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Review

Nemo-like kinase, a multifaceted cell signaling regulator

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ABSTRACT

Nemo-like kinase (NLK) is an evolutionarily conserved MAP kinase-related kinase. Although NLK was originally identified as a *Drosophila* gene affecting cell movement during eye development, recent studies show that NLK also contributes to cell proliferation, differentiation, and morphological changes during early embryogenesis and nervous system development in vertebrates. In addition, NLK has been reported to be involved in the development of several human cancers. NLK is able to play a role in multiple processes due to its capacity to regulate a diverse array of signaling pathways, including the Wnt/β-catenin, Activin, IL-6, and Notch signaling pathways. Although the molecular mechanisms that regulate NLK activity remain unclear, our recent research has presented a new model for NLK activation. Here, we summarize the current understanding of the function and regulation of NLK and discuss the aspects of NLK regulation that remain to be resolved.

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Contents

Abbreviations: NLK, Nemo-like kinase; IL-6, intereukin-6; MAPK, mitogen activated protein kinase; ERK, extracellular-signal regulated kinase; Pro, proline; Ser, serine; Thr, threonine; *C. elegans*, *Caenorhabditis elegans*; POP-1, Posterior pharynx defect protein 1; LEF1, Lymphoid enhancer factor; TCF, T-cell factor; NARF, NLK associated RING finger protein; NPC, neural progenitor cell; HDAC1, histone deacetylase 1; Foxo, forkhead box O; STAT3, signal tranducer and activator of transcription 3; CPEB, cytoplasmic polyadenylation element-binding protein; Notch1-ICD, Notch1 intracellular domain; CSL, CBF-1, suppressor of hairless, LAG-1; SETDB1, SET domain bifurcated 1; PPAR-γ, peroxisome proliferator activated receptor-γ; BMP, bone morphogenetic protein; Eya, Eyes absent; Even-skipped, Eve; MAP1B, microtubule-associated protein 1B; NGF, nerve growth factor; TGF-β, transforming growth factor-β; MAPKK, MAPK kinase; Tyr, tyrosine; MAP3K, MAPK kinase kinase; Glu, glutamic acid; Cys, cysteine; TAK1, TGF-β-activated kinase 1; HIPK2, homeodomain interacting protein kinase 2; miRNA, microRNA; HCC, Hepatocellular carcinoma; ZIPK, Zipper-interacting protein kinase; GSK-3β, Glycogen synthase kinase-3β; LiCl, lithium chloride; IMPase, inositol monophosphatase; IPPase, inositol polyphosphate 1-phosphatase.

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1. Introduction

Nemo-like kinase (NLK) was originally identified as *nemo*, a gene involved in cell motility (ommatidia rotation) during eye development in *Drosophila*. While wild-type flies form hexagonal-shaped ommatidia, *nemo* mutants form square-shaped ommatidia [1]. The name "nemo" derives from the Korean word for square. The vertebrate homolog of the *nemo* gene was discovered by Brott et al. in 1998, and was named "Nemo-like kinase" [2]. NLK is evolutionarily conserved from worms to humans (Fig. 1A). Invertebrate genomes possess only one NLK gene, while vertebrates have either one or two NLK genes. Vertebrate NLK proteins can be classified into two groups, type-I and type-II, by phylogenetic analysis (Fig. 1A) [3]. Amphibians and fish possess both type-I and type-II NLK, while mammals and chickens have only type-II NLK [3]. Type-II NLK, but not type-I NLK, contains histidine-rich amino-terminal and carboxyl-terminal conserved regions (Fig. 1B) [3]. Type-I NLK is known to be involved in early embryogenesis, in processes such as mesoderm induction [4,5]. However, type-II NLK knockout mice [6] and zebrafish *nlk2* knockdown embryos [3] display no early embryonic deficiencies. This suggests that the two NLKs have different functions in vertebrates. The differences in the biochemical properties of type-I NLK and type-II NLK remain unclear. In mice, the type-II NLK amino acid sequence is 54.5% similar and 41.7% identical to that of mouse mitogen activated protein kinase-1/extracellular-signal regulated kinase-2 (MAPK1/ERK2) [2]. Therefore, similar to MAPK1/ERK2, NLK is thought to function as a proline (Pro)-directed kinase, which phosphorylates proteins at a serine (Ser) or threonine (Thr) residue that is immediately preceding a Pro residue. In fact, NLK phosphorylates Lymphoid enhancer factor 1 (LEF1), a pivotal transcription factor in the Wnt/β-catenin signaling pathway, at the Thr and Ser residues of the Thr155-Pro156 and Ser166-Pro167 sequences [3,7]. However, the exact consensus target sequence of NLK has not been characterized. Over the past several years, evidence has emerged showing that NLK plays crucial roles in the regulation of diverse signaling pathways, including Wnt/β-catenin and Notch signaling pathways, and is involved in embryonic patterning, nervous system development, and cancer cell proliferation. Here, we discuss the function and regulation of NLK, with particular focus on vertebrate NLK.

2. NLK as a cellular signaling modifier

2.1. Discovery of the molecular function of NLK

In 1999, we and others found that the *C. elegans* mutant lacking endoderm, *lit-1*, possessed a mutation in a NLK homolog gene and that the gene product of *lit-1* inhibited nuclear localization of Posterior pharynx defect protein 1 (POP-1) by phosphorylating it during endoderm induction [8,9]. This was the first discovery of a molecular function of NLK. POP-1 is a homolog of the mammalian T-cell factor/lymphoid enhancer factor (TCF/LEF) family of transcription factors that regulate Wnt/β-catenin signaling. Therefore, we hypothesized that mammalian NLK was involved in Wnt/β-catenin signaling. We found that mammalian NLK could phosphorylate vertebrate TCF/LEF transcription factors, including *Xenopus laevis* TCF7L1/TCF3 and human TCF7L2/TCF4 and LEF1. Moreover, the TCF7L2 proteins phosphorylated by NLK in the human embryonic kidney cell line HEK293 lacked DNA-binding activity in electron mobility shift assays [7,10] (Fig. 2A). In addition, NLK-mediated LEF1 phosphorylation inhibited binding of LEF1 to its target gene, the *Axin2* promoter, in HeLa cells [3]. Furthermore, we discovered that overexpression of NLK inhibited TCF/LEF-mediated transcription in both HeLa and HEK293 cells [3,7,10] (Fig. 2A). Yamada et al. also reported that NLK promotes NARF (NLK associated RING finger protein)-mediated ubiquitination and the subsequent proteasomal degradation of TCF7L2 and LEF1 [11]. Thus, NLK is considered a negative regulator of TCF/LEF in vertebrates.

2.2. Dual and opposite effects of NLK-mediated LEF1 phosphorylation in Wnt/β-catenin signaling

Interestingly, LIT-1 functions as a positive regulator of POP-1 during the fate specification of gonadal precursor cells in *C. elegans* [12–14]. Recently, we reported that vertebrate NLK also functions as a positive regulator of LEF1 in neural progenitor cells (NPCs) [3] (Fig. 2B). In the NPC-like mammalian cell lines, rat pheochromocytoma tumor PC12 cells and mouse neuroblastoma neuro-2a cells, NLK-mediated LEF1 phosphorylation at Thr-155 and Ser-166 induced

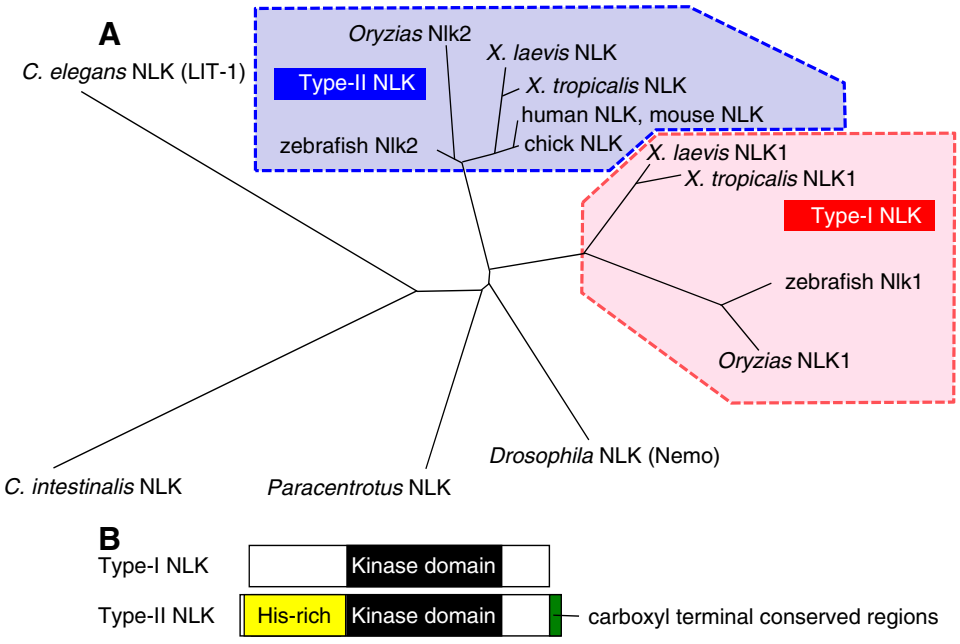

Fig. 1. NLK family proteins. (A) Phylogenetic analysis of NLK homologs by comparison of amino acid sequences. Vertebrate type-I and type-II NLKs are shown in blue and red, respectively. (B) Schematic diagrams of Type-I and Type-II NLKs. Note that type-II NLKs, but not type-I NLKs, have conserved histidine-rich (His-rich) and carboxyl-terminal regions, which are indicated by yellow and green boxes, respectively.

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