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Emerging roles of NudC family: from molecular regulation to clinical implications

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Nuclear distribution gene C (*NudC*) was first found in *Aspergillus nidulans* as an upstream regulator of *NudF*, whose mammalian homolog is *Lissencephaly 1* (*Lis1*). *NudC* is conserved from fungi to mammals. Vertebrate NudC has three homologs: NudC, NudC-like protein (NudCL), and NudC-like protein 2 (NudCL2). All members of the NudC family share a conserved p23 domain, which possesses chaperone activity both in conjunction with and independently of heat shock protein 90 (Hsp90). Our group and the others found that NudC homologs were involved in cell cycle regulation by stabilizing the components of the LIS1/dynein complex. Additionally, NudC plays important roles in cell migration, ciliogenesis, thrombopoiesis, and the inflammatory response. It has been reported that NudCL is essential for the stability of the dynein intermediate chain and ciliogenesis via its interaction with the dynein 2 complex. Our data showed that NudCL2 regulates the LIS1/dynein pathway by stabilizing LIS1 with Hsp90 chaperone. The fourth distantly related member of the NudC family, CML66, a tumor-associated antigen in human leukemia, contains a p23 domain and appears to promote oncogenesis by regulating the IGF-1R-MAPK signaling pathway. In this review, we summarize our current knowledge of the NudC family and highlight its potential clinical relevance.

nuclear distribution gene C, heat shock protein 90, p23, dynein, Lissencephaly 1, cell cycle, ciliogenesis

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INTRODUCTION

Cytoplasmic dynein is a well-known minus-end-directed microtubule motor present in most eukaryotic cells (Cianfrocco et al., 2015; Chen et al., 2014; Can et al., 2014). It has two ~550 kD heavy chains with multiple ATP binding sites, three to four intermediate chains of ~74 kD, four light intermediate chains of ~55 kD, and several light chains of 8–22 kD (Nishikawa et al., 2014; Belyy et al., 2014; Bhabha et al., 2016). Cytoplasmic dynein plays essential roles in many cellular processes, as it can hydrolysis ATP to generate force to move on and towards the minus end of the microtubule (Karki and Holzbaur, 1999; Roberts et al., 2013). Dynein is able to power the trafficking of various cargo towards microtubule minus ends including endosomes, lysosomes, components of the centrosomes, and mRNAs (Yao et al., 2015; De Rossi et al., 2015). It also contributes to Golgi positioning in the perinuclear region, nuclear rotation and positioning, centrosome separation, and nuclear envelope breakdown for entry into mitosis (Busson et al., 1998; Howell et al., 2001; Salina et al., 2002; Raaijmakers and Medema, 2014; Barisic and Maiato, 2015). During mitosis, dynein localizes to the kinetochore where it is thought to remove spindle-assembly checkpoint proteins by transporting them towards the spindle poles (Howell et al., 2001; Raaijmakers et al., 2014).

A number of studies in *Aspergillus nidulans* have demonstrated that genes in the nuclear distribution (*Nud*)

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pathway are homologous to components or regulators of the cytoplasmic dynein complex. For example, *NudA*, *NudI*, and *NudG* encode the cytoplasmic dynein heavy, intermediate, and light chains, respectively. Genetic screening revealed another fungal *Nud* gene, *NudF*, whose mutation causes phenotypes similar to that of the cytoplasmic dynein complex in fungus (Xiang et al., 1994). Hemizygous deletion or mutation of *Lissencephaly 1* (*Lis1*), a mammalian homolog of *NudF*, causes type I lissencephaly, a neuronal migration obstacle during brain development manifested by smooth brain surface and disorganized cortical layering (Hirotsune et al., 1998; Dobyns et al., 1993). *NudE* was identified as a multicopy suppressor of the *NudF* phenotype. The phenotypes caused by *NudE* homozygous mutants were similar to those of the *NudF* and *NudA* heterozygous mutants, indicating that *NudF*, *NudE*, and *NudA* are in the same genetic pathway (Feng et al., 2000). *NudE* has two homologs, *Ndel* and *Ndel1*, which are involved in dynein recruitment to the mitotic kinetochores to promote mitotic progression (Ma et al., 2009; Stehman et al., 2007).

NudC gene was first cloned by Osmani et al. at 1990 in *A. nidulans* (Osmani et al., 1990). In 1995, Xiang et al. found that the *NudC3* mutation in *A. nidulan*s greatly decreased the protein level of NudF, in which the codon "CGG" replaced "CAG" at codon 146 of the *NudC* gene. Extra copies of the *NudF* gene can complement the *NudC3* mutation (Chiu and Morris, 1995, 1997; Xiang et al., 1995). Deletion of *NudA* or *NudF* affects nuclear migration but is not lethal. However, deletion of *NudC* in *A. nidulans* causes marked changes in the morphology and composition of the cell wall, which leads to cell death (Chiu et al., 1997). *NudC* orthologs have been identified from fungi to mammals, which show high sequence and structure conservation. Here, we summarize the current knowledge of the NudC family.

CHARACTERIZATION OF NUDC FAMILY

NudC gene is highly conserved from *Schizosaccharomyces pombe* to *Homo sapiens* (Table 1). The first mammalian *NudC* was originally identified as a prolactin-inducible gene in rat T cells that were activated by the addition of prolactin to the culture medium (Morris et al., 1997). Our group further cloned two new paralogs of the mammalian *NudC*, *NudC-like* (*NudCL*), and *NudC-like 2* (*NudCL2*) genes (Zhou et al., 2006; Yang et al., 2010), which are present in vertebrates. All *NudC* gene products share a similar conserved p23 domain (Figure 1). p23 protein is a cochaperone of heat shock protein 90 (Hsp90) and participates in the folding various client proteins, such as progesterone receptor and estrogen receptor (Echtenkamp et al., 2011). The p23 domain is a core structure responsible for binding to p23 and/or Hsp90 client proteins (Garcia-Ranea et al., 2002). Interestingly, p23 itself has chaperone activity independently of Hsp90 (Echtenkamp et al., 2011). NudC also has a conserved region consisting of a predicted three-helix bundle known as the NudC-N-terminal domain (Figure 1). Similar to NudC, NudCL contains a p23 domain and a NudC-N-terminal domain. However, NudCL2 is a smaller protein only containing a p23 domain without the NudC-N-terminal domain.

In addition, another distantly related gene, *CML66* (also termed as NudCD1, NudC domain containing 1), first cloned from a chronic myelogenous leukemia (CML) cDNA expression library (Yang et al., 2001), also contains a p23 domain (Zheng et al., 2011). Interestingly, *CML66* appears to be a product of gene shuffling, in which the p23 domain has been predicted to be inserted into a split canonical seven-blade β-propeller (Zheng et al., 2011). Although CML66 was previously regarded as a member of the NudC family because of its conserved domain (Zheng et al., 2011; Riera and Lazo, 2009), further studies are needed to determine whether CML66 plays a role in the regulation of Hsp90 ATPase activity and client protein stability via its p23 domain.

CHAPERONE ACTIVITY OF NUDC FAMILY

The structure of the p23 domain in the NudC family sug-

Table 1 Similarity of NudC family in different species

Organism	Similarity (% identity)			
	NudC	NudCL	NudCL2	CML66
Homo sapiens	100	100	100	100
Pan troglodytes	99.09	98.39	100	99.45
Canis lupus familiaris	96.07	92.54	99.36	77.59
Rattus norvegicus	95.17	88.03	98.73	80.28
Mus musculus	94.26	88.08	99.36	87.78
Xenopus laevis	70.99	66.53	75.16	66.28
Danio rerio	72.56	56.71	70.06	58.41
Drosophila melanogaster	53.11	–	–	–
Caenorhabditis elegans	49.21	–	–	–
Aspergillus nidulans	47.65	–	–	–
Schizosaccharomyces pombe	39.26	–	–	–

gests that the NudC family has chaperone activities, acting as Hsp90 cochaperones or as chaperones independently of Hsp90. Emerging studies have shown that NudC family proteins are involved in protein homeostasis. Our previous studies revealed that the L279P mutation of NudC, which resembles the *Aspergillus* NudC3 mutant, induces the degradation of LIS1 (Zhu et al., 2010). This mutation effectively impairs the inhibitory effect of NudC on Hsp90 ATPase activity *in vitro*. NudCL2 also plays a role in the stability of LIS1 by enhancing the interaction between Hsp90 and LIS1 (Yang et al., 2010). Either disruption of the LIS1-Hsp90 interaction or inhibition of Hsp90 activity reduces the protein level of LIS1. Additionally, a study of a quantitative chaperone interaction network showed that the NudC family is not only associated with Hsp90, but also preferentially binds to structurally related but evolutionarily distinct β-propeller folds, such as WD40, Kelch, and RCC1 domains (Taipale et al., 2014). These findings indicate that the NudC family may function as an Hsp90 cochaperone by modulating its ATPase activity (Figure 2).

On the other hand, NudC family also exhibits its intrinsic molecular chaperone activity, which is consistent with p23. Under thermal inactivation, the *Caenorhabditis elegans* NudC homolog NUD-1 has been shown to prevent the aggregation of citrate synthase and luciferase and maintain luciferase in a folding-competent state (Faircloth et al., 2009). The *Arabidopsis* NudC homolog BOBBER1 was found to be a heat shock protein that inhibits the aggregation of malate dehydrogenase (Perez et al., 2009). Additionally, NudC and NudCL were confirmed to have intrinsic chaperone activity *in vitro* by preventing the aggregation of both luciferase and citrate synthase (Zheng et al., 2011; Zhu et al., 2010). Recently, we found that NudC was able to form a physiological complex with cofilin 1, a key regulator of the actin cytoskeleton (Zhang et al., 2015). Depletion of NudC markedly reduces the stability of cofilin 1, possibly

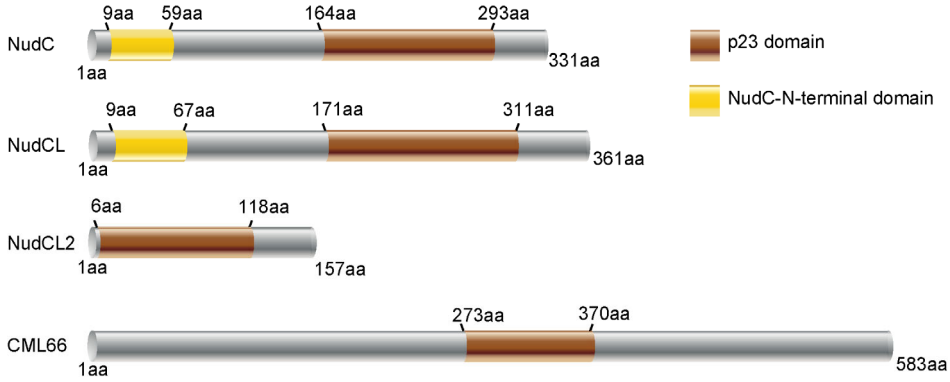

Figure 1 Schematic comparison of human NudC homologs. Protein lengths and relative amino acid positions are shown. The p23 domains are highlighted in brown. NudC-N-terminal domains are indicated in yellow.

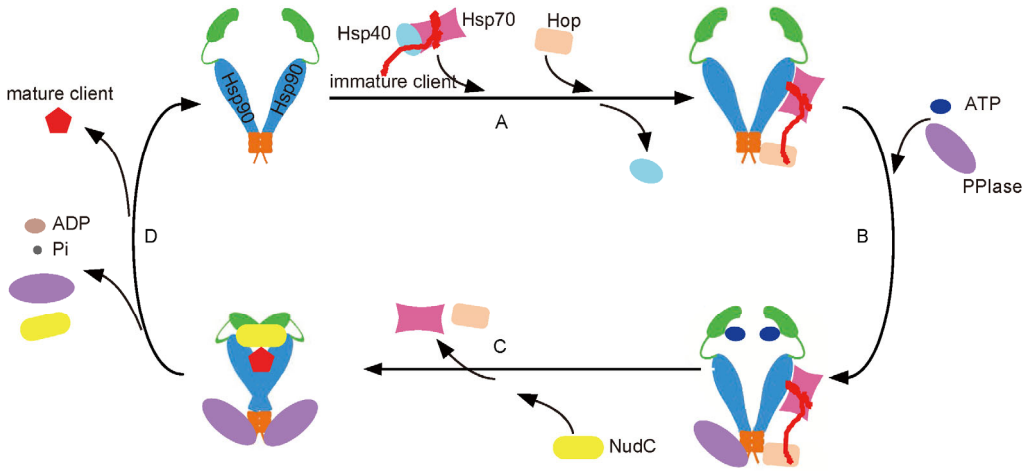

Figure 2 Model for the role of NudC in the Hsp90 ATPase cycle. A, An immature client protein first binds to the Hsp40/Hsp70 complex and is then transferred from Hsp70 to Hsp90 mediated by Hop. B, After ATP binding, Hsp90 starts to form the closed conformation and PPIase occupies the dimerized C-terminus. C, NudC interacts with Hsp90 and inhibits its ATPase, which enhances the folding of client protein. D, After ATP hydrolysis, the mature client protein is released from Hsp90, while NudC, PPIase, ADP, and Pi are dissociated from Hsp90. Hop, Hsp70/Hsp90 organizing protein. PPIase, peptidyl-prolyl isomerase.

through the ubiquitination-proteasome pathway. Furthermore, our data showed that inhibition of Hsp90 did not significantly affect cofilin 1 stability, indicating that NudC stabilizes cofilin 1 via an Hsp90-independent pathway.

CELLULAR FUNCTIONS OF NUDC FAMILY

NudC

Accumulating data have demonstrated that NudC plays multiple roles in cell cycle progression, neuronal migration, inflammatory response, platelet production, and ciliogenesis (Figure 3). Human NudC has been found to be highly expressed in proliferating cells (Gocke et al., 2000). During mitosis, NudC is phosphorylated by polo-like kinase 1 (PLK1), a crucial mitotic kinase, at its conserved S274 and S326 residues (Zhou et al., 2003). PLK1-phosphorylated NudC, in turn, functions as a spatial regulator of PLK1 at the kinetochore to promote stable kinetochore-microtubule interactions and proper chromosome congression (Nishino et al., 2006). Depletion of NudC leads to the formation of multiple spindles at metaphase and induces lagging chromosomes at anaphase (Zhou et al., 2003). Moreover, NudC acetylation is also involved in mitotic progression (Chuang et al., 2013). NudC is acetylated at K39 in interphase and deacetylated by histone deacetylase 3 during mitosis. Failure in NudC deacetylation induces mitotic phenotypes, including chromosome misalignment and mis-segregation. In addition, either depletion or overexpression of NudC induces cytokinesis defects (Zhou et al., 2003; Aumais et al., 2003).

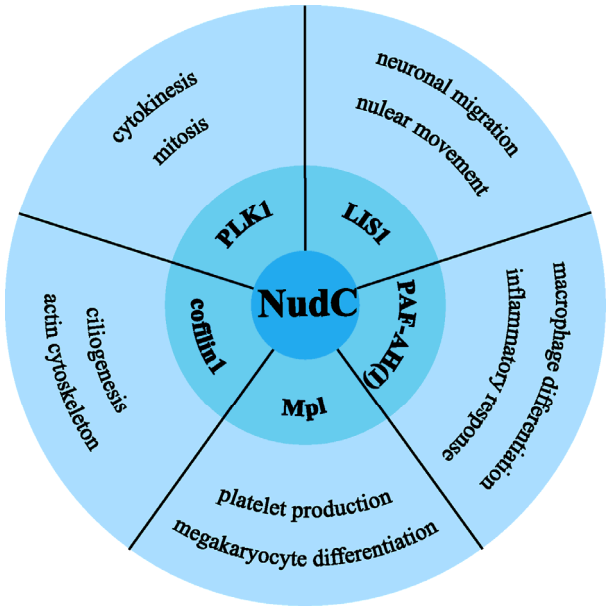

Figure 3 (color online) Cellular functions of mammalian NudC. NudC has been shown to interact with several important proteins, including PLK1, LIS1, PAH-AH (I), Mpl, and cofilin 1 and to regulate cell cycle progression, neuronal migration, inflammatory response, megakaryocyte differentiation, and ciliogenesis.

NudC has been implicated in the regulation of neuronal migration. NudC has been detected in regions of the embryonic neocortex undergoing neuronal migration and colocalizes with LIS1 at the microtubule-organizing center in cortical neurons (Aumais et al., 2001). NudC depletion results in defects in the nuclear migration of radial glial progenitor cells (Aumais et al., 2001; Cappello et al., 2011). Further data showed that both NudC depletion and overexpression in the embryonic rat brain by *in utero* electroporation caused radial glial progenitor cells to accumulate in the ventricular and subventricular zones and failed to reach the cortical plate (Cappello et al., 2011).

Interestingly, NudC is induced by inflammatory stimuli in mouse RAW 264.7 macrophages (Riera et al., 2007). Previous results showed that NudC interacts with LIS1 (Morris et al., 1998), which is the regulatory β subunit of platelet activating factor acetylhydrolase type I (PAF-AH(I)) (Hattori et al., 1994). PAF-AH(I) reduces the acetylation and activity of PAF, which acts as an important pro-inflammatory secondary lipidic messenger to regulate monocyte-macrophage differentiation (Peplow, 1999; Elstad et al., 1989). Additionally, NudC was found to increase the catalytic activity of PAF-AH(I) (Riera et al., 2007). These data suggest that NudC may play an important role in the differentiation of macrophages.

Unexpectedly, the results of Xu et al. revealed that NudC binds to the extracellular domain of thrombopoietin receptor (Mpl) and triggers megakaryocyte differentiation, indicating that NudC, similarly to thrombopoietin, may be a candidate cytokine for binding Mpl (Pan et al., 2005; Tang et al., 2008; Zhang et al., 2007). Further results showed that NudC induces the activation of the ERK1/2 and p38 MAPK pathways in Mpl-expressing cells (Tang et al., 2008; Zhang et al., 2007). Moreover, daily administration of NudC enhances the number of circulating platelets in mice (Tang et al., 2008; Zhang et al., 2007). These data imply that NudC may be involved in megakaryocytopoiesis and thrombopoiesis.

Recently, our group finds that NudC plays essential roles in regulating actin dynamics and ciliogenesis by stabilizing cofilin 1 (Zhang et al., 2015). Depletion of NudC causes the accumulation of bundled stress fibers and inhibits cell spreading and lamellipodia formation, indicating that NudC is a crucial regulator of actin dynamics. Further results show that NudC colocalizes with cofilin 1 especially at the leading edge, and influences the stability of cofilin 1 via an Hsp90-independent pathway. Knockdown of NudC promotes cilia elongation and increases the percentage of ciliated cells, which is similar to those by actin cytoskeleton disruption or cofilin 1 depletion (Zhang et al., 2015). Exogenous expression of cofilin 1 significantly suppresses the defective ciliogenesis induced by NudC depletion, but not vice versa.

NudCL

NudCL has been reported to be essential for cell cycle pro-

gression and cell viability by stabilizing the dynein intermediate chain (Zhou et al., 2006). We found that depletion of NudCL induces multiple mitotic defects, including chromosome misalignment, multipolar spindles, failure of chromosome segregation, formation of dumbbell-like DNA structures, and accumulation of micronuclei, leading to cell death. Moreover, NudCL was shown to bind to the dynein intermediate chain, and knockdown of NudCL promoted degradation of the dynein intermediate chain. Additionally, overexpression of NudCL that is localized to the centrosome and midbody results in cytokinesis defects and inhibits cell proliferation (Cai et al., 2009). Recently, NudCL has been found to play a role in retrograde mitochondrial motility (Shao et al., 2013). Depletion of both NudCL and Ndel1 almost blocks retrograde mitochondrial transport, suggesting these proteins may work together to regulate retrograde mitochondrial transport, possibly by linking the LIS1/dynein complex (Shao et al., 2013).

Previous studies showed that the cytoplasmic dynein 2 complex is the motor for retrograde intraflagellar transport to drive the transport of activated components from the cilia tip to the cell body (Liu et al., 2005). Asante et al. showed that depletion of dynein 2 components diminished the ability of cells to generate primary cilia (Asante et al., 2014). Interestingly, NudCL associates with dynein 2, and knockdown of NudCL exhibits similar cilia phenotypes to that of dynein 2 depletion. However, the underlying mechanism how NudCL modulates dynein 2 requires further analysis.

NudCL2

Our recent study showed that NudCL2 regulates the LIS1/dynein pathway by stabilizing LIS1 with Hsp90 chaperone (Yang et al., 2010). Depletion of NudCL2 reduces the stability of LIS1 and leads to phenotypes resembling those of LIS1 deficiency, such as dispersion of the Golgi apparatus, perinuclear accumulation of microtubules, and uncoupling of the centrosome and nucleus. Ectopic expression of LIS1 partially reverses the phenotypes of NudCL2- depleted cells, but not vice versa, indicating that NudCL2 is an upstream regulator of LIS1. Moreover, NudCL2 forms a complex with LIS1 and Hsp90 and enhances their interaction, suggesting that NudCL2 is involved in regulating the LIS1/dynein complex via the Hsp90 chaperone pathway (Yang et al., 2010).

CML66

CML66 was initially identified as an immunogenic tumor antigen (Yang et al., 2001). CML66 is highly expressed in leukemia, some solid tumors, and tumor cell lines (Yang et al., 2001; Wang et al., 2008). Knockdown of CML66 inhibits cell proliferation, migration, and invasion (Wang et al., 2008). Additionally, CML66 appears to influence tumorigenesis by regulating the IGF-1R-MAPK signaling pathway (Rao et al., 2014). Depletion of CML66 attenuates the phosphorylation of IGF-1R and ERK1/2-Hsp27 in ovarian cancer cell lines and inhibits xenograft tumorigenesis in nude mice (Rao et al., 2014).

PHYSIOLOGICAL SIGNIFICANCE OF NUDC FAMILY

Although the members of the NudC family play essential roles in various cellular processes, little is known about their *in vivo* functions. Depletion of NUD-1 in *Caenorhabditis elegans* showed that the cleavage furrow stalled and quickly regressed, resulting in a multinucleated one-celled embryo (Rao et al., 2014). NUD-1-depleted embryos contain weak midzone microtubules and undergo multiple rounds of the cell cycle without completing cytokinesis after the first cell cycle (Rao et al., 2014). These results are consistent with the function of NudC in mammalian cells (Zhou et al., 2003; Aumais et al., 2003). Depletion of NudC in zebrafish by morpholinos exhibited several ciliary defects, such as body curvature, pericardial edema, hydrocephalus, and defective left-right asymmetry, which are similar to that of Cas9/NudC-gRNA-treated embryos (Zhang et al., 2015). Furthermore, the cilia in NudC morphants were abnormally elongated, orientated in random directions, and beat in an uncoordinated manner. These data suggest that NudC plays a crucial role in cilia-mediated developmental processes in zebrafish.

CLINICAL IMPLICATION OF NUDC FAMILY

Emerging evidence has indicated that NudC may be involved in carcinogenesis (Miller et al., 1999; Lin et al., 2004; Hatakeyama et al., 2006; Suzuki et al., 2007; Hartmann et al., 2008). NudC is highly expressed in early myeloid and erythroid precursors and declines as these cells terminally differentiate (Miller et al., 1999). A significant increase of NudC is observed in bone marrow aspirates from patients with acute lymphoblastic leukemia and acute myelogenous leukemia compared to that from normal donors, indicating that NudC may be associated with hematopoietic cell proliferation and leukemogenesis. NudC has also been identified as an up-regulated gene in cutaneous T-cell lymphoma (Hartmann et al., 2008). Interestingly, Hatakeyama et al. find an inverse correlation between NudC expression levels and nodal metastasis in esophageal cancer by using a comprehensive and quantitative proteomic strategy (Hatakeyama et al., 2006).

PERSPECTIVE

All four members of the NudC family contain the conserved p23 domain. Based on the similarity of amino acid residues, CML66 is the most distant member. The *NudC* gene is highly conserved from fungus to human, while the other three members only exist in vertebrates (Table 1). Data from our lab and others strongly indicate that NudC, NudCL, and NudCL2 act upstream of the LIS1/dynein

pathway to regulate the stability of the regulator or component of dynein complex possibly via the Hsp90 pathway (Figure 4). Some evidence suggests that NudC appears to be a cochaperone of Hsp90 to suppress its ATPase activity; however, the precise mechanism is largely unknown. Additionally, the exact roles of NudCL, NudCL2, and CML66 in the regulation of the Hsp90 pathway are also deserved to be explored in the future.

Knockdown of NudC in zebrafish embryos induces several cilia-related disorders, suggesting that NudC plays important roles in cilia-mediated developmental processes. Since a number of diseases, known as ciliopathies (Cortes et al., 2015; Madhivanan and Aguilar, 2014), are attributed to ciliary dysfunction, it will be interesting to determine whether NudC is associated with ciliopathies. Although several studies imply that NudC may influence tumorigenesis, there is no *in vivo* evidence to directly support the hypothesis, especially in solid tumors. Hsp90 is an ATP- dependent molecular chaperone that facilitates the maturation, stability, and activity of hundreds of client proteins (Hong et al., 2013; Neckers and Workman, 2012; Centenera et al., 2013). Hsp90 is frequently upregulated in various cancer cells and contributes to cell proliferation, survival, invasion, and metastasis (Pillai and Ramalingam, 2014; Garcia-Carbonero et al., 2013). Hsp90 stabilizes many important oncogenic proteins including human epidermal growth factor receptor 2, epidermal growth factor receptor, and matrix metalloproteinase-2, which are abnormally activated in numerous cancers (Hong et al., 2013; Pillai and Ramalingam, 2014). Inhibition of Hsp90 effectively suppresses cancer cell proliferation and induces apoptosis, indicating that Hsp90 is a promising target for cancer therapy (Lianos et al., 2015). Hsp90 requires several cochaperones to fold client proteins and execute its diverse cellular functions (Barrott and Haystead, 2013). Our data strongly suggest that the NudC family acts as a cochaperone of Hsp90 to regulate cell proliferation and survival (Yang et al., 2010; Zhu et al., 2010). Thus, inhibition of the NudC-Hsp90 pathway may have important potential for cancer therapeutics. The role of NudC is clearly needed to be further investigated in carcinogenesis.

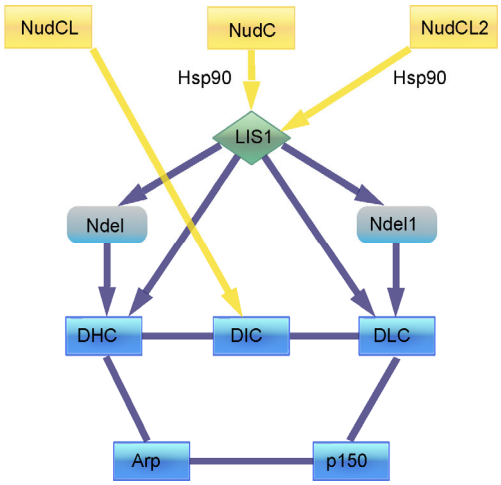

Figure 4 (color online) Regulation of the LIS1/dynein pathway by the NudC family. NudC and NudCL2 appear to act as Hsp90 cochaperones to stabilize LIS1. NudCL is essential for the stability of DIC. DHC, dynein heavy chain. DIC, dynein intermediate chain. DLC, dynein light chain. Arp, actin-related protein.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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