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综 述

NEK 家族在细胞周期调控中的作用

李园园[1]，郭磊[2]，韩之明[1,3]

1. 中国科学院动物研究所，干细胞与生殖生物学国家重点实验室，北京 100101
2. 广东省第二人民医院生殖医学中心，生殖力保护实验室，广州 510317
3. 北京干细胞与再生医学研究院，北京 100101

摘要: NIMA 相关激酶(NIMA-related kinases, NEKs)是丝氨酸/苏氨酸激酶，在细胞周期调控中发挥着重要的作用，参与了中心体分离、纺锤体组装、染色质凝集、核膜破裂、纺锤体组装检验点信号、胞质分裂、纤毛形成及 DNA 损伤反应等多种细胞活动。本文结合近年来在该激酶家族的相关研究，从 NEK 家族的组成、结构特征及其在有丝分裂和减数分裂过程中的作用等多个方面展开综述，以期为进一步研究 NEKs 在细胞周期调控中的作用提供重要基础，也为肿瘤的临床诊断和治疗提供理论依据。

关键词: NIMA 相关激酶；有丝分裂；减数分裂

Roles of NEK family in cell cycle regulation

Yuanyuan Li[1], Lei Guo[2], Zhiming Han[1,3]

1. State Key Laboratory of Stem Cell and Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China
2. Fertility Preservation Lab, Reproductive Medicine Center, Guangdong Second Provincial General Hospital, Guangzhou 510317, China
3. Beijing Institute for Stem Cell and Regenerative Medicine, Beijing 100101, China

Abstract: As a serine/threonine kinase, NIMA-related kinases (NEKs) play important roles in the regulation of cell cycle, and involve in several cellular activities such as centrosome separation, spindle assembly, chromatin condensation, nuclear envelope breakdown, spindle assembly checkpoint signaling, cytokinesis, cilia formation and DNA damage response. In this review, we summarize the component, structural characteristics and functions of NEK family in mitosis and meiosis based on the relevant researches in recent years, providing a reference for the further study on the roles of NEKs in the regulation of cell cycle and a theoretical basis for the clinical diagnosis and treatment of tumors.

Keywords: NIMA-related kinases; mitosis; meiosis

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作者简介: 李园园，博士，专业方向：发育生物学。E-mail: liyuanyuan891116@163.com
通讯作者: 韩之明，博士，副研究员，专业方向：发育生物学。E-mail: hanzm@ioz.ac.cn

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细胞是生命活动的基本单位。细胞周期是一个非常复杂和精细的调节过程，该过程受到细胞内外各种因素的精密调控，细胞周期的紊乱与许多疾病的发生发展相关。研究显示，许多蛋白激酶家族，如细胞周期蛋白依赖性激酶(cyclin-dependent kinases, CDK)、Aurora 激酶、Polo 样激酶(polo-like kinase, PLK)和 NIMA 相关激酶(NIMA-related kinases, NEKs)，都参与了细胞周期调控的过程。近年的研究发现，NEK 家族蛋白在细胞周期调控的过程中扮演了重要的角色，参与中心体复制和分离、纺锤体形成、染色体在赤道板上的排列、纺锤体检验点(spindle assembly checkpoint，SAC)调控、纤毛形成及 DNA 损伤反应(DNA damage response, DDR)等多种细胞活动。本文主要综述了 NEK 家族成员的生物学特性及其在细胞周期调控中的作用，同时对 NEK 家族的未来研究方向进行了探讨，以期让相关科研人员更充分、更全面地了解 NEK 家族的研究进展，为进一步研究其在细胞周期调控中的作用提供有力的支撑，也为深入了解肿瘤发生机制及抗肿瘤药物设计提供研究基础。

1　NEK 家族及其生物学特性

1.1　NEK 家族的发现

NIMA (never in mitosis A)最早是在对曲霉属真菌 *Aspergillus nidulans* 的有丝分裂突变体的研究中发现的[1,2]。20 世纪 80 年代中期，Osmani 等[3]通过调控 *nimA* 基因的 mRNA 表达水平证明 *nimA* 参与了曲霉有丝分裂的 G_2/M 期转换。进一步的研究证明，*nimA* 的过表达可以促进有丝分裂的提前发生，有丝分裂过程中 NIMA 与 CDK1-cyclin B 复合体是同等重要的调节因子[4,5]。在对曲霉的研究中发现，NIMA 的降解是细胞完成正确的有丝分裂进程所必需的[6]。一系列的研究表明，NIMA 激酶在曲霉和酵母(*Schizosaccharomyces pombe*)中参与了染色质凝集、纺锤体组装和胞质分裂等多个细胞周期过程[7~11]。20 世纪 90 年代初期，Letwin 等[12]从小鼠(*Mus musculus*)中分离出 *Nek1*，发现 *Nek1* 编码一种与 NIMA 相关的蛋白激酶，在结构、组成和表达上与 NIMA 存在较高的一致性，从而提出了在哺乳动物中可能存在一个 *Nek* 基因家族。随后的研究发现了小鼠和人(*Homo sapiens*)的细胞中均存在与 *Nek1* 相关的基因，证明了高等哺乳动物确实存在 NEK 家族[13,14]。研究已证明，NEKs 存在于多种生物体中，从原生生物如衣藻(*Chlamydomonas*)[15]、疟原虫(*Plasmodium falciparum*)[16]等到多细胞真核生物如果蝇(*Drosophila melanogaster*)[17]、非洲爪蟾(*Xenopus laevis*)[18]、小鼠[13]和人[14]。

1.2　NEK 家族成员的结构特征

人类 NEK 家族由 11 种 NIMA 相关激酶组成[19,20]，这些激酶具有与曲霉 NIMA 相似的氨基末端催化区域，是含有典型的丝氨酸/苏氨酸激酶序列的高度保守的激酶结构域，其氨基末端和羧基末端的调节结构域在序列组成和长度上有显著差异。一般来讲，NEK 家族的氨基末端激酶区域是中度保守的，与 NIMA 的激酶区域的氨基酸序列有 40%~50%的同源性。NEK10 的激酶区域位于整个氨基酸序列的中段，与 NEK 家族典型的氨基末端催化区域不同。在 NEK 家族中，人 NEK2 和 NIMA 的同源性最高，能达到 44%[21]。除此之外，NEK6 和 NEK7 的激酶区域的序列一致性达到了 85%以上[22]。人类 NEK 家族的催化区域均含有一个 His-Arg-Asp(HRD)基序，在激活环中都有一个丝氨酸/苏氨酸残基，而这个残基很可能是激活修饰的作用位点。在一些 NEK 家族成员中，这个残基是自磷酸化的，而其他成员则是通过一个上游激酶进行磷酸化修饰的[23~26]。就磷酸化识别序列而言，NIMA 的第 3 位残基具有对苯丙氨酸的强烈偏好[27]，人类 NEK 家族也具有相似的偏好，例如 NEK2 和 NEK6 的第 3 位残基更喜欢疏水残基，尤其偏爱苯丙氨酸或亮氨酸[28,29]。

NEK 家族成员具有保守的氨基末端催化区域，而羧基末端区域在长度、序列和结构上都存在很大差异(图 1)。其常见的特点就是寡聚化序列，通常是一种卷曲螺旋结构，可通过自磷酸化而被激活。一般而言，自磷酸化通常是在激酶结构域的激活环内进行，但是也可发生在蛋白质的其他区域，例如 NEK8 和 NEK9 羧基末端的非催化区域可以通过自磷酸化调控自身的定位和激活[23,30]。研究发现，包括曲霉 NIMA 和脊椎动物 NEK2 在内的几种 NEKs 均显示在非催化区域内存在靶向蛋白质降解的破坏

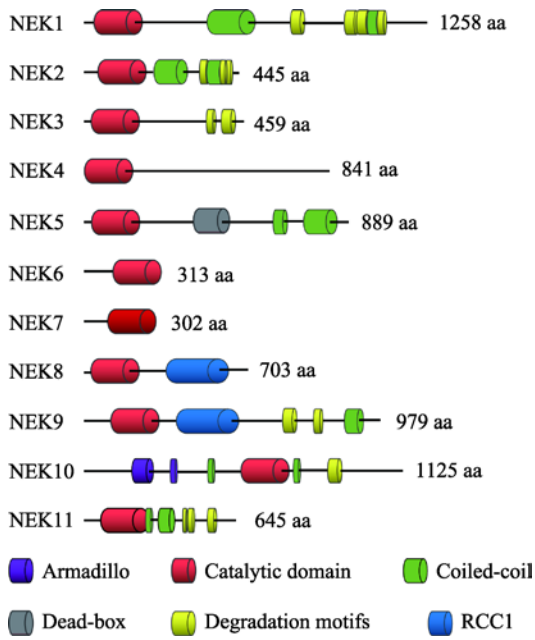

图 1　人 NEK 家族的结构特征

Fig. 1　The structural features of the human NEK family

基序[6,31]，例如 NEK2 含有一个 KEN (Lys-Glu-Asn)-box 和羧基末端 MR (methionine-arginine dipeptide)-tail，均能被后期促进复合物/环状体(anaphase-promoting complex/cyclosome, APC/C)所识别，其中 MR-tail 还可介导 NEK2 与 APC/C 的核心亚基 CDC20 直接作用，从而导致 NEK2 以一种不依赖于纺锤体组装检验点的方式进行降解[32]。在 NEK 家族中，NEK6 和 NEK7 仅由一个催化区域和短的氨基末端延伸区域组成[33,34]，而后者可能与底物识别有关[35]。NEK6 和 NEK7 是 NEK9 的下游激酶，可以和 NEK9 蛋白中 RCC1 域和 coiled-coil 域之间的一个序列结合[25]。

2　NEK 家族在细胞周期调控中的作用

作为蛋白激酶，NEK 家族参与了细胞周期、细胞分裂、纤毛形成和 DNA 损伤反应等多种细胞活动(表 1)。人和哺乳动物 NEK 家族在细胞有丝分裂和减数分裂过程中的作用主要有以下几个方面。

2.1　NEK 家族在有丝分裂中的作用

nimA 的过表达可以诱导处于细胞周期任何阶段的曲霉细胞、酵母细胞、非洲爪蟾卵母细胞或人类细胞进入有丝分裂[82,83]，研究发现，人类 NEK 家族参与细胞周期进程和分化过程中的多个事件。在有丝分裂中，NEK2、NEK6、NEK7 和 NEK9 相互配合调控双极纺锤体的形成、染色质凝集、核膜破裂和胞质分裂等。NEK3 除参与调控有丝分裂外，还可促进催乳素依赖性信号传导[45]，而 NEK1、NEK4、NEK5、NEK7、NEK8、NEK10 和 NEK11 均与 DNA 损伤应答有关。

2.1.1　有丝分裂起始

有丝分裂的起始和退出是由 CDK1、cyclins、有

表 1　人和哺乳动物 NEK 家族的亚细胞定位和功能

Table 1　Subcellular localization and functions of human and mammalian NEK family

NEK	亚细胞定位	功能
1	细胞质、中心体、纤毛、DNA 损伤部位	纤毛发生[36,37]、DNA 损伤反应[38,39]、线粒体[39]、纺锤体组装[40]
2	中心体	有丝分裂[41]、减数分裂[42]、纤毛发生[43,44]
3	细胞质	催乳素依赖性信号传导[45]
4	纤毛基体、纤毛小根	DNA 损伤反应[46]、微管[47]、RNA 剪接[48]、纤毛稳定[49]
5	细胞质、中心体、纺锤体、线粒体	中心体分离[50]、减数分裂恢复[51]、DNA 损伤反应[52]、成肌分化[53]、线粒体[54,55]
6	细胞质、纺锤体、中心体	有丝分裂[24,56,57]、DNA 损伤反应[58]、炎症反应[59]、中心体分离[23,60]
7	纺锤体两极	中心体分离[23,60]、炎症反应[61~63]、DNA 损伤反应[64,65]、纺锤体组装[56,66,67]
8	中心体、纤毛	纤毛发生[68,69]、DNA 损伤反应[70,71]
9	中心体，纺锤体两极	纺锤体形成[72]、中心体成熟和分离[73]、DNA 损伤反应[74]
10	线粒体	细胞周期[75]、DNA 损伤反应[75]、线粒体[76]、纤毛发生[77]
11	细胞核、核仁、纺锤体	细胞周期[78,79]、DNA 损伤反应[80]、细胞不对称分裂[81]

丝分裂相关激酶和磷酸酶驱动的细胞周期转换。在高等真核生物中，有丝分裂的起始导致多个细胞结构的改变，例如中心体分离、微管生长和收缩、核膜破裂以及染色质凝集等[84]。尽管没有研究证明 NEK 家族是有丝分裂起始所必需的，但是已确定 NEK2、NEK6、NEK7 和 NEK9 参与调控了细胞从间期进入 M 期的中心体的分离、纺锤体的组装、核孔复合物的去组装和核膜破裂等。

研究发现，一些 NEK 家族成员在从真菌到人类的微管组织中心均有定位[9,17,85~87]。在人类细胞中，NEK2 作为中心体的核心组分，参与调控中心体的分离[41,88,89]。在有丝分裂间期，两个中心粒由一些蛋白质连接体结合在一起，而该连接体是由卷曲螺旋蛋白组成的，包括 C-Nap1、rootletin、Cep68、centlein 和 LRRC45，而 NEK2 不仅可通过磷酸化连接蛋白[90~94]和中心粒相关蛋白 GAS2L1[95,96]，还可通过失活驱动蛋白 KIFC3[97]，共同调控有丝分裂前期的中心体分离和双极纺锤体形成。在有丝分裂间期，NEK2 与蛋白激酶 MST-2 和磷酸酶 PP1 形成三聚体结构，维持在一个去磷酸化的失活状态。当有丝分裂启动时，PLK1 可通过磷酸化 MST-2 破坏这种结构，导致 NEK2 的激活。除此之外，NEK2 也可通过自磷酸化而被激活[98]。在有丝分裂过程中，NEK5 与 NEK2 的定位模式相似。人 *NEK5* 基因的敲降导致分裂间期 NEK2 减少、中心粒周围物质(pericentriolar material, PCM)缺失、微管生长缓慢以及中心体连接蛋白 rootletin 被过度募集到中心体上，从而导致中心体的过早分离，分离的中心体之间相对较接近[50]，这个现象与过表达人 *NEK2* 基因的结果是一致的[41,91]，而且同时敲降 *NEK5* 和 *NEK2* 基因后中心体的过早分离被加重。我们推测，NEK5 可能与 NEK2 协同调控中心体的分离。

研究发现，在有丝分裂的 G_1 期和 S 期，NEK7 可通过调控 PCM 的募集促进中心体的复制[99]。人 *NEK7* 基因的敲降导致 PCM 组分和原中心粒组装相关蛋白 PLK4、CPAP、SAS-6 以及 STIL 不能被募集到中心体，从而调控中心体的复制[100]，而人 *NEK7* 基因和 *NEK6* 基因的过表达能够诱导额外的中心体形成[101]。在有丝分裂中，人 *NEK6*、*NEK7* 和 *NEK9* 基因的敲降导致前期中心体的分离失败、分裂中期形成脆弱的纺锤体、纺锤体两极的距离减小以及微管密度降低[23,56,66]。事实上，对于这些纺锤体的缺陷最简单的解释是中心体和纺锤体两极的微管成核作用减少。研究显示，NEK9 能与启动微管成核的 γ-tubulin 环状复合体(γ-tubulin ring complex, γ-TuRC)的多个组分互作，如磷酸化 γ-TuRC 的衔接蛋白 NEDD1[73,102]，后者的激活促进了 γ-tubulin 被募集到中心体上，而 *Nek9* 的缺失会导致纺锤体组装延迟、双极纺锤体的形成减少和微管结构异常[102]。此外，NEK6 和 NEK7 均定位到纺锤体两极，NEK6 在有丝分裂的中期和后期定位到纺锤体微管上[56]，NEK7 可将 γ-tubulin 募集到纺锤体的两极[66]。研究结果提示，这些激酶对微管成核的调控可能不仅是通过纺锤体两极和纺锤体本身，还有可能是通过 augmin 复合体将 γ-TuRCs 募集到纺锤体的两极[103]。除此之外，这些激酶调控纺锤体形成的另一种途径可能是通过磷酸化微管相关蛋白进行的，例如 Eg5 作为一种驱动蛋白，参与了有丝分裂双极纺锤体的形成和维持过程，而 Eg5 被募集到纺锤体微管上的过程依赖于 CDK1 对 Eg5 的磷酸化作用[104,105]。研究发现，NEK6 也可磷酸化 Eg5[106]，这一发现有助于阐明 NEK6 或 NEK9 在双极纺锤体的形成和维持中的作用[23,106]。另一项研究显示，EML4 作为一种促进微管稳定性的微管相关蛋白参与微管动力学的调控，NEK6 和 NEK7 可通过磷酸化 EML4 降低其与微管的亲和力，从而促进染色体中板聚合[107]。NEK6 和 NEK7 还可以直接将微管蛋白磷酸化，这一发现提示 NEK6 和 NEK7 可能通过磷酸化微管蛋白直接参与微管动力学的调控[56]。这些研究均表明，NEK6、NEK7 和 NEK9 在纺锤体的形成中发挥了重要作用。

NEK2、NEK6、NEK7 和 NEK9 除影响纺锤体形成之外，也发挥其他的功能。例如，NEK2 的剪接异构体 NEK2C 定位在细胞核中，这可能与 NEK2 在细胞核中的功能有关[108]。研究显示，Nup98 是核孔复合体(nuclear pore complexes, NPCs)的组成成分，CDK1 和 NIMA 可磷酸化 Nup98，从而促进 Nup98 从 NPCs 的解离。CDK1 还可磷酸化 NEK9 的 Ser869 位点，进而激活 NEK9，而 NEK6 和 NEK7 可通过与激活的 NEK9 结合而被激活[23]。因此，我们推测 NEKs 也可能参与 NPCs 的解体和核膜破裂[109]。除

此之外，NEK9 还可与 BICD2 相互作用。而 BICD2 作为一种动粒蛋白相关蛋白，在有丝分裂前期可与动力蛋白结合，促进核孔复合体的去组装[110]。这些研究结果均表明，NEK 家族在有丝分裂起始中发挥重要作用。

2.1.2 细胞周期检验点

细胞周期阻滞可发生在细胞周期的 G_1/S、S 期和 G_2/M 期，是由内源性因素(如停滞的复制叉)或者外源性因素(包括紫外线(UV)辐射、电离辐射(IR)、活性氧(ROS)和某些化疗药物)所造成的 DNA 损伤引起的。细胞周期由一系列的检验点所监控，当 DNA 出现损伤时，这些检验点蛋白被激活，进而导致细胞周期的延迟或阻滞。检验点的激活是由 PIKK (phosphatidylinositol-3 kinase-related kinase)家族成员共济失调毛细血管扩张突变(ataxia telangiectasia mutated, ATM)蛋白和共济失调毛细血管扩张突变与 *Rad3* 相关(ataxia telangiectasia mutated and *Rad3* related, ATR)蛋白及其效应激酶 CHK1/2 (checkpoint kinase 1/2)启动的，ERK1/2 (extracellular signal-regulated kinase 1/2)和 p38 及其下游激酶 MK2 (MAPK activated protein kinase 2)在细胞周期阻滞中也发挥重要作用。在 NEK 家族中，NEK2 和 NEK6 作为 DNA 损伤反应的靶点，是受 DNA 损伤抑制的[58,111]，而其他的 NEK 家族成员在 DNA 损伤修复中发挥重要作用。

在有丝分裂的 G_1/S 和 G_2/M 转换中，NEK1 在 DNA 损伤修复中起作用[112~115]。当 *Nek1* 敲除的细胞暴露于 IR 和 UV 辐射时，CHK1 和 CHK2 不能被激活。此外，NEK1 的激活不依赖于 ATM 和 ATR。这些研究结果提示，NEK1 可能是作为损伤信号的独立传感器发挥作用。

研究发现，NEK2 不仅可与 SAC 蛋白相互作用，还可促进动粒复合蛋白 HEC1 的 Ser165 位点磷酸化[116~118]。除此之外，在紊乱的染色体动粒上可检测到磷酸化 HEC1 (Ser165)的表达，而 HEC1 可将 MPS1 和 MAD1/MAD2 复合体募集到动粒上[119]。由此推测，NEK2 可能参与纺锤体组装检验点 SAC 蛋白完整性的调控。

研究还发现，NEK8 可通过 RAD51 蛋白和 DNA 损伤修复调控复制叉的稳定性[71]，而 NEK10 和 NEK11 参与调控 G_2/M 期的 DNA 损伤反应检验点。当细胞暴露于 UV 辐射时，NEK10 与 MEK1、RAF1 形成一个三聚体的结构，NEK10 可通过促进 MEK1 的激活，进而导致 G_2/M 期阻滞和 ERK1/2 的磷酸化[75]，敲降人 *NEK10* 基因可以抑制 MEK1 和 ERK1/2 的磷酸化。当发生 DNA 损伤和遗传毒性应激时，NEK11 活性显著增加，而当抑制 ATM 和 ATR 激酶时，NEK11 不能被激活[79,80]。当细胞暴露于 IR 辐射时，ATR 和 ATM 激活 CHK1，CHK1 的激活促进 NEK11 和 CDC25A 的磷酸化，而 NEK11 的激活可进一步磷酸化 CDC25A，这一过程促进 SCF 泛素连接酶复合物与 CDC25A 的结合，从而促进 CDC25A 的降解，最终导致 G_2/M 期阻滞[79]，使细胞有充足的时间进行 DNA 修复，不会过早进入有丝分裂。

2.1.3 胞质分裂

胞质分裂发生在细胞分裂后期姐妹染色单体分离之后，是细胞周期和生物个体发育过程中的一个重要环节，直接关系到遗传物质和细胞质组分能否在 2 个子细胞中正常分配。胞质分裂是由许多亚细胞结构和生物分子相互协调作用的结果。动物细胞胞质分裂过程主要包括分裂沟的定位、胞质分裂结构收缩的组装、分裂沟的产生和收缩、分裂沟膜泡的融合以及中间体的形成和剪切。

在真核生物中，NEK 家族也参与胞质分裂的调控。在裂殖酵母中，Grallert 等[11]发现 FIN1 在胞质分裂中起重要作用。在果蝇中，NEK2 定位在有丝分裂后期的中体上，它的过表达可导致 actin 和 anillin 在卵裂沟的形成部位发生错位[17]。人 NEK2 剪接异构体 NEK2B 的敲降可导致细胞无法完成胞质分裂而形成多核细胞[120]。NEK6 和 NEK7 也定位在有丝分裂后期的中体上，在胞质分裂中 NEK6 的激酶活性达到最大[56,66,106]。人 *NEK6* 或 *NEK7* 基因敲降的细胞可成功进入中期，但不能完成胞质分裂，而且人 *NEK6* 或 *NEK7* 的等位基因突变体细胞也经常出现胞质分裂的失败[56,66]。研究还发现，来自小鼠 *Nek7* 敲除胚胎的胚胎成纤维细胞也表现出胞质分裂失败的缺陷[121]。除此之外，NEK6 和 NEK9 还可介导与胞质分裂有关的驱动蛋白 MKLP2 和 KIF14

的定位和募集[122]。以上证据均表明，NEK 家族可能通过胞质分裂相关因子的定位和活性改变调控胞质分裂[56,122]。

2.2　NEK 家族在减数分裂中的作用

如上所述，NEK 家族在有丝分裂过程中发挥重要的调节作用。减数分裂作为一种特殊的细胞分裂方式，是真核生物和二倍体生物有性生殖和配子产生所必需的。在减数分裂中，染色体的错误分离有可能导致非整倍体受精卵或后代的产生。与有丝分裂相比，人们对 NEK 家族在减数分裂中的作用了解较少。近些年的研究发现，一些 NEK 家族成员，如 NEK1、NEK2、NEK5、NEK9 和 NEK11，在减数分裂中也发挥重要的作用。

在哺乳动物生殖细胞中，NEK1 高表达，并参与减数分裂中纺锤体形成的调控[36]。在 *Nek1* 敲除小鼠的精母细胞和卵母细胞中，第一次减数分裂的纺锤体组装和染色体排列异常，调控纺锤体动力相关蛋白-肌球蛋白 X (myosin X, MYO10)和 α-adducin 的定位和表达改变[64,123,124]。我们推测，NEK1 可能通过与 MYO10 和 α-adducin 的相互作用调控纺锤体的形成。在小鼠卵母细胞中，NEK2 是微管组织中心的组成成分，它的敲降导致第一次减数分裂纺锤体两极的异常和染色体排列异常[42]，研究证明 centrobin/Nip2 是 NEK2 的作用底物，在微管组织中心发挥重要作用[125,126]，而且在卵母细胞中敲降 *centrobin* 与敲降 *Nek2* 的表型是一致的[42]。这些结果提示，NEK2 可能通过磷酸化 centrobin 参与调控卵母细胞减数分裂 I 中纺锤体组装。在小鼠精母细胞减数分裂过程中，NEK2 可磷酸化染色质结构蛋白 HMGA2，通过降低后者与 DNA 的亲和力调控染色质的凝集[127]。我们最近的一项研究发现，NEK5 在减数分裂 G_2/M 转换过程中发挥了重要作用，在 *Nek5* 敲降的卵母细胞中 MPF 活性降低，导致了卵母细胞减数分裂恢复的失败[51]。同时，我们还发现 NEK5 定位在 MI~MII 期纺锤体上，推测 NEK5 也可能参与减数分裂纺锤体的组装。在 *Nek9* 敲降的小鼠卵母细胞中，纺锤体组装和染色体排列异常，γ-tubulin 在纺锤体两极的定位异常，SAC 被激活[128]。在小鼠卵母细胞中敲降 *Nek11* 影响了 MI 期纺锤体的迁移，导致卵母细胞的均等分裂[81]。上述研究结果表明，在生殖细胞中 NEK1、NEK2、NEK5 和 NEK9 等是保证减数分裂正常进行和染色体正确分离的关键蛋白，其表达的改变会导致纺锤体组装相关因子的定位和活性改变进而干扰纺锤体组装和减数分裂细胞周期进程。

3　结语与展望

自发现以来，NEK 家族一直是细胞生物学的研究热点，研究证明 NEK 家族在细胞周期调控中发挥着关键的作用，但其在减数分裂中的功能和分子机制还有待于进一步深入的研究。细胞周期高度有序的运转是通过 G_1/S 期转换、G_2/M 转换和中/后期转换等多个过程的调控来实现的。细胞周期紊乱是肿瘤发生的主要原因，细胞周期相关蛋白的表达异常在肿瘤细胞增殖中扮演着重要角色。因此，对 NEK 家族的生物学功能及其在细胞周期调控中作用的研究，不仅可以更深入地了解细胞周期过程及调控机制，还有助于阐明 NEK 家族在肿瘤发生发展中的作用机制，对肿瘤的临床诊断和治疗也具有重要意义。

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(责任编委: 史庆华)