1. Phylogeny  
   NEK7, also known as Never in mitosis A‐related kinase 7, is a member of the NIMA‐related kinase (NEK) family of serine/threonine kinases. Comparative sequence analyses demonstrate that its catalytic domain is highly conserved among metazoans and retains significant similarity to the ancestral NIMA kinase originally identified in Aspergillus nidulans. NEK7 shares a high degree of sequence identity with NEK6 and forms a regulatory pair with NEK9 in higher eukaryotes, grouping phylogenetically with other mitotic kinases such as NEK6, NEK2, and NEK9. Orthologs of NEK7 have been identified across species including yeast and filamentous fungi, suggesting that NEK7 is part of an evolutionarily ancient kinase network that has been maintained throughout eukaryotic evolution (bachus2022inmitosisyou pages 14-15, moniz2011nekfamilyof pages 1-3). In addition, phylogenetic studies indicate that the conservation of the core catalytic domain in NEK7 is accompanied by the preservation of regulatory interactions with upstream activators, which is essential for the proper execution of mitosis in diverse organisms (bachus2022inmitosisyou pages 29-30).
2. Reaction Catalyzed  
   NEK7 catalyzes the transfer of a phosphate group from ATP to the hydroxyl group of a serine or threonine residue on its substrate proteins. This biochemical reaction can be summarized as follows:  
    ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine or L-threonine)-phosphate + H⁺  
   The phosphorylation reaction modulates the activity, localization, or interaction capability of target proteins, thereby influencing key cellular processes such as mitotic spindle assembly and cytokinesis (bayliss2015theysand pages 4-6, haq2015mechanisticbasisof pages 1-2).
3. Cofactor Requirements  
   The kinase activity of NEK7 is dependent on divalent metal ions, with Mg²⁺ serving as an essential cofactor. Magnesium ions facilitate the coordination and proper positioning of ATP within the active site, which is crucial for efficient phosphoryl transfer to substrate proteins (bayliss2015theysand pages 4-6).
4. Substrate Specificity  
   NEK7 displays substrate specificity for proteins that are critical in mitotic progression. One well‐characterized substrate is EML4, which is phosphorylated on Ser146. This modification promotes the release of EML4 from microtubules, a necessary step that contributes to efficient chromosome congression during mitosis (bachus2022inmitosisyou pages 14-15). Furthermore, NEK7 has been implicated in the phosphorylation of mitotic kinesins, such as Eg5, ensuring proper centrosome separation and spindle assembly (fry2017mitoticregulationby pages 4-5, bayliss2015theysand pages 4-6). By similarity to other serine/threonine kinases, NEK7 is also proposed to phosphorylate targets like RPS6KB1, although the precise consensus motif remains to be fully defined. Collectively, its substrate specificity allows NEK7 to modulate a network of proteins that govern microtubule dynamics and cell division (bachus2022inmitosisyou pages 15-17, meirelles2014“stopne(c) pages 7-8).
5. Structure  
   NEK7 is one of the smallest members of the NEK family, comprising approximately 302 amino acids and exhibiting a molecular weight on the order of 34 kDa. Its structure is dominated by a central catalytic kinase domain that displays the characteristic bilobal architecture of serine/threonine kinases. The N-terminal lobe contains a glycine-rich loop (P-loop) responsible for ATP binding, while the C-terminal lobe houses the activation loop, which undergoes conformational changes upon phosphorylation, and the catalytic hinge region (bachus2022inmitosisyou pages 13-14, bayliss2015theysand pages 4-6).

A key structural feature of NEK7 is the presence of an autoinhibitory tyrosine residue (Tyr97). In its inactive conformation, Tyr97 adopts a “Tyr-down” position that interferes with the formation of the critical salt bridge between a conserved lysine and glutamate, thereby disrupting the proper alignment of the catalytic machinery. Structural studies have revealed that disruption of this autoinhibitory interaction, either by mutation of Tyr97 or by binding of the NEK9 noncatalytic domain (which promotes back-to-back dimerization), shifts NEK7 to an active conformation. Furthermore, NEK7 contains a DLG motif that functions in a manner analogous to the canonical DFG motif found in many other kinases, thereby contributing to the formation of the regulatory spine necessary for full catalytic function (haq2015mechanisticbasisof pages 1-2, trask2021probingthefunctions pages 29-33). The overall structure is notable in its lack of extended C-terminal regulatory domains such as coiled-coil regions, simplifying its regulatory integration into mitotic signaling cascades (bachus2022inmitosisyou pages 24-25, bachus2022inmitosisyou pages 25-26).

1. Regulation  
   The regulation of NEK7 is achieved through a combination of phosphorylation events and protein–protein interactions. Activation is initiated when the upstream kinase NEK9 interacts with NEK7 via its noncatalytic C-terminal domain; this binding event displaces the inhibitory Tyr97 from the active site, permitting subsequent phosphorylation of the activation loop, notably at Ser195 (haq2015mechanisticbasisof pages 1-2, bachus2022inmitosisyou pages 14-15). In addition, regulatory kinases such as CDK1 and PLK1 modulate the activity of NEK9, thereby indirectly controlling NEK7 activation during the progression of mitosis (fry2017mitoticregulationby pages 4-5, freixo2016novelrolesfor pages 44-48). Post-translational modifications, particularly phosphorylation, are critical in switching NEK7 from an autoinhibited state to an active conformation. Beyond its role in phosphorylating substrates during mitosis, NEK7 also functions as an essential activator of the NLRP3 inflammasome. In this context, NEK7 binds directly to the leucine-rich repeat domain of NLRP3, relieving NLRP3 autoinhibition and promoting assembly of the inflammasome complex; notably, this function is independent of its catalytic activity (shi2016nlrp3activationand pages 6-8, sun2020physiologicalandpathological pages 1-2). The convergence of these regulatory mechanisms ensures that NEK7 activity is tightly restricted to the appropriate phases of the cell cycle and to specific signaling contexts (bachus2022inmitosisyou pages 31-33, trask2021probingthefunctions pages 33-37).
2. Function  
   NEK7 plays an indispensable role in the regulation of the mitotic cell cycle. It is critical for ensuring proper centrosome function through the nucleation of microtubules, the assembly of a robust mitotic spindle, and the successful execution of cytokinesis. A key aspect of NEK7’s mitotic role is the phosphorylation of EML4 at Ser146, which promotes dissociation of EML4 from microtubules thereby facilitating efficient chromosome congression (bachus2022inmitosisyou pages 14-15). Additionally, NEK7 phosphorylates substrates such as mitotic kinesins (e.g., Eg5) that are essential for centrosome separation and spindle dynamics, thereby directly contributing to the fidelity of chromosome segregation (fry2017mitoticregulationby pages 4-5, bayliss2015theysand pages 4-6).

In addition to its roles in mitosis, NEK7 is implicated in maintaining genome stability by phosphorylating telomere-associated proteins, such as TRF1, thereby safeguarding telomere integrity under conditions of DNA damage (bachus2022inmitosisyou pages 15-17). Beyond cell cycle regulation, NEK7 has a noncanonical function in innate immunity where it acts as a cellular switch to activate the NLRP3 inflammasome. This activation involves direct binding to NLRP3, which facilitates the oligomerization of NLRP3 with the adaptor protein PYCARD and the subsequent activation of caspase-1, leading to the maturation and secretion of pro-inflammatory cytokines such as IL-1β (shi2016nlrp3activationand pages 6-8, nguyen2023nekfamilyreview pages 7-8). The multifunctional nature of NEK7 is further highlighted by its aberrant expression in various cancers, where elevated NEK7 levels correlate with enhanced cell proliferation, mitotic defects, and genomic instability (bachus2022inmitosisyou pages 17-18).

1. Other Comments  
   Elevated expression of NEK7 has been observed in several human malignancies, including pancreatic, gastric, lung, retinoblastoma, and other tumor types, suggesting its potential utility as a prognostic biomarker as well as a therapeutic target (bachus2022inmitosisyou pages 17-18, nguyen2023nekfamilyreview pages 7-8). In the context of inflammatory diseases, NEK7’s critical role in licensing NLRP3 inflammasome activation positions it as an attractive candidate for anti‐inflammatory drug development. Several studies have also focused on the identification and characterization of small molecule inhibitors with selectivity for NEK7; however, further research is necessary to develop clinically applicable agents (trask2021probingthefunctions pages 33-37). Known disease‐associated mutations and alterations in NEK7 expression further reinforce its importance in mitotic control and inflammatory signaling, although detailed mutational profiles are still emerging (bachus2022inmitosisyou pages 15-17).
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