

转移消失蛋白研究进展

曹萌^{①②}, 叶子琦^③, 林绪波^①, 顾宁^{①*}

① 东南大学生物科学与医学工程学院, 南京 210096;

② 东南大学公共卫生学院, 南京 210096;

③ 温州大学生命与环境科学学院, 温州 325035

* 联系人, E-mail: guning@seu.edu.cn

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摘要 转移消失蛋白(missing in metastasis, MIM)是一种重要的胞内膜调控蛋白, 属于inverse BAR (I-BAR)家族成员, 能结合细胞膜并在细胞极化、运动和内存作用等过程中发挥调节功能, 其表达异常与多种疾病尤其是肿瘤发生或转移相关, 在神经系统、循环系统和生殖泌尿系统中也有一定作用. MIM蛋白的生物学功能包括调节肌动蛋白细胞骨架、与皮动蛋白等其他蛋白相互作用、参与细胞信号通路调控、改变细胞膜形态并促进细胞极化等, 在结构上表现出典型I-BAR家族成员特征, 借助其N端的I-BAR区域自聚合形成二聚体, 促使细胞膜形成伪足状突起, 甚至可以调控人造磷脂囊泡, 但二聚体的形成也可被靶向的多肽等抑制剂阻断. 除作用于蛋白I-BAR, RPTP结合域的特异性多肽外, MIM也可被RNAi干涉, 在肿瘤生物治疗领域具有开发潜力. 本文回顾了MIM蛋白相关医学研究进展, 综述了MIM蛋白已知的生物功能, 分析了MIM蛋白靶向治疗及其他应用前景, 并提出了可能的研究新方向、新思路.

关键词

转移消失蛋白
细胞膜
肿瘤
神经系统
B 细胞
肾脏功能
信号传导
靶向药物

细胞膜是细胞与外界环境之间重要的屏障, 也是细胞与周围物质交换、信号传导的重要平台. 细胞膜在二维上看, 是由流动的磷脂分子组成的双分子层面结构, 但是这种“二维平面”并非光滑平坦, 而是布满了包括突起、内陷、囊泡、褶皱、管道、多型性液泡、丝状伪足以及板状伪足等在内的各种精细结构. 这些功能各异的构造赋予了细胞膜发挥重要生理过程的能力, 同时将细胞质和细胞器保护在磷脂双分子层内, 并协同细胞骨架和胞内代谢变化实现细胞器生物合成、膜内运输、细胞分裂、细胞迁徙等过程. 膜变化也直接关系到细胞间相互作用的发生, 对发育、感染、合胞体形成和免疫响应等生物学过程也非常重要^[1,2]. 细胞膜变化大多是通过膜相关蛋白进行调控. 例如, 细胞内存作用就与网格蛋白(clathrin)、小窝蛋白(caveolin)、发动蛋白(dynamin)

等的功能密切相关^[3-5]. 大量研究已经证实, 此类蛋白对维持细胞正常生理过程至关重要, 因此细胞膜相关蛋白是医学领域长期以来的研究热点. 而Bin-Amphiphysin-Rvs (BAR)家族蛋白也是膜调控蛋白中重要的一类^[6-9].

BAR家族蛋白具有相似的膜结合结构域, 也称BAR结构域, 会以自发形成的反向平行的二聚体形式结合细胞内膜, 利用自身独特的曲率使膜产生形态变化^[10-13]. 许多证据表明, BAR家族蛋白在疾病发生过程中可能起到了关键的作用^[14], 因此相关的医学研究近期颇受关注. 目前已经发现许多蛋白带有BAR结构域, 这些蛋白根据结构特征不同又分为若干子家族, 包括N-BAR (N-terminal amphipathic helix-BAR), BAR-PH (BAR-pleckstrin homology), PX-BAR (PhoX-BAR), F-BAR (Fes/CIP4 homology BAR)以及

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I-BAR (inverse BAR)等^[1]. 大多数的BAR结构域能够使细胞膜产生凹陷结构, 但I-BAR子家族的蛋白却表现出不同的特性, 倾向于诱导细胞膜产生向外凸起的结构^[15]. 哺乳动物I-BAR子家族蛋白包括胰岛素受体底物p53蛋白(IRS p53或BAIAP2), BAIAP2同源性肌动蛋白结合蛋白(ABBA或Mtss1L), 胰岛素受体酪氨酸激酶底物(IRTks或BAIAP2L1), 平面型肠道和肾特异性BAR蛋白(PINKBAR), FLJ22582蛋白(BAIAP2L2)和转移消失蛋白(MIM或Mtss1)^[6,8,9]. 其中, 转移消失蛋白MIM因其在肿瘤组织当中的异常表达而尤其受到关注^[16-22].

近年来, 针对MIM蛋白的研究在逐步深入, 相关的报道也越来越多, 但是在MIM蛋白部分生物功能和临床表现得到揭示的同时, 还存在较多的问题未能阐明; MIM蛋白在肿瘤等疾病诊断预后、血液系统病变以及在体外磷脂膜生物材料结合应用等方面开发潜力巨大, 但相关工作目前才刚刚起步. 因此, 转移消失蛋白在生物医学领域具有较广阔的研究前景.

1 转移消失蛋白的构成及其功能

MIM蛋白的结构模式如图1所示. 蛋白的功能基本来自于其各个结构域, 主要包括I-BAR, SRD, PRD, WH2等. 我们将MIM蛋白功能主要归纳为个方面, 下面逐一作简要介绍.

1.1 MIM蛋白是重要的细胞骨架调控蛋白

MIM在体内和体外研究中表现出典型的I-BAR蛋白的特性, 其功能的发挥主要与该蛋白对细胞骨架的直接/间接调控密切相关. MIM蛋白能够通过I-BAR区结合小GTP酶Rac, 且其激活Rac的效率要比

同源蛋白胰岛素受体底物p53高得多^[23,24], 并通过I-BAR区影响小GTP酶Rac1从而促进细胞-细胞间的连接^[25]. MIM-I-BAR在小脑浦肯野细胞内可与脚手架蛋白NEDD9相互作用^[26]. MIM还能通过偶联和调控微丝相关蛋白, 诱导细胞膜发生形态变化. MIM包含一个富丝氨酸结构域SRD, 一个富脯氨酸结构域PRD和一个位于C末端的Wiskott-Aldrich syndrome homology region 2基序(WH2)^[27,28], 这些也与其他I-BAR蛋白有所不同, 其详细的生化功能目前尚未阐明, 但这些功能结构分别与肌动蛋白单体^[29]、皮动蛋白^[28]以及松散蛋白相关形态发生激活因子Daam1等^[30]胞内蛋白有相互作用. 而众所周知, 这些蛋白恰恰是细胞骨架驱动细胞膜动态变化的主要力量——皮质微丝的重要组成部分^[31]. MIM能够通过脯氨酸富集区附近的404~705氨基酸残基结合细胞膜酪氨酸磷酸酶RPTP^[27]. MIM介导的细胞骨架调控也有PTP δ 蛋白参与, 且MIM协助RPTP δ 细胞膜的重定位不受后者磷酸化活性影响^[32]. MIM蛋白WH2对ATP的亲能力是ADP-G-actin的5倍, 与actin-ciboulot复合物类似的MIM/ATP-G-actin的复合物可以在actin聚合物快速生长末端聚集. 同时, MIM对actin亲和能力高于其他actin单体配合蛋白, 暗示活性MIM蛋白能够结合ATP-G-actin^[29]. 对MIM-WH2与G-actin和DNase-I复合物的晶体结构解析表明, 其作用序列与thymosin β 4/WASP相互作用蛋白、WIP/WH2基序与actin的复合物相似^[33]. 在细胞骨架调控蛋白中, MIM是十分重要和关键的, 可随细胞环境变化而做出调整. 近期即有研究发现, 在低重力环境下甲状腺滤泡癌细胞会下调MIM表达, 推测其原因就是人类的细胞能通过调控蛋白表达而稳定自身的细胞骨架以适应低重力条件^[34].

1.2 MIM参与多种信号通路调控

MIM蛋白对多种类型细胞信号传导有响应, 并有可能参与其中的调控. GFP标记的MIM重组蛋白在血小板源生长因子PDGF的刺激下发生细胞内重定位, 并在特定赖氨酸位点出现Src介导的磷酸化^[35]. MIM还是首个被筛选出的Sonic hedgehog (Shh)响应基因, 在多种Shh通路激活的细胞中能检测到MIM的mRNA的编码, 而且MIM可能通过独特的细胞生物学机制促进了Shh靶基因*Gli*的转录^[36]. 使用抗体对*ptch1*^{-/-}成纤维细胞染色发现, MIM主要累积在细胞

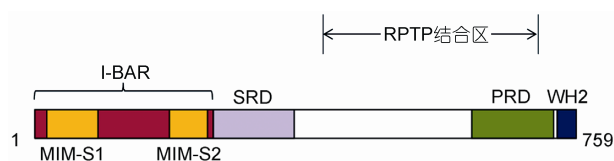


图1 (网络版彩色)MIM蛋白结构模式图. I-BAR, 反向Bin-Amphiphysin-Rvs; MIM-S1和MIM-S2, 二聚体相互作用界面位置; SRD, 富丝氨酸结构域; PRD, 富脯氨酸结构域; WH2, Wiskott-Aldrich综合征同源基序-2; RPTP, 受体蛋白酪氨酸磷酸酶

Figure 1 Demonstration of the MIM protein structure. I-BAR, reverse Bin-Amphiphysin-Rvs; MIM-S1 and MIM-S2, interface area of the dimer; SRD, serine-rich domain; PRD, proline-rich domain; WH2, Wiskott-Aldrich syndrome homology region-2; RPTP, receptor protein tyrosine phosphatase

质和细胞膜应力纤维和肌动蛋白相关的结构附近^[32]. MIM还是参与细胞膜初级纤毛维持和Shh信号的基体复合体的一部分,对皮肤突起和毛囊再生等过程发挥重要作用^[37].最近一项研究发现,在中心体上MIM可与aPKC- ι/λ 及其信号伙伴蛋白形成复合物,参与癌基因Gli的磷酸化和激活过程^[38].在神经管闭锁过程中,MIM蛋白可在非经典Wnt信号通路刺激下强化与Daam1蛋白的结合,并对非经典Wnt信号通路起到协同作用^[30].在B淋巴细胞脾脏分化调控过程中,MIM蛋白对B细胞在主要趋化因子CXCL13作用下的迁移响应能力至关重要,并参与和促进趋化因子信号通路受体CXCR5的内化^[39].虽然MIM是多种细胞信号通路的参与者和调节者,但是否具有独立的“MIM信号通路”目前还未见报道,需要对MIM蛋白的分子生物学、细胞生物学和生物化学进一步研究,以深入认识MIM蛋白参与的复杂生理功能,理解和指导相关疾病的治疗.

1.3 MIM蛋白塑造磷脂膜需依赖I-BAR结构域

MIM蛋白利用自身I-BAR区两两结合所形成的同二聚体结构(图2),对MIM与细胞膜的结合和调控至关重要^[28,29].这种调控不仅限于细胞内表达的蛋白调控细胞质膜,在体外制备的单纯磷脂双分子膜结构也可与MIM I-BAR结合并发生形变.纯化后的MIM I-BAR蛋白能在水溶液中亲和磷脂酰肌醇PI(4,5)P₂富集的人造双层磷脂膜并诱导膜结构产生管道样的结构^[40].同样,其他BAR家族蛋白也有相类似的膜亲和特性^[8,41~44].这些研究都表明,MIM蛋白的I-BAR结构域很可能在生物膜研究和应用领域具有潜力.此外,在计算机模拟BAR家族蛋白与细胞膜相互作用^[45~47]、蛋白寡聚化^[48,49]以及蛋白引起细胞膜形态和力学性质变化作用^[50~53]等的理论计算领域,也已有很多工作相继报道,这些研究结果同样对我们更深入地认识细胞膜调控过程中的生物物理机制有重要推动作用.但是目前尚缺乏通过模拟计算探讨MIM蛋白的自身性质和磷脂膜调控过程相关的报道.在这一领域,本课题组已着手研究并已取得一些进展,正在逐步深入推进.

2 MIM生理功能及其在肿瘤发生和迁移中的作用

生物体内在很多种类的细胞中能检测到MIM表

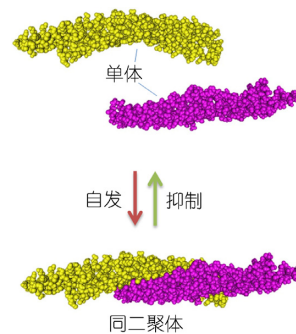


图2 (网络版彩色)MIM蛋白I-BAR结构域同二聚体
Figure 2 MIM protein I-BAR domain dimer formation

达,并且其表达程度具有组织特异性.在发育中小鼠的心脏、骨骼肌、中枢神经系统,成年小鼠的肝脏以及脑和肾的中心区域检测到了MIM蛋白的高表达^[29].在对人血细胞生物芯片分析中发现,MIM是血细胞中唯一高表达的I-BAR家族蛋白,人类的初B细胞MIM表达最高,其次是单核细胞,T细胞和粒细胞中也有一定的表达^[39].MIM的表达受到包括基因甲基化水平等因素的调控^[54].MIM作为人类疾病相关基因,最早在肿瘤侵袭转移研究中发现^[55],目前科研人员针对MIM开展的有关研究也较多集中在肿瘤病理、诊断和治疗方面.近年来,在神经系统、循环系统和泌尿系统中,MIM的异常和有关病变也在逐渐受到关注.一方面对MIM深入探索还有待于进一步加强;另一方面也说明MIM基因/蛋白在医学研究领域的价值是较为重要的.

2.1 MIM下调与转移抑制

转移侵袭性是恶性肿瘤最显著的特征之一,是导致癌症患者死亡的最主要原因,占恶性肿瘤致死病例的绝大多数^[56].目前研究较为深入的“转移抑制基因”包括*nm23*^[57],*DCC*^[58,59],*p16*^[60],*p53*^[61],*KAI1*^[62],*KISS1*^[62],*MKK4*^[63]以及*BrMSI*^[64,65]等,这些基因功能各异,被认为具有抑制特定肿瘤转移的作用.由于肿瘤遗传复杂性以及患者的个体差异性,全面而明确地阐释肿瘤转移侵袭性的病理和分子机制难度极大,从潜在“转移抑制基因”为切入点进行研究,是目前根据病理机制而开发针对性治疗方法的较为可行的途径.转移抑制蛋白编码基因MIM也被认为是潜在的转移抑制基因之一.MIM得到关注之初即是由于其在某些人源高转移性膀胱癌细胞系中出现缺失.2002年, Lee等人^[55]用mRNA荧光标记差异显示技术对5组人源膀胱癌细胞系进行了分析,以发现和研究基因

表达方面的异常。这5组膀胱癌细胞的恶性情况从低等级到高转移性不等。研究分离出一条316 bp的cDNA (C11-300), 与KIAA 0429完全一致, 具有5.3 kb的转录序列, 位于人类基因座8q24.1, 在转移细胞系TccSuP中不表达。预测的蛋白表达产物含356个氨基酸, 并带WH2结构域, 可结合actin蛋白。Northern blot结果表明, 相比正常组织, 该基因在包括乳腺癌细胞系(SKBR3)以及转移性前列腺癌细胞系(LNCaP, PC3)等转移性细胞中表达缺失, 因此将此基因命名为Missing in Metastasis (MIM)。同时根据研究数据推测, 该基因与细胞骨架的调控有密切关系。

MIM异常与肿瘤的关系一直备受关注。除了高转移性膀胱癌^[66,67], 在其他一些肿瘤细胞中也发现了MIM蛋白表达下调, 包括肺癌^[68~71]、乳腺癌^[72,73]、胃癌^[74~76]、食管鳞癌^[77,78]、肝细胞性肝癌^[79]、肝门部胆管癌^[80]、前列腺癌^[73,81,82]、结直肠癌^[83~87]等, 肿瘤转移或预后不良可能与低水平MIM相关。在这些领域, MIM或有希望被开发成为今后肿瘤临床诊断和治疗新的指标或依据。

肿瘤细胞编码的一些miRNA可通过沉默抑癌基因等方式, 参与肿瘤发生发展^[88]。近期对一些肿瘤相关miRNA的研究表明, MIM也是部分miRNA的靶基因, 其表达下调可能与这些肿瘤miRNA有关, 包括miR-23a^[89~91], miR-135a^[92,93], miR-135b^[94]以及miR-182^[95~97]等。目前, 靶向MIM的miRNA正在受到越来越多关注, 相关研究的深入将有助于解释MIM的确切生理病理作用以及不同肿瘤组织之间迥异的表达调控。

其实MIM的转移抑制能力目前还尚有争论。如一项针对膀胱癌的研究^[98]与Lee等人^[55]的最初结论有所不同, 这一研究发现不论在体内或体外实验中, MIM表达情况经统计与肿瘤侵袭行为之间其实并无联系。此外, MIM表达可能具有一定广泛性, 例如有很多转移性细胞系其实保留了MIM的表达^[23]。因此该蛋白是否具有普遍意义上的肿瘤转移抑制作用, 尚有待商榷。

2.2 MIM上调与肿瘤发生和恶化

与前述的一些恶性肿瘤出现MIM表达的缺失或下调的情况相反, 部分肿瘤会出现MIM表达增高的情况。在MIM最初受到关注时, 即有研究发现该蛋白在人类基底细胞癌的肿瘤上皮组织中富集, 响应Hedgehog信号通路, 并促进癌基因*Gli*等的功能^[32,36]。针对大肠恶性组织的研究数据表明, 肿瘤预后不良

可能与MIM过表达有关, 肿瘤组织相对于正常组织的MIM表达明显提高, 且MIM表达程度高与肿瘤低分化、组织侵袭和较高术前癌胚抗原水平相关^[99,100], 但对于结直肠癌MIM水平与转移的具体关系, 还有待于进一步揭示^[101]。此外, 一项针对60例乳腺癌及癌旁组织的研究指出, 对于这些患者MIM过表达可导致淋巴结转移、肿物增大和病程恶化^[102]。MIM蛋白还可能与乳腺癌等肿瘤的化疗敏感性有关^[103,104]。近期, 一项针对黑素瘤的研究发现, 在某些肿瘤子群中MIM的高表达将导致肿瘤转移和不良预后, 而如对这些细胞中的MIM表达进行抑制则可降低肿瘤侵袭能力^[105]。Ji等人^[106]通过对结肠癌、神经外胚层细胞染色体研究发现, MIM有可能通过增多的双微体的负载而在细胞中富集, 造成肿瘤增殖和侵袭。Chen等人^[107]发现, 在结肠癌肝脏转移的肿瘤细胞中, MIM表达是上调的, 很可能与侵袭能力相关。对一些肝细胞性肝癌患者的肿瘤组织和临近组织研究表明, MIM基因高表达可能在早期癌变过程中发挥重要作用, 但与肿瘤的侵袭和转移关系不大^[108]。在头颈部鳞状细胞癌中, MIM似乎在不同的肿瘤部位或生长阶段发挥不同的作用, 即在肿瘤早期阶段通过调节生长因子信号通路促进细胞增殖, 而在细胞较为致密时则对生长不再有利, 可能在一定程度上暗示了MIM蛋白在不同的肿瘤中表达调控也不尽相同现象中的内在机制^[109]。以现有的研究至少可以推断, MIM蛋白在人类疾病中扮演的角色是复杂的, 其下调或上调均可能涉及一系列的生物学过程。

2.3 神经系统方面

脑部是MIM蛋白高表达的区域之一^[29]。MIM表达和剪接在鼠小脑发育时出现复杂和变化的调节过程^[110]。MIM在小脑浦肯野细胞中的表达可能受En-2蛋白的调控^[111]。中枢神经系统中的MIM在小脑皮质分裂期后神经元中表达, 其中在浦肯野细胞突触体腔分布高于树突腔, 而且有可能起到调控神经细胞膜形态的作用^[112]。MIM在脊椎动物神经管闭锁过程中发挥重要作用, 参与神经褶抬升和顶端收缩, 促进前神经板细胞的极化和伸长^[30]。利用GST-pulldown后凝胶分离并质谱分析发现, 神经发育和分化相关蛋白NEDD9与MIM I-BAR相互作用于小脑的浦肯野细胞^[26]。以MIM兔多克隆抗体用研究小脑中不同MIM亚型磷酸化水平, 发现成年和发育期大鼠小脑

MIM酪氨酸磷酸化明显,且磷酸化酪氨酸残基可能不仅局限于Src磷酸化位点^[113].此外有研究发现,去神经支配后大鼠海马细胞内MIM的表达上调,并据这一现象推测MIM可能与神经干细胞参与的神经再生有关^[114].大鼠神经发育研究显示,在轴突和树突形态建成过程中,小脑颗粒神经元和浦肯野细胞的MIM蛋白表达显著上调^[115].以上研究表明,MIM可能在神经系统发育和完善过程中发挥作用,其具体功能和机制还有待进一步研究.

2.4 循环系统方面

MIM基因敲除的小鼠脾脏发育偏大,并且1~2龄鼠的弥漫性大B细胞淋巴瘤样疾病发病率高达78%.进一步研究发现,虽然正常的B细胞相对于其他血液免疫细胞有很高的MIM蛋白表达,但所检测的B细胞恶性肿瘤组织中MIM却出现低表达或不表达现象^[39].由于MIM与血液细胞异常尤其是淋巴瘤发生密切相关,并且在肾脏对血液的过滤功能中发挥重要作用,因此在循环系统对MIM蛋白进行深入研究将是很有意义的.对基因敲除小鼠的研究揭示了MIM蛋白在血细胞相关病理过程中的一些作用,进一步阐明MIM蛋白在B细胞淋巴瘤中的具体机制,将有利于开发新的、更可靠的临床诊断方案.

2.5 生殖和泌尿系统方面

一项有关生殖的研究发现,在注射促性腺激素后,牛排卵期前卵泡中的MIM表达升高近2.5倍,但注射吲哚美辛抑制卵泡内前列腺素类合成对MIM表达影响不明显,推测上述现象可能与激素调控Hedgehog信号通路有关,但MIM在排卵前表达调控的具体意义尚不十分明确^[116].在泌尿系统方面,针对模式动物的研究显示MIM敲除虽不显著影响胚胎整体发育,但是敲除的小鼠肾脏会因肾上皮细胞间连接受损而导致严重的尿浓缩功能缺陷,继而造成骨骼畸形和终末期肾功能衰竭,表明MIM在维持肾上皮细胞间相互作用方面发挥了积极作用^[117].

3 MIM医药领域开发及前景

3.1 靶向多肽序列可抑制MIM与RPTP相互作用

MIM蛋白第404~705号氨基酸可与膜受体蛋白酪氨酸激酶RPTP δ 相结合,并可能在细胞极化和actin组

装方面协同作用^[127].Gonzalez-Quevedo等人^[32]根据RPTP δ 的MIM作用域设计制备了相应的多肽,成功地阻断MIM蛋白与RPTP δ 的相互作用的同时,发现RPTP δ 影响MIM介导的细胞骨架重构;还发现MIM对RPTP δ 在胞质膜特殊区域的定位起调控作用,该过程并不影响其磷酸酶活性.受体蛋白酪氨酸激酶RPTP与细胞运动和actin细胞骨架相关,同时也是调控细胞外基质结合和细胞间相互作用的重要蛋白,因此其自身也是重要的分子治疗靶点^[118].该多肽抑制剂除了有助于研究MIM蛋白与RPTP的相互作用、探讨生物学机制外,还有望推动针对与RPTP异常有关疾病,如肿瘤、糖尿病、自体免疫疾病和神经系统疾病等患者的新治疗手段开发.

3.2 靶向MIM I-BAR功能的相关研究

以二聚体形式存在的I-BAR结构域是MIM蛋白的核心构造,MIM蛋白的生物学功能大多与I-BAR有关.为深入了解MIM蛋白二聚体发挥生物活性的内在机制,本课题组也在进行一些具有针对性的研究^[119].我们先前根据MIM蛋白I-BAR区二聚体的结构特点,设计制备了一系列多肽作为靶向抑制剂对MIM I-BAR的二聚化过程进行干扰.通过表征发现一些氨基酸序列可以有效地结合MIM I-BAR单体并抑制MIM二聚化,且活性多肽经简化后仅33个氨基酸,容易直接合成.借助抑制剂多肽对MIM蛋白二聚化功能的分子机制进行研究,我们发现抑制二聚化作用能够减弱MIM介导的细胞膜变化,并降低MIM引起的内吞作用增加,同时不影响MIM蛋白与皮动蛋白或肌动蛋白间的相互作用.在介导膜褶皱形成的过程中,I-BAR与其他结构域协同影响actin纤维丝的组装,其功能可能涉及多种不同信号通路.研究还表明,MIM双分子二聚体是该蛋白调控膜形态的结构基础,而且膜调控过程并不依赖于MIM蛋白对肌动蛋白细胞骨架的调节,因此我们认为二聚化的MIM I-BAR作用更多地体现为功能性而非调节性.重要的是,我们发现的MIM蛋白抑制剂^[119]实际上提供了一种实用的研究工具,甚至可能成为新型治疗手段的先导.目前我们在上述多肽优化、生物材料修饰以及小分子药物开发方面也已取得进展.

3.3 针对MIM的RNAi相关研究

RNAi是抑制靶基因表达的有效手段,在MIM研

究方面也有开发和应用的相关报道。毛亚江等人^[120]即通过分子克隆设计制备了一组MIM基因的shRNA序列,并成功构建了相应的慢病毒载体,可用于MIM基因表达抑制。张曙光等人^[78]借助siRNA敲降食管鳞癌MIM表达发现MIM可抑制肿瘤细胞迁徙和侵袭。Mertz等人^[105]利用si-MTSS1(MIM特异性siRNA)抑制高侵袭性A375黑素瘤细胞,成功降低了侵袭细胞的数量,这一新的发现将有望指导开发针对MIM功能的早期、精确且病理针对性强的治疗手段。由此可见,MIM作为潜在的靶点蛋白,其医药开发前景还是较为广阔的。

4 展望

转移消失蛋白作为重要的细胞膜调控蛋白之一受到了越来越多的关注,围绕其进行深入的研究是有广泛意义和非常必要的,有助于更详细地理解细

胞行为,探讨有关疾病的致病机理。在肿瘤诊断、恶性程度判断和肿瘤预后领域,MIM蛋白也有可能会出现更多的应用。但是,在不同器官不同细胞的表达差异,暗示可能还有更多的MIM生物学作用或MIM异常造成的病理机制有待阐明。在血细胞中,MIM的重要性已得到充分证实,但MIM蛋白在血细胞分化过程中的角色、对血液运输能力的作用以及在血液肿瘤治疗方面的价值还有待于进一步的开发,而本课题组近期的研究已在血细胞MIM蛋白领域取得一些结果。此外,体外纯化的MIM I-BAR蛋白对磷脂膜的独特作用也有重要的应用前景,这一方面我们正在进行探讨,希望会有有意义的发现。另外随着本课题组对MIM I-BAR抑制剂研究的不断研究,新型的MIM蛋白靶向药物也在陆续得到开发,相信这些成果可以作为科学研究和医学实践的重要工具,对MIM蛋白相关疾病机制研究和探索新型的治疗方法起到推动作用。

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Advances in missing-in-metastasis research

CAO Meng^{1,2}, YE ZiQi^{1,3}, LIN XuBo¹ & GU Ning¹

¹ School of Biological Science and Medical Engineering, Southeast University, Nanjing 210096, China;

² School of Public Health, Southeast University, Nanjing 210096, China;

³ College of Life and Environmental Science, Wenzhou University, Wenzhou 325035, China

Missing-in-metastasis (MIM, also known as metastasis suppressor 1) belongs to the inverse BAR (I-BAR) family of intracellular membrane remodeling proteins. Structurally, MIM displays typical I-BAR family protein features including the ability to dimerize through its N-terminal I-BAR domain, which can be arrested by specific peptide inhibitors. It also induces filopodia-like membrane protrusions, and can reform artificial phospholipid vesicles. MIM binds to the inner plasma membrane and participates in multiple cellular activities including cell polarization, mobility, actin cytoskeleton regulation, protein interaction, cellular signal pathway facilitation, membrane shaping, and endocytosis. These activities are mostly performed in the nervous, circulatory, urinary, and reproductive systems. MIM abnormalities occur in a number of human diseases, especially those involving tumor genesis and metastasis. As well as MIM-specific peptides, RNA interference can be used to inhibit MIM expression. These molecular tools have the potential to be used in future bio-pharmaceutical developments. In this review, advances in MIM-related research are summarized, and the prospect of MIM targeting therapy and other MIM-based applications are introduced.

missing-in-metastasis, plasma membrane, neoplasm, nervous system, B cells, renal function, signaling pathway, targeting drugs

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