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中间纤维的功能和研究进展

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摘要　中间纤维(intermediate filaments, IFs)与微丝、微管共同组成细胞骨架的纤维网络体系。除了结构支撑作用, 中间纤维在诸多信号转导通路中发挥了重要调控功能。此外, 中间纤维还参与调控细胞运动、增殖、分化和凋亡等过程, 相关基因突变或翻译后修饰会导致癌症、创伤、炎症、病原体感染及自身免疫等多种疾病。该综述将简要介绍中间纤维参与的细胞功能调控, 并重点介绍与其他骨架体系的协同互作及参与相关疾病的调控。中间纤维作为参与多种生物功能和组织特异调控的重要元素, 对其深入全面的研究将会对相关生理过程、病理机制和临床治疗具有重要意义。

关键词　中间纤维; 结构支撑; 信号通路; 细胞运动; 细胞骨架互作; 病理效应

The Function and Research Progress of Intermediate Filaments

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Abstract　Intermediate filaments (IFs), together with actin filaments and microtubules comprise a diverse and flexible cytoskeletal system. Besides mechanical support, IFs are involved in a wide range of cell signaling pathways. In addition, IFs-associated functions are essential for cell migration, cell proliferation, cell differentiation and apoptosis. Characteristically, the mutations and posttranslational modifications of IFs were found in various pathological processes, including cancer, tissue regeneration, inflammation, pathogen infection as well as immune responses. This review briefly summarizes the cellular function of IFs, and focuses on its interplay with other cytoskeletal systems and regulation of a variety of diseases. As multifactorial and tissue-specific integrators, the

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comprehensive study on IFs will contribute to diverse range of pathologies.

Keywords intermediate filaments; structural support; signaling pathway; cell migration; cytoskeletal interplay; pathological effects

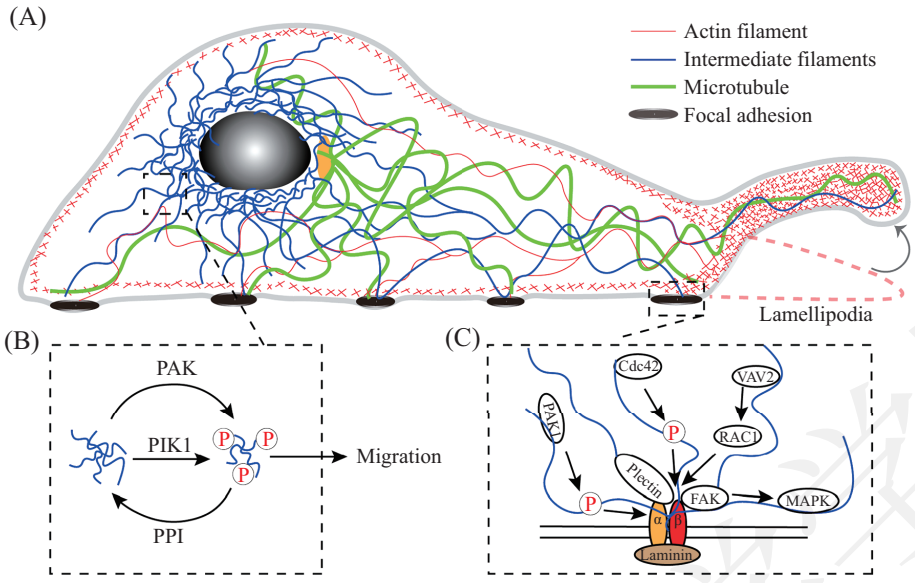
1 中间纤维的概述和基本功能

微丝、微管与中间纤维共同组成了真核细胞的骨架系统。相较于被广泛研究的微丝和微管, 人们对中间纤维的了解并不深入。1968年, Ishikawa等[1]首次利用电子显微镜在肌肉细胞中发现了中间纤维, 随后关于中间纤维的研究逐渐丰富。中间纤维直径约10 nm, 介于微丝(7 nm)和微管(25 nm)之间, 其结构、组装机制和表达模式相对复杂[1]。目前发现共有73个编码中间纤维的基因[2], 根据氨基酸序列可分为6类, 分别是: (1)酸性角蛋白('acidic' keratins); (2)中性和碱性角蛋白('basic' keratins); (3)波形蛋白(vimentin)和神经元酸性蛋白(GFAP)等; (4)神经丝蛋白(neurofilament)和巢蛋白(nestin); (5)核纤层蛋白(lamins); (6)晶丝蛋白(filensin)和晶状体蛋白(phakinin)。中间纤维具有组织表达特异性, 如'acidic' keratins特异表达于上皮组织, desmin表达于平滑肌, neurofilament表达于神经系统等[3-4]。不同类型的中间纤维具有高度保守的由310个氨基酸残基(核纤层蛋白是352个)组成的α螺旋杆状域, 以及可变的非螺旋状N-端和C-端。中间纤维装配时, 首先相邻两条蛋白肽链的α-螺旋区首尾同向盘成双股超螺旋二聚体(coiled-coil dimer), 随后两个二聚体反向平行组装成四聚体, 并最终组装成中间纤维[5]。由于中间纤维在组装过程中彼此反向排列, 因而不具备极性, 这是与微丝、微管的重要区别之一, 也使中间纤维成为最稳定的细胞骨架体系。

中间纤维是保持细胞结构完整的主要因素之一, 相较于微丝和微管其具有更强的弹性, 能够承受更高强度的机械压力[6], 故早期的研究主要局限于其机械支撑功能。在细胞内, 中间纤维连接核表面和细胞膜表面, 形成一个连续的由细胞核向四周辐射的网状结构, 既维持细胞形态又能够为其他细胞器提供附着的结构基础[7]。随着研究的深入, 人们发现中间纤维还参与调控重要的信号转导过程。例如, 压力情况下中间纤维会发生磷酸化进而改变其组装结构和物理弹性[8]。高温下, 中间纤维可与热激蛋白结合, vimentin、desmin、peripherin、GFAP等能与HSP27、αβcrystallin等作用以应对各种应激情况[9]。中间纤维还参与氧化应激, keratin具有抗氧化特性, 小鼠keratin 18发生突变能够引起氧化代谢基因和氧化还原信号通路相关基因的变化, 进而引起肝脏细胞色素和脂质过氧化物(丙二醛)的表达上调[10]。中间纤维的磷酸化还可保护细胞免于凋亡, 例如*keratin*基因缺失的小鼠通常更易感由毒素或其他压力因子诱导的细胞凋亡[11]。研究表明, vimentin参与Raf-1和RhoA等信号通路, 调节肿瘤坏死因子α介导的细胞凋亡[12]。Vimentin能与促分泌素结合引发不同类型的癌细胞凋亡[13]。这些研究提示, vimentin可作为潜在靶点用于抗肿瘤治疗。中间纤维还参与调控14-3-3和mTOR信号通路, keratin 17缺失会导致14-3-3蛋白无法在胞质内聚集, 进而激活mTOR信号通路, 引起细胞的形态变化[14]。在非洲爪蟾卵的中胚层细胞连接处keratin能够与14-3-3结合, 反之抑制14-3-3会导致keratin的组装缺陷[15]。Nestin还参与调控Cdk5激酶信号通路, nestin的缺失可引起致敏细胞内Cdk5介导的凋亡活性[16]。在某些压力条件下, nestin通过表达上调来隔离Cdk5减弱细胞凋亡[17]。除此之外中间纤维还影响很多信号通路, 如PKC、PKA、JNK、CaMK II、Akt和磷酸酶通路等[18-20]。因此, 中间纤维除了作为细胞骨架维持细胞结构的完整性, 更是一个调控诸多信号通路的枢纽平台。

2 中间纤维与细胞运动和迁移

研究表明, 除微丝和微管外中间纤维也在细胞黏附、细胞机械感受和细胞运动过程中直接或间接地发挥重要作用[21]。中间纤维vimentin可调控板状伪足(lamellipodia)的生成(图1A)和细胞的收缩[22], 还可通过磷酸化重组结构网络促进细胞机械力的转导[22]。Vimentin缺失能够抑制平滑肌机械力传导, 还可导致成纤维细胞的收缩能力受损[23-24]。PAK1与PLK1通过催化vimentin第52位丝氨酸的磷酸化促进细胞的收缩[25], 而PPI则通过对vimentin的去磷酸化作用抑制细胞的收缩[26](图1B)。Vimentin不仅通过磷酸化与各种信号通路作用, 还被证明与黏附因子相互作用并加强细胞与基质的黏连[27]。研究发现,



A: 运动中的细胞形态示意图, 板状伪足向前伸展。B: 中间纤维vmentin通过磷酸化调控细胞收缩。C: 中间纤维通过不同方式与黏附斑互作, 调控其动力学。

A: schematic diagram of a migrating cell, which forms a protrusion called lamellipodia at leading edge. B: the intermediate filaments vimentin regulates cell contraction by phosphorylation. C: intermediate filaments interact with focal adhesion and regulate it's dynamics by various means.

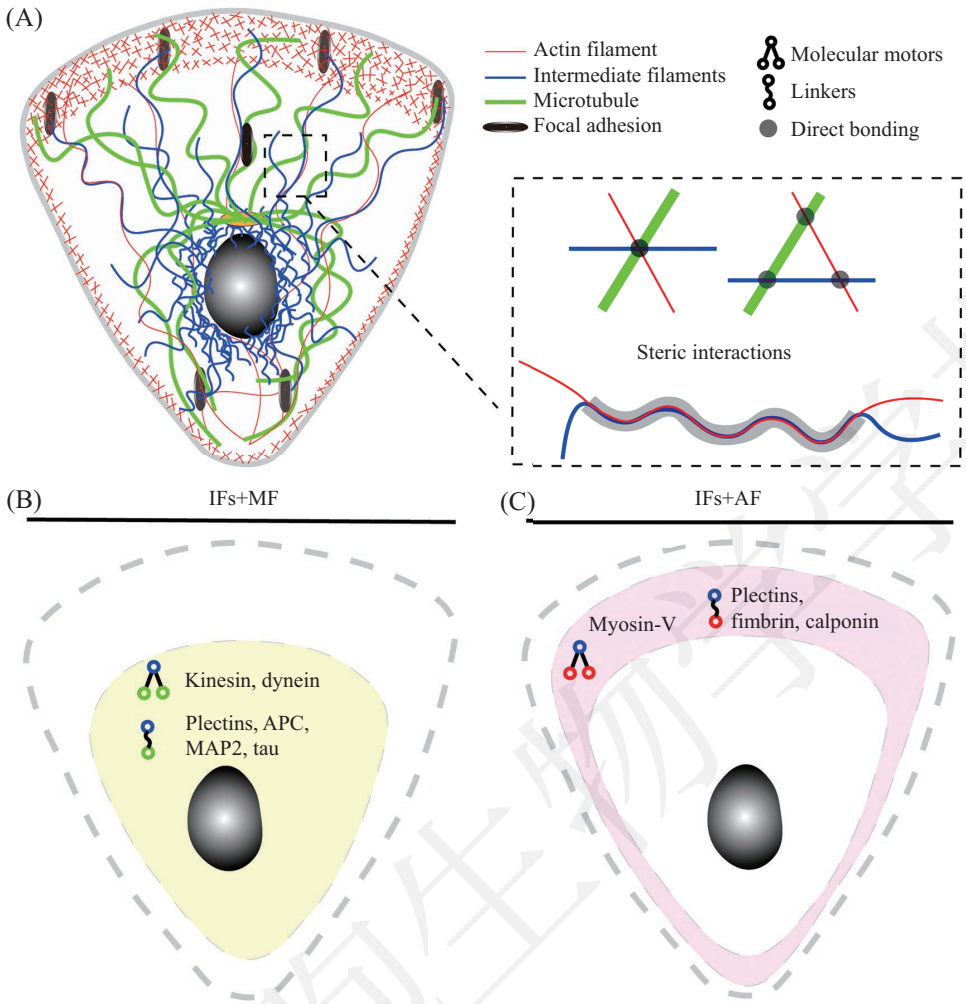
图1 中间纤维调节细胞运动(根据参考文献[22]修改)

Fig.1 Intermediate filaments regulate cell migration (modified from reference [22])

vimentin通过多种方式与黏附斑(focal adhesion)互作, 其高表达可增强黏附斑的活力进而促进细胞运动[21,28-29]。Vimentin可与整合素(integrin)直接相连调节与胞外配体的结合[28], 也可通过交联因子plectin或FAK信号的介导发挥功能[30-31]。此外, vimentin可将Rac的鸟嘌呤核苷酸交换因子VAV2招募到黏附斑以促进FAK激活[21], 黏附斑处的vimentin解聚会破坏FAK、Src和下游MAPK的活性[32]。Vimentin与黏附斑的相互作用同样受磷酸化调节: PAK1介导的vimentin磷酸化引起其结构网络重组从而改变黏附斑的装配[33]; PKC介导的vimentin磷酸化能促进整合素迁移至质膜[34]; 而Cdc2介导的vimentin磷酸化可增强整合素的活性[21](图1C)。

近期的研究表明, 群体细胞迁移和伤口愈合很大程度上依赖于中间纤维的网络重组[27]。受伤的组织会诱导一系列编码中间纤维基因的表达, 加强细胞的运动和迁移进而加快伤口的愈合[35]。Vimentin的高表达是组织受伤的标志, 其基因缺失的小鼠不管在胚胎发生还是成熟阶段都会因细胞迁移缺陷而导致伤口愈合延缓和组织再生能力下降[24,36]。此外, vimentin也是上皮–间质转变(epithelial interstitial transformation, EMT)的重要标志蛋白, 转化生长因子TGFβ1通过激活vimentin-slug信号复合体触发EMT和角质细胞迁移[37]。肺部损伤修复过程中, 肺泡中的TGFβ1能诱导*vimentin*基因表达进而促进上皮细胞迁移。抑制或增强vimentin的表达都会抑制肺部细胞的迁移和伤口愈合[38]。受损晶状体的恢复过程中, vimentin与肌球蛋白myosin IIB结合调节上皮细胞的集体迁移[39]。此外中间纤维可连接细胞核和细胞质的骨架体系, 在细胞运动过程中实时整合细胞核与细胞质的动态变化[40]。缺乏vimentin和GFAP的星形胶质细胞表现出细胞核形态异常和细胞运动缺陷[40-41]。最新的研究还表明, vimentin在胞内的定位还参与调控单细胞的极性建立和定向运动[42]。

在细胞运动过程中, keratin通过桥粒和半桥粒调控细胞形态、细胞黏附、细胞内和细胞间的张力。研究发现, keratin缺失能够减弱细胞间的连接, 促进伤口愈合[43]。伤口愈合过程中, 鼠胶质细胞内keratin的缺失可引起半桥粒的紊乱, 提高细胞基质黏附性进而促进细胞迁移, 而keratin 5和keratin 14的重新表达可以很好地恢复这个表型[43-44]。此外, 中枢神经系统中的胶质瘢痕形成、受伤的肌肉再生等病理过程都可诱导nestin的表达上调[16]。脑垂体梗塞时nestin在新生毛细血管中表达, 但当梗塞组织转化成纤维组织时它的表达水平很快下降[45]。有趣的



A: 中间纤维与微丝、微管的几种空间互作方式。B: 中间纤维在靠近细胞核位置上与微管相互重叠并通过分子马达和交联蛋白与微管相互作用。C: 中间纤维在靠近细胞外周位置上与微丝相互重叠并通过分子马达和交联蛋白与微丝相互作用。IFs: 中间纤维; AFs: 微丝; MTs: 微管。
A: multiple physical interactions exist between the intermediate filaments and the other two cytoskeletal subsystems. B: in regions of spatial overlap, the subsystems interact via steric effects between IFs and MTs (mainly in the cell interior). Crosstalk between IFs and MTs is facilitated by cross-linkers and motors. C: spatial overlap of IFs and AFs exist mainly in the cell periphery, crosstalk between AFs and IFs is facilitated by cross-linkers and motors. IFs: intermediate filaments; AFs: actin filaments; MTs: microtubules.

图2 中间纤维与微丝、微管的相互作用(根据参考文献[47]修改)

Fig.2 The interplay between intermediate filaments and actin filaments, microtubules (modified from reference [47])

是, 新血管中nestin的表达下调会引起vimentin的表达上调, 这表明, nestin的上调很可能是为了补偿组织再生过程中内皮细胞中间纤维的重组缺陷[46]。

3 中间纤维与其他细胞骨架的互作及相关细胞功能

中间纤维与微丝、微管组成的细胞骨架体系几乎参与所有细胞生命进程的调控, 中间纤维在细胞内既独立地装配, 行使特异功能, 同时也与微丝、微管及其他重要组分蛋白相互作用[47]。在小鼠成纤维细胞(fibroblast)中发现, 微管能直接连接细胞质膜内层的微丝和细胞质中的中间纤维[48]。细胞骨架在胞内的表达都各有特征, 中间纤维主要绕核分布并向四周发散, 微丝在胞质内形成应力纤维(stress fibers)、板状伪足和黏附斑, 微管由中心体发出分布于细胞质中(图1A和图2A)。通常中间纤维和微管在近核区域相互交叉缠绕, 其相互作用主要由分子马达kinesin、dynein[49-51]及交联蛋白plectin、APC、MAP2、tau[52-53]等介导(图2B), 而中间纤维在胞质外周区域能和微丝发生空间重叠, 其相互作用主要由分子马达myosin[49]及交联蛋白plectin、fimbrin、calponin[52]等介导(图2C)。早期对细胞骨架在空间层面的交互研究相对较少, 但近期越来越多的证据表明, 细胞骨架的直接相互作用可调控细胞的多种

功能, 包括形态、运动和机械感受力等[54]。

有研究证据表明, 三个细胞骨架体系不仅可直接地交叉连接、或在细胞空间内非特异地相互作用, 还可通过信号通路和基因表达调控间接相互作用[55-56]。在细胞内使用药物或基因编辑方法调控一个细胞骨架组分时, 通常会导致其他两个体系也相应发生变化, 如当微丝解聚时会导致中间纤维*keratin*的基因表达上调[55]。中间纤维和微丝通常被认为是细胞应力和张力的决定性因素[44,57], 它们对细胞应力的调控比重取决于胞外基质的硬度或施加机械压力的大小等条件[58], 其中中间纤维主要负责细胞质的应力, 而微丝则主要负责细胞质膜的应力[59]。近期的研究发现, 微丝和中间纤维能协同调控微管的力学属性, 中间纤维可嵌入微管使其机械应力显著提高[60], 微管同时也可加强微丝的机械应力[61]。研究发现, 中间纤维vimentin可通过plectin的介导与黏附因子互作, 进而调控微丝参与的黏附斑功能[30,50,62]。此外, vimentin还可通过对整合素和细丝蛋白(filamin)的回收来影响细胞与基质的特异连接[63]。因此, 不同的细胞骨架网络之间的相互渗透、特定的交叉连接等对细胞的整体动力学影响显著。

由肌动蛋白和肌球蛋白组成的微丝应力纤维被认为是调控细胞运动的主要结构[64], 然而基于一系列细胞骨架相互作用的研究, 人们发现微管和中间纤维对细胞运动也有重要调控功能[27,65-66]。细胞运动的初始条件是建立极性, 之前的研究主要将其归因于肌动蛋白和微管以及它们与细胞基质黏连的调控, 然而目前越来越多的证据表明中间纤维在其中也发挥重要作用。例如vimentin可通过磷酸化与外周的微丝网络相互作用进而调控细胞运动。破坏vimentin可导致由微丝组成的板状伪足的结构变化和细胞极性的缺失[67]。Vimentin的装配和空间结构与微管密切相关, 微管末端的APC(adenomatous polyposis coli)能直接结合vimentin并促进其沿微管的延伸[68], 同时, 微管对细胞极性的调控也离不开vimentin的参与[48,69]。中间纤维可以和微丝、微管同时互作, 微丝限制vimentin沿着微管的运输[70]。Keratin被报道与微丝相互作用[71], 通常其表达会抑制细胞运动[27], 同时最近也有研究发现, keratin可能通过plectin的交联影响微管的稳定[72]。

我们之前的研究发现, 除了通过黏附斑以外, 中间纤维还和微丝通过其他的方式相互作用进而协同调节细胞的形态和运动。具有收缩力的微丝结构actomyosin arc能特异地调节vimentin和nestin在细胞内的核周表达并促进其在胞内做向心运动, 这种动态相互作用对细胞发起运动的结构lamellum也有重要调控作用[73]。此外, vimentin的缺失引起鸟嘌呤核苷酸交换因子GEF-H1的磷酸化, 并激活下游小G蛋白RhoA, 进而促进微丝的组装[74]。

4 中间纤维参与的相关疾病发病机理

中间纤维保守的螺旋结构域和杆状结构域包含了一些与重大疾病相关的遗传性突变位点, 这些突变会直接破坏中间纤维的装配及其结构网络的稳定, 进而引发多种疾病。几乎所有的皮肤疾病都能够在相应细胞内发现中间纤维keratin的突变。有报道表明, 表皮细胞中keratin 14的单点突变和大疱表皮松懈症相关[75], keratin缺失的小鼠也出现同样的患病表型[76]。Hard keratins的突变会导致与头发或指甲相关的疾病, 如念珠状发、头发易断和指甲畸形等[77]。在小鼠中引入引发人类白内障相关的vimentin、phakinin和filensin的突变体同样会导致小鼠的眼球浑浊, 产生白内障[78]。而desmin的突变会导致骨骼肌虚弱、心律不齐和心力衰竭[79]。细胞质中突变的GFAP蛋白高度聚集能够导致所谓的亚历山大病[80]。Neurofilament突变与神经退行性疾病腓骨肌萎缩症相关, 并使个体的触觉受到影响。Lamin A的突变会导致核膜硬化, 病患出现早衰和心脏功能紊乱等症状[81]。另一方面, lamin B的突变会引起核膜硬度降低, 被认为是肌肉萎缩症的致病原因[82]。

中间纤维在肿瘤侵袭中也扮演着重要角色, 乳腺癌、甲状腺乳头状癌、食道癌、肺癌、肝癌、妇科肿瘤发生时, 都会伴随胞内vimentin的高表达[83]。有研究表明, bvimentin通过PI3K/Akt信号通路介导的磷酸化会保护其自身不被caspases水解, 进而导致肺癌肿瘤细胞的迁移能力增强[84]。此外, vimentin会激活β-Catenin途径下游的靶点蛋白Wnt的表达, 从而促进癌细胞的侵袭[85]。Twist1通过调节vimentin促进肝癌细胞的EMT[86]。很多癌基因可通过调控vimentin诱导细胞骨架的改变增强癌细胞的侵袭能力[74,87]。Nestin作为干细胞的生物标记常被用来识别肿瘤干细胞, 近期的研究表明, nestin能够调控乳腺癌细胞[88]和成神经管细胞瘤的入侵和转移[89]。

中间纤维也参与调控诸多自身免疫和炎症反应的过程。Vimentin经过肽基精氨酸脱亚胺酶(PAD)瓜氨酸化形成的cVimentin作为类风湿性关节炎的主要抗原之一, 与抗体形成抗原抗体复合体大量聚集在关节滑膜中, 刺激相关因子的释放促进关节损伤[90]。内皮细胞内, vimentin的α螺旋结构域能与链球菌的HSP70和SRRP1进行交叉反应, 激活促炎因子和生长因子, 造成异常免疫反应, 诱发急性风湿热[91]。中间纤维还具有细胞因子特性, 单核细胞趋化蛋白-1(MCP-1)能够促进单核细胞释放vimentin到胞外参与固有免疫应答[92]。此外, vimentin能够被人的巨噬细胞分泌到胞外, 而且这种分泌受促炎信号通道TNF-α的正向和IL-10的负向调节[91]。

细胞表面的vimentin在病原体入侵宿主细胞的过程中参与宿主细胞的防御。当病原体是细菌时, vimentin可与NOD2相互作用激活识别细菌肽聚糖片段的受体[93], 信号传递至核因子κB最终影响细菌的感染和存活, 同时vimentin也可以由大肠埃希菌毒力因子IbeA介导调控细菌感染的免疫应答[94]。不仅如此, 病原体感染的过程能够对中间纤维的结构产生显著影响, 并且激活促炎信号的转导[95]。当病原体是病毒时, vimentin在细胞表面可作为病毒入侵的附着点[96]。病毒感染引起宿主细胞中间纤维结构的重组不仅能促发炎症信号的转导, 而且重组的vimentin与病毒的相关组分在核周区域能形成聚集体结构从而加强病毒的复制[97]。在各种病毒的初始复制过程中, vimentin作为物理支架能够对病毒蛋白扩散到细胞质的过程产生明显抑制[98]。同时研究表明, SARS、冠状病毒、登革热病毒在其入侵时能够直接与中间纤维发生互作[99-100]。*Vimentin*的基因敲除会抑制HIV-1的感染, 同时细胞毒性也明显降低, 这提示vimentin可以作为抑制HIV-1感染的靶点[101], 进一步也提示中间纤维或许能够作为降低病毒易感性的有效靶标。

5 总结与展望

中间纤维家族由多种蛋白组成, 且为组织特异性表达, 其分子功能、调控的细胞行为和致病机制相对复杂。中间纤维除了结构支撑的功能外, 还主要作为信号枢纽参与调控诸多信号转导通路。细胞水平上, 中间纤维影响细胞的运动、增殖、分化和凋亡等过程; 个体水平上, 中间纤维参与癌症转移、炎症、创伤、病原体感染及自身免疫等病理过程。然而, 对其生物学功能的相关机制及其与人类疾病的关系还有很多问题有待深入研究。一方面, 利用新发展的基因编辑、组织工程和生物成像等前沿技术和方法, 科研人员正在开始对不同中间纤维蛋白的调控功能进行全面而深入的探究, 期望找到相关致病靶点和诊疗工具; 另一方面, 与国际上对中间纤维逐渐重视起来的趋势相比, 国内针对中间纤维的研究还需要组织化和系统化, 包括与其他细胞骨架体系的相互协同作用、对胞外基质的调控功能、参与伤口恢复和组织再生的过程等, 都需要研究者给与更多的关注。未来, 对中间纤维分子功能和致病机理的研究将对解决细胞生物学的基本科学问题, 并对多种相关疾病的临床诊断和治疗具有重要指导意义。

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