving cellular energy homeostasis and genomic integrity (Pavan et al. 2021, pages 3-5). Furthermore, through its cleavage by caspase‐3 and subsequent participation in myogenic differentiation, Nek5 is linked to programmed cell death and differentiation signaling cascades that have implications for muscle development (Bibi et al. 2013, pages 12-13).
8. Other Comments  
   Nek5 is recognized as one of the least studied members of the NEK kinase family, and its detailed mechanisms of substrate recognition, catalytic regulation, and potential roles in disease remain to be fully characterized in the peer‐reviewed literature (Bachus et al. 2022, pages 13-14; Pavan et al. 2021, pages 3-5). To date, no specific inhibitors have been reported for Nek5, and its disease associations as well as any notable mutations affecting its activity have not been comprehensively defined, underscoring the need for further investigation into its functional and biological impact.
9. References
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