N-cadherin的作用及其作为肿瘤治疗靶点的展望

李雄锋[1] 程海东[1] 莎仁高娃[2] 范惠莲[3] 侯明星[1]*

([1]内蒙古医科大学附属医院, 胃肠外科, 呼和浩特 010000; [2]内蒙古医科大学基础学院, 呼和浩特 010110; [3]内蒙古国际蒙医医院, 药学部, 呼和浩特 010011)

摘要 N-cadherin又被称为神经钙黏蛋白, 属于钙黏蛋白家族, 主要存在于人体神经组织、晶状体、横纹肌、心肌等组织细胞, 其通过瞬时表达和永久表达, 在胚胎发育、突触功能、血管稳定性和骨内稳态等正常生理功能中发挥重要作用。N-cadherin表达异常时, 可通过多种途径影响肿瘤侵袭转移过程。近年来, 随着对N-cadherin研究的不断深入, 其作为肿瘤治疗靶点的潜力日益凸显。该文就N-cadherin的结构功能、在生理病理中的作用及其作为肿瘤治疗靶点等方面作一综述。

关键词 神经钙黏蛋白; 肿瘤; 治疗靶点; 侵袭转移

The Role of N-cadherin and Its Prospect as a Target for Tumor Therapy

LI Xiongfeng[1], CHENG Haidong[1], SHAREN Gaowa[2], FAN Huilian[3], HOU Mingxing[1]*

([1]*Gastroenterology Surgery, Affiliated Hospital of Inner Mongolia Medical University, Hohhot 010000, China*; [2]*College of Basic Medicine, Inner Mongolia Medical University, Hohhot 010110, China*; [3]*Department of Medicine, Inner Mongolia International Mongolian Medical Hospital, Hohhot 010011, China*)

Abstract N-cadherin, also known as neuro-cadherin, belongs to the cadherin family, which mainly exists in human nerve tissues, lenses, striated muscles, and myocardium. N-cadherin has an important role in normal physiologic functions, such as embryonic development, synaptic function, vascular stability, and intraosseous homeostasis, through transient and permanent expression. When the expression of N-cadherin is abnormal, N-cadherin affects tumor invasion and metastases in many ways. Based on extensive research involving N-cadherin in recent years, the potential of N-cadherin as a target for tumor therapy has become increasingly apparent. This article reviews the structure and function of N-cadherin, the role of N-cadherin in physiology and pathology, and the use of N-cadherin as a target for tumor therapy.

Keywords N-cadherin; tumor; therapeutic target; invasion and metastasis

1 N-cadherin的背景介绍

1.1 钙黏蛋白家族及N-cadherin的发现

N-cadherin又被称为神经钙黏蛋白, 属于钙黏蛋白家族, 在动物组织形成中起关键作用。该分子家族的发现最早可以追溯到1970年左右, TAKEICHI等[1]在研究鸡胚胎晶状体分化的实验中发现, Ca^{2+}能够促进细胞之间的相互黏附。在随后的研究中, 他发现细胞间存在两种黏附机制: Ca^{2+}依赖性黏附和Ca^{2+}非依赖性黏附, Ca^{2+}依赖性黏附机制介导的细胞间黏附因受Ca^{2+}的保护, 所以不易被胰蛋白酶消化, 这种机制可能由一种分子量为150 kDa的表面蛋白介导[2]。后来研究发现, 使用抗F9抗体作用于F9

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*通讯作者。Tel: 13704713301, E-mail: 1459192978@qq.com

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*Corresponding author. Tel: +86-13704713301, E-mail:1459192978@qq.com

畸胎瘤细胞, 在实验中出现了一种类似于阻断Ca^{2+}依赖性细胞–细胞黏附的现象(阻止桑葚胚压实的现象)[3]。于是TAKEICHI团队[1]用F9细胞免疫大鼠分离出一种名为ECCD1的单抗, 它能阻断Ca^{2+}依赖性黏附, 且用它识别出了介导Ca^{2+}依赖性黏附的表面蛋白, 并将其分子量重新估算为124 kDa。至此, TAKEICHI博士的团队[4]终于发现了这种介导Ca^{2+}依赖性黏附的表面蛋白, 并将其命名为“钙黏蛋白”。

该团队还发现, 同样在各自细胞系中表现出Ca^{2+}依赖性黏附的两种细胞, 在混合培养中却表现出了同种细胞间黏附作用更强的现象, 即同种细胞间表现为Ca^{2+}依赖性黏附, 异种细胞间仅存在微弱的Ca^{2+}非依赖性黏附, 利用放射性碘标记的方法, 他们发现了两种细胞中介导各自Ca^{2+}依赖性黏附的两种不同表面蛋白[5]。最终, 该团队分离出针对神经细胞Ca^{2+}依赖性黏附的单克隆抗体-NCD1, 其能结合的抗原主要存在于神经组织、晶状体、横纹肌、心肌等组织细胞中, 且NCD1和ECCD1特异性地与各自抗原结合[6]。因ECCD1和NCD1对应的靶标分别存在于上皮组织和神经组织, 故HATTA等[6]分别将其靶标分子命名为E-cadherin(上皮钙黏素)和N-cadherin(神经钙黏素)。其间, 他们还发现另外一些Ca^{2+}依赖性黏附细胞既不与ECCD1反应也不与NCD1反应, 由此推断, 在体内细胞中至少存在3种不同的Ca^{2+}依赖性细胞–细胞黏附系统(Ca^{2+}-dependent cell-cell adhesion system, CDS)。自此, HATTA等[6]便揭开了钙黏蛋白家族的序幕。值得一提的是, 该家族的发现并不完全由TAKEICHI团队[1]所发现, 在该团队实验期间, 陆续有多个团队也同时发现了不同的钙黏蛋白, 如, VOLK等[7-9]发现的A-CAM(后证实与N-cadherin相同); GALLIN等[10]发现的L-CAM; HYAFIL等[11]发现的UMt(实为N-cadherin的一个片段)。到目前为止, 在人类中已发现有80多个钙黏蛋白超家族成员[12]。

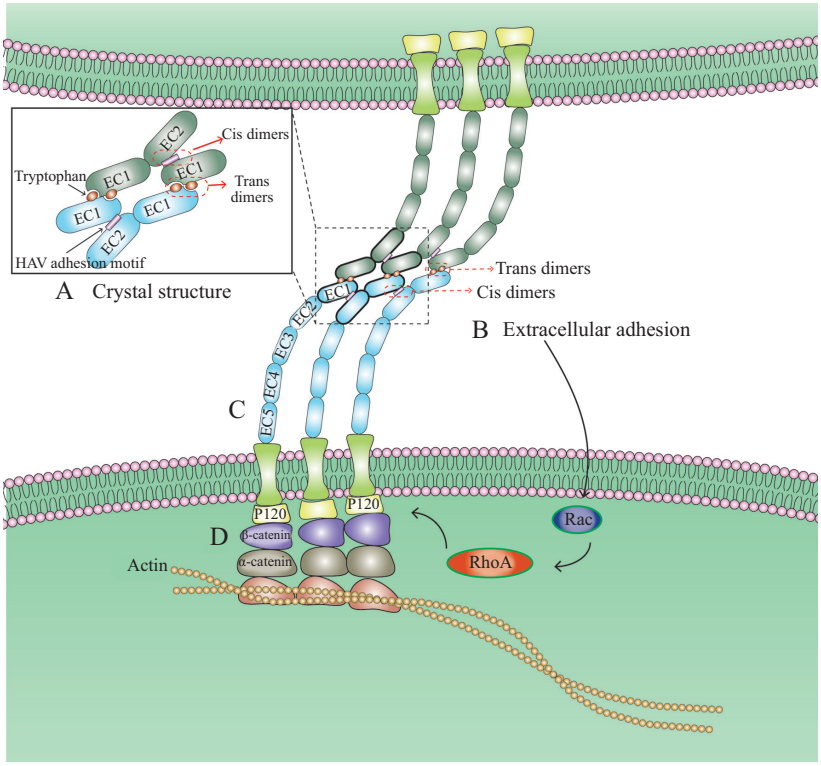
1.2 N-cadherin主要结构功能

*N-cadherin*基因定位于染色体18q11.2的250 Kb区域, 该基因由16个外显子组成, 不仅在人和小鼠间存在同源性, 在其他钙黏蛋白之间也被发现了其同源性[13]。N-cadherin属于脊椎动物I型经典钙黏蛋白, 是一种膜钙结合糖蛋白, 由胞外段、跨膜段和胞浆段三部分组成, 介导神经细胞及其他多种类型细胞的黏附[14-16]。胞外部分含有5个相似的结构域(ec1-ec5)(图1), 每个结构域为由110个左右的氨基酸组成的重复序列(extracellular region, EC)[14-15,17-18]。I型经典钙黏蛋白的共同特征为在第一个胞外结构域的重复序列上有HAV(His-Ala-Val)序列[17]。这些特殊序列是实现其功能的结构基础, 可能成为日后治疗N-cadherin介导的某些疾病的特异性靶点。

目前研究最广泛的是N-cadherin作为细胞黏附分子介导的同型或异型细胞间黏附功能。关于N-cadherin介导的同型细胞间黏附, 普遍认可的是在顺式和反式两种二聚体基础上形成稳定黏附的理论。该理论认为, 在同一细胞上, N-cadherin单体之间相互聚集, 形成顺式二聚体, 在此基础上与另一细胞上的N-cadherin形成反式二聚体, 从而建立一种稳定的细胞–细胞间黏附[17]。单一的反式二聚体难以形成稳固结构, 在发生反式黏附之前, 同一细胞上的N-cadherin单体会发生聚集, N-cadherin胞外部分的第一结构域上的HAV(His-Ala-Val)序列会和相邻单体第二结构域上的识别序列相结合, 形成顺式二聚体[15,19]。顺式二聚体能够发生在两个甚至更多相邻的N-cadherin单体上。在顺式二聚体的形成过程中, 钙离子的作用是必不可少的。有研究表明, 钙离子是形成顺式二聚体的核心, 每个二聚体通过位于EC1和EC2之间的接头区域的残基与6个钙离子缔合, 而钙离子结合位点的单个氨基酸取代可破坏细胞在体内的集聚, 钙离子结合使ECs排列成抗蛋白水解的刚性结构[11,17,20-23]。顺式二聚体一般以同型二聚体为主, 但有文献报道, N-cadherin和R-cadherin之间会形成功能性顺式二聚体[24]。反式二聚体发生在相对的细胞之间, 存在于N-cadherin单体第一胞外结构域上的色氨酸残基侧链通过插入到另外一个细胞的N-cadherin单体第一胞外结构域上的疏水口袋中, 来实现相对细胞间的反式黏附[17]。N-cadherin通过顺式和反式二聚体形成稳定的晶体结构(图1), 从而介导细胞–细胞间黏附作用[25]。

N-cadherin介导的黏附由多个分子介导、多个生物学过程连续参与, 且伴随信号转导。N-cadherin胞质部分与多种分子[如p120-catenin(p120-连环蛋白)、β-catenin(β-连环蛋白)和α-catenin(α-连环蛋白)]结合, 三者共同形成一个核心功能单元, 即cadherin-catenin复合体(cadherin-catenin complex, CCC)(图1), 它们可能是钙黏附性蛋白功能的调节因子[12]。其中, p120-catenin参与N-cadherin的膜表达和侧向聚集, 进而将N-cadherin定位于富含胆固醇的微区, p120-

catenin与膜旁结构域结合, 是调节黏附或运动表型的关键分子; p120-catenin被磷酸化时, 与N-cadherin的结合增加, 降低了后者的黏附活性[12,26-27]。N-cadherin的黏附活性也受Rho GTP酶的调节。N-cadherin胞外区的初始连接触发Rho GTP酶家族成员Rac的激活, 从而刺激细胞–细胞接触点的局部肌动蛋白细丝组装和膜突起的形成[28-29]。Rho GTP酶家族成员Ras同源家族成员A(Ras homolog family member A, RhoA)随后被激活, 以牺牲Rac功能为代价, 通过触发β-catenin与钙黏蛋白细胞内结构域的隔离, 促进了基于N-cadherin的细胞–细胞连接的成熟[30-31](图1)。而β-catenin和α-catenin通过与钙黏蛋白细胞内结构域的结合参与黏附界面和肌动蛋白细胞骨架的连接。β-catenin结合钙黏蛋白胞内结构域的C末端和α-catenin的N末端, α-catenin与许多参与肌动蛋白结合、捆绑和聚合的蛋白质结合, 也与F-actin直接结合, 缺乏α-catenin或β-catenin会导致细胞黏附缺陷, cadherin-catenin复合物无法与肌动蛋白细胞骨架结合, CCC复合体是上皮细胞之间形成顶端连接的主要成分[32]。有文献报道, 这种cadherin-catenin复合体的稳定性受E-cadherin和N-cadherin表达平衡的影响。当E-cadherin下调时, β-catenin会从复合体中解离出来, 进而导致N-cadherin表达上调[33]。N-cadherin的黏附功能受N-cadherin-catenin复合体的翻译后修饰的调



A: 在同一细胞上, N-cadherin的胞外第一结构域(EC1)与相邻N-cadherin的胞外第二结构域(EC2)通过HAV基序形成顺式二聚体; 在相邻细胞上, N-cadherin的胞外第一结构域(EC1)与相邻细胞N-cadherin的胞外第一结构域(EC1)通过色氨酸残基相互插入对方疏水口袋形成反式二聚体; 顺式二聚体和反式二聚体共同构成晶体结构, 稳定细胞间黏附。B: N-cadherin胞外区的初始连接通过激活Rac、RhoA, 促进了基于N-cadherin的细胞–细胞连接的成熟。C: 胞外部分含有5个相似的结构域组成(EC1~EC5), 每个结构域为由110个左右的氨基酸组成的重复序列(EC)。D: N-cadherin胞质部分与p120-catenin、α-catenin、β-catenin三种连环蛋白一起形成cadherin-catenin复合体(cadherin-catenin complex, CCC), 介导多种生物学过程。

A: the EC1 (extracellular first domain) of N-cadherin and the EC2 (extracellular second domain) of adjacent N-cadherin form a cis dimer through the HAV motif on the same cell; on adjacent cells, the EC1 (extracellular first domain) of N-cadherin in opposing cells are inserted into the hydrophobic pockets of the opposing cells through tryptophan residues to form a trans dimer; together, CIS and trans dimers form a crystal structure and stabilize cell-cell adhesion. B: the initial ligation of the N-cadherin extracellular domain promotes the maturation of N-cadherin-based cell-cell junctions by activating Rac and RhoA . C: the extracellular part contains five similar domains (EC1-EC5), each of which is a repetitive sequence (EC) consisting of approximately 110 amino acids. D: the cytoplasmic part of N-cadherin is associated with p120 catenin α-catenin, β-catenin. The three catenins form a CCC complex (cadherin-catenin complex) that mediates a variety of biological processes.

图1 N-cadherin的主要结构和功能

Fig.1 Main structure and function of N-cadherin

节, 例如, N-cadherin-catenin复合物的稳定性高度依赖N-cadherin及其相关的catenins的磷酸化状态, 其受酪氨酸激酶(如Fer和Src)和酪氨酸磷酸酶PTP1B(protein-tyrosine phosphatase 1B)的调节[34-36]。PS1(presenilin 1)在N-cadherin向质膜的运输中发挥作用。当PS1低表达时, 细胞间的接触受到抑制, N-cadherin定位于核周的内质网和高尔基体[37]。在激活细胞黏附的过程中, 同时伴随着一系列的细胞信号转导过程, 包括促进集体细胞迁移、增强成纤维细胞生长因子受体信号转导、调节典型的Wnt信号转导、调节PI3K-AKT信号通路等, 在文章后面的部分, 我们会进行详细的介绍。

2 N-cadherin在正常生理中的作用

N-cadherin在发育过程中以及心脏和神经组织形成的形态发生过程中也发挥重要作用[36]。还有研究发现其参与成骨、骨骼肌生成和血管系统的成熟, 在胚胎发育和成年期起着时空调节的作用[38]。

2.1 N-cadherin在胚胎发育中的作用

在原肠胚形成时期, 在位于原线外胚层(上皮细胞)的一些即将内陷的细胞中检测到N-cadherin表达, 此时, 这些细胞同时表达N-cadherin和E-cadherin, 但随着发育的进行, 分化成中胚层的细胞不再是表达E-cadherin, 而是仅表达N-cadherin, 而进入内胚层的细胞仍继续表达N-cadherin和E-cadherin两种钙黏蛋白[39]。在中胚层分化为各组织的过程中, N-cadherin的表达呈现动态变化, 最典型的例子为体结的分化和肾单位的分化[39]。体节是由间充质(节段板)形成的上皮细胞, 随后重组为皮节、肌节和硬化节。节段板细胞和体节细胞在体外均表现出钙依赖和钙非依赖的细胞聚集系统, 可被抗N-cadherin抗体抑制。在体内, N-cadherin的时空表达与体节的形成和局部破坏密切相关[40]。在中肾发育过程中, 原始细胞的凝聚伴随着N-cadherin表达量的增加。这种强烈的表达一直持续到细胞组织成中肾小管。中肾小管与沃尔夫管融合后, N-cadherin被替换为E-cadherin。在后肾发育过程中观察到类似的N-cadherin瞬时表达模式。源自中胚层的许多其他组织瞬时或永久表达N-cadherin[39]。在神经发育过程中的内陷期间, N-cadherin出现在神经板中, 此过程与E-cadherin从该细胞中消失相协调。在神经管形成后, N-cadherin成为该组织的主要钙黏蛋白。在中枢神经系统分化过程中, N-cadherin的表达量在区域上有所不同。例如, 在神经视网膜中, 包括视神经在内的所有细胞在早期发育阶段均表达N-cadherin[39]。心脏是胚胎中随着原始循环系统的建立而形成的第一个器官。N-cadherin与心脏发育的各个方面有关, 包括心前中胚层的整理、心脏环的形态发生、心肌壁的小梁形成等[41]。N-cadherin在心脏前中胚层强烈表达, 并且在成人心肌细胞发育和分化过程中持续表达[41-42]。这些研究均表明, 在胚胎发育的过程中, N-cadherin起不可或缺的作用。

2.2 N-cadherin在正常细胞中的作用

N-cadherin的表达在整个发育阶段和成年期都受到时空调控。在发育过程中, N-cadherin在心脏和神经组织形成的形态发生过程中发挥着重要作用, 并参与成骨、骨骼肌生成和血管系统的发育。在成年期, N-cadherin由多种细胞表达, 包括神经细胞、内皮细胞、基质细胞和成骨细胞, 是突触功能、血管稳定性和骨内稳态的组成部分[36,43-47]。有研究表明, N-cadherin在骨谱系中具有双重作用: 一方面维持了成骨祖细胞的数量; 另一方面通过对Wnt信号的负性干扰抑制了成骨细胞的分化和/或功能[43,48]。在血管内皮细胞和壁细胞中, N-cadherin、Rac1以及RhoA共同发挥作用, 介导血管内皮细胞以及壁细胞的屏障功能[46]。使用簇状规则间隔短链重复序列技术(clustered regularly interspaced short palindromic repeats, CRISPR)敲除*N-cadherin*后, 屏障功能丧失; 在CHO细胞中, N-cadherin的过表达促进屏障功能增强[46]。在神经系统中, 神经元生长锥上的N-cadherin与其他轴突或非神经元细胞表面上的N-cadherin的结合决定了神经元延伸轴突的方式和支配靶标的能力[44,49-50]。体外研究表明了神经元细胞黏附分子N-cadherin和Ll是促进多种非神经元细胞(如星形胶质细胞、肌肉细胞和施万细胞)轴突生长的主要CAM[44,51-52]。WILLIAMS等[44]研究表明, N-cadherin和Ll可通过与成纤维细胞生长因子受体(fibroblast growth factor recepetor, FGFR)上的特定结构域结合从而刺激神经突的生长。

3 N-cadherin在肿瘤发生发展中的作用

3.1 N-cadherin在肿瘤中的表达

典型的N-cadherin在神经系统中广泛表达, 介导神经细胞间的黏附, 而在其他正常细胞中低表达。然而, 近年来发现, N-cadherin在人类多种恶性

肿瘤, 如乳腺癌、前列腺癌、肺癌、肝癌和尿路上皮癌中异常表达[53-58]。在一项研究中, 研究者评估了827例非肌层浸润性膀胱癌患者中N-cadherin的表达状态, 从而评估N-cadherin作为预后生物标志物在经尿道电切术治疗非肌层浸润性膀胱癌患者中的作用(伴或不伴辅助膀胱内治疗), 结果发现N-cadherin在大约2/5的非肌层浸润性膀胱癌患者中表达。其表达与不良病理特征和疾病复发风险相关[59]。在另一项针对乳腺浸润性导管癌的研究中, 研究者采用免疫组织化学方法检测了132例浸润性乳腺癌中N-cadherin蛋白的表达水平, 发现N-cadherin蛋白在51.9%的患者中过表达, 其过表达可能在浸润性导管癌的发生发展中起重要作用[60]。在一项纳入146例接受根治性胃切除术的胃癌患者的临床研究中, 研究者得到N-cadherin阳性表达31例, 阴性表达115例, 发现N-cadherin表达与血行复发呈正相关(P<0.01), 与患者术后预后呈负相关[61]。另外有文献报道, 当从N-cadherin的胞外区酶切时, 会产生一个分子量为90 kDa的可溶N-cadherin片段, 其在兔角膜实验和绒毛尿囊实验中促进血管生成, 在伤口愈合实验中刺激内皮细胞的迁移, 并刺激细胞外调节激酶的磷酸化[62]。这种分子量为90 kDa的可溶N-cadherin片段在前列腺癌、乳腺癌和膀胱癌患者的血清中高于正常人[63-65]。

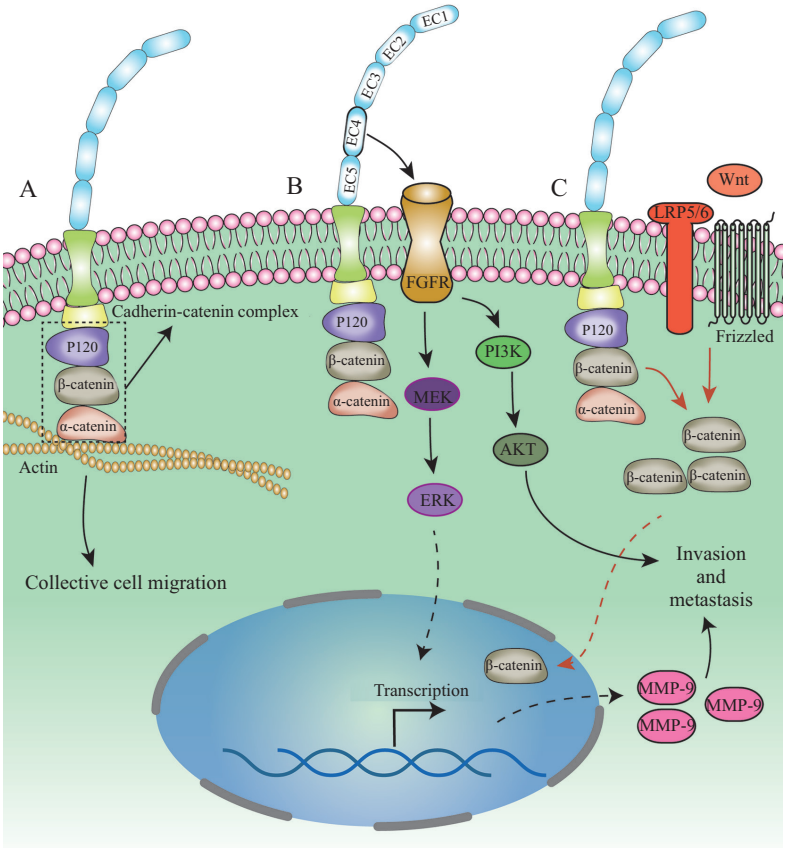
3.2 N-cadherin通过多种途径促进肿瘤转移

恶性肿瘤的转移一直是肿瘤发生发展过程中的重要环节, 也是肿瘤治疗中难以攻克的环节。N-cadherin的异常表达除了影响恶性肿瘤预后外, 还与肿瘤的侵袭和转移密切相关, 且是上皮–间充质转化间质标志物[58,66]。在体外, N-cadherin的过表达增强了多种上皮性癌细胞的迁移和侵袭能力[67-71]。在体内转基因MMTV-PyMT小鼠乳腺癌模型中, 乳腺上皮中N-cadherin的表达导致肺转移灶的数量增加了3倍, 却不影响原发肿瘤的生长[72]。N-cadherin主要通过促进集体细胞迁移、增强FGFR信号、调节典型的Wnt信号转导三种途径促进肿瘤的转移[36](图2)。

3.2.1 促进集体细胞迁移 癌细胞使用不同的迁移模式, 可以单个细胞的形式传播, 也可以片状、簇状、或链状的形式集体迁移。白血病、淋巴瘤和大多数肉瘤以单个细胞的形式传播, 而上皮细胞通常以集体迁移的方式传播[12]。研究表明, 上皮癌细胞表达N-cadherin可促进其集体迁移能力。例如, N-cadherin被证明可促进肺癌或卵巢癌细胞在体外形成聚集体并共同侵入三维胶原基质或穿透腹膜间皮样细胞层[71,73]。在这些细胞中, N-cadherin细胞内域或β-catenin结合域的缺失导致更多的单个细胞从细胞团中分离和迁移, 突显了N-cadherin-肌动蛋白细胞骨架相互作用在集体细胞迁移中的重要性[74]。

3.2.2 增强成纤维细胞生长因子受体(FGFR)信号 研究表明, N-cadherin的第四个胞外区(ec4)可以反式激活FGFRs, 促进神经突起的生长, 但并不依赖于FGF配体, 这表明N-cadherin可以作为FGFRs的替代配体[75-76]。N-cadherin和FGFR的相互作用也可能通过激活磷脂酰肌醇-3激酶/Akt(PI3K/Akt)信号通路促进某些癌细胞的转移[74]。例如, FGFR激活后表达N-cadherin的ErbB2/Neu乳腺癌细胞的侵袭性是由PI3K/Akt信号介导的。N-cadherin增强ErbB2/Neu细胞的FGFR-Akt信号转导和对FGFR抑制的敏感性, 提示N-cadherin-FGFR-PI3K/Akt信号轴参与乳腺癌细胞侵袭[74,77]。最近的研究表明, N-钙黏蛋白的表达是FGFR1/4在非小细胞肺癌中致癌作用的关键[78]。

3.2.3 调节典型的Wnt信号 典型Wnt信号促进β-catenin的细胞质积累和核易位, β-catenin激活T细胞因子/淋巴增强因子(TCF/LEF)介导的基因转录, 这些基因编码肿瘤侵袭和转移促进分子(例如MMP和CD44)[74,79-81]。如前文所述, N-cadherin通过p120-catenin、α-catenin和β-catenin以N-cadherin-catenin复合物的形式与肌动蛋白细胞骨架结合。当肿瘤细胞中N-cadherin-β-catenin复合物降解时, 解离的β-catenin转位到癌细胞的细胞核, 激活Tcf/Lef介导的肿瘤转移促进分子编码基因, 如*CD44*和*MMPs*的转录[58,74,82-83]。在黑色素瘤细胞的跨内皮迁移过程中, 在初始阶段时β-catenin与N-cadherin共定位; 在跨内皮迁移期间, 酪氨酸激酶Src被激活并磷酸化N-cadherin细胞质结构域, 从而解离N-cadherin-β-catenin复合物。然后β-catenin易位至黑素瘤细胞核并激活TCF/LEF介导的基因转录, 导致黏附分子CD44的上调[84-85]。MANSOORI等[86]通过切除balb/c雌性小鼠卵巢来研究抗IL-17抗体和PTH(1-34)在缓解卵巢切除引起的骨丢失方面的联合作用, 得出IL-17通过上调N-钙黏蛋白, 干扰PTHR1/LRP-6相互作用, 从而抑制Wnt信号转导并促进骨丢失。LÜ等[87]的研究结果证实了吡非尼酮通过调节Wnt/GSK-3β/β-catenin和



A: N-cadherin通过cadherin-catenin复合体与肌动蛋白骨架结合, 促进集体细胞迁移。B: N-cadherin可作为FGFRs的替代配体, 抑制FGFR内化, 激活MAPK/ERK和PI3K/AKT信号通路, 介导肿瘤侵袭转移。C: cadherin-catenin复合体的解离增加胞内β-catenin含量, 从而调节Wnt信号通路, 促进肿瘤转移。

A: N-cadherin binds to the actin skeleton via the cadherin-catenin complex and promotes collective cell migration. B: N-cadherin acts as an alternative ligand for FGFRs, inhibits FGFR internalization, activates MAPK/ERK and PI3K/AKT signaling pathways, and mediates tumor invasion and metastasis. C: dissociation of the cadherin-catenin complex increases intracellular β-catenin content, thereby regulating the Wnt signaling pathway and promoting tumor metastasis.

图2　N-cadherin通过多种途径促进肿瘤转移

Fig.2　N-cadherin promotes tumor metastasis through multiple pathways

TGF-β1/Smad2/3信号通路在体内外能够减轻肺纤维化。QU等[48]发现N-钙黏蛋白可以通过抑制Wnt信号通路最终促进骨髓间充质干细胞的软骨分化。

4　N-cadherin可能成为未来肿瘤治疗中的新靶点

介于N-cadherin在肿瘤发生发展过程中的重要作用, 以及其与肿瘤预后息息相关, 如若开发出一种针对N-cadherin的拮抗剂, 则有望为肿瘤的治疗提供一种新的思路。目前已有数种针对N-cadherin的拮抗剂, 根据其作用机制的不同, 大致可分为: (1) 针对其HAV序列的三种拮抗剂, 合成线状肽、合成环肽和非肽基肽类药物[88-89]; (2) 针对其色氨酸残基的人工合成的线状肽[90]; (3) 针对其胞外区的单克隆抗体[91]。含有HAV基序的合成线性多肽如十肽N-Ac-LRAHAVDING-NH, 被证明可以阻止轴突生长[92]、肌母细胞融合[93]和星形胶质细胞上的雪旺细胞迁移[94]。含有HAV基序的合成环肽如N-Ac-cha VC-NH2(命名为ADH-1)被证明能够抑制血管生成, 引起多发性骨髓瘤、神经母细胞瘤和胰腺癌细胞的凋亡[88]。针对N-cadherin胞外区的单克隆抗体能够在体外抑制表达N-cadherin的PC3人前列腺癌细胞的侵袭和增殖[88,91]。这些拮抗剂均有望发展应用到临床, 使N-cadherin成为肿瘤治疗的新靶点。

5　总结与展望

自上世纪70年代TAKEICHI等[1]发现N-cadherin以来, 随着研究的不断深入, 笼罩在N-cadherin身上的神秘面纱也逐渐被一层层揭开, 包括其分子结构和主要结构功能的探索, 以及它在发育成熟以及肿

瘤发生发展过程中的机制作用。另外, 作为肿瘤发生发展过程中的重要分子之一, N-cadherin不仅在促进肿瘤增殖、转移、血管生成等方面发挥重要作用, 且与肿瘤的预后关系密切, 其血清片段可作为未来诊断肿瘤的血清标志物, 针对N-cadherin的拮抗剂已被发现有很多种类, 虽然其距离临床应用尚有一段距离, 但是这些拮抗剂的发现也为今后N-cadherin作为肿瘤治疗的新靶点提供了一种可能, N-cadherin有望成为未来肿瘤治疗中的一种重要手段。因此, 针对N-cadherin的进一步研究, 将会有十分重要的意义。

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