促凋亡蛋白 Bim 在肿瘤治疗中的研究进展

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摘　要：Bim(Bcl-2 interacting mediator of cell death)是 Bcl-2 家族中 BH3-only 亚家族的成员，是一种重要的凋亡调节蛋白，在维持内环境稳定中有着重要的作用。Bim 蛋白低表达与人类多种肿瘤的发生、发展和预后相关，为基因治疗提供新靶点。另外，Bim 在肿瘤的化疗及靶向治疗中也起到十分重要的作用。
主题词：肿瘤；Bim；凋亡；靶向治疗
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Research Progress on Pro-apoptotic Protein Bim in Tumor Therapy

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Abstract：The pro-apoptotic protein Bim (Bcl-2 interacting mediator of cell death) is a member of BH3-only subfamily in BCL-2 family. Bim works in concert with other pro-apoptotic proteins and anti-apoptotic proteins to regulate cell death and survival which is essential for normal tissue homeostasis. Reduced Bim expression is associated with the occurrence，development and prognosis of many human tumors，suggesting that it provides a new target for gene therapy. In addition，Bim plays an important role in tumor chemotherapy and targeted therapy. In this article we review the recent progress on Bim protein in cancer therapy and its perspective.
Subject words：tumor; Bim; apoptosis; targeted therapy

凋亡是哺乳动物普遍存在的一种病理过程，既存在于生理状态下，也可发生在病理状态下，是一种程序性细胞死亡[1]。凋亡过程失控可导致许多疾病发生，如肿瘤、自身免疫性疾病、退行性疾病及细胞老化等疾病[2-4]。细胞凋亡缺陷，可导致癌细胞具有内在的生存优势，同时也赋予癌细胞对化疗药物固有的抗性。

Bcl-2 蛋白家族的抗凋亡及促凋亡成员之间的平衡可以调节细胞凋亡，根据其在凋亡中所起的不同功能及所含结构域的区别，Bcl-2 家族成员可分为三大类：多域抗凋亡成员（例如 Bcl-2、MCL-1、Bcl-XL）时，多域促凋亡成员（例如 BAX、BAK）和仅含有 BH3 区域的的促凋亡成员（例如 BAD、BID、Bim、PUMA）[5,6]。Bim 是仅含有 BH3 区域的促凋亡成员之一，与 Bcl-2 家族中的促凋亡成员高亲和力结合，发挥其促凋亡作用[7]。

1　Bim 在维持正常组织稳态中的作用

Bouillet 等研究发现 Bim 在造血细胞的稳态维持中发挥重要作用。在各种信号诱导的淋巴细胞死亡的过程中，Bim 是非常重要的效应器。在敲除 Bim 基因的小鼠中，由于多余的淋巴及髓细胞积聚而出现淋巴结及脾肿大[8,9]。在自身反应性 T 细胞及 B 细胞的清除、生发中心的记忆性 B 细胞及抗体形成细胞的死亡、初始及记忆性 T 细胞稳态的调节及免疫应答

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适当终止等过程中,Bim 都是必不可少的因子[10-14]。

仅含有 BH-3 区域的的促凋亡成员主要有 Bim、BID 及 PUMA 等，可以直接激活 BAX、BAK 等促凋亡蛋白,同时也受到抗凋亡蛋白的抑制。研究发现,大多数 BH-3 域结构松散，但可以 α 螺旋方式与 BAX 结构域结合,诱导 BAX 构象发生改变,快速引起其寡聚化,导致其活化,促进线粒体途径凋亡的产生[15]。

2 Bim 对肿瘤的抑制作用

Bim 与肿瘤的发生密切相关。Egle 等通过对 Eμ-Myc 转基因小鼠的研究发现,Bim 表达不足可加速 Myc 诱导小鼠 B 细胞性白血病的发生，与 Bcl-2 转基因小鼠相比较,主要使 IgM 阳性的成熟 B 细胞发生恶性转化[16]。在肾细胞癌中患者中检测出 Bim mRNA 和蛋白质的表达缺失。研究报道,在 43 例肾细胞癌患者中有 35 例 Bim 低表达(81%),而正常肾小管组织中 Bim 均高表达;在 9 种肾细胞癌细胞系中,其中有 6 种细胞系为 Bim 阴性或低表达[17]。Dai 等[18]在皮肤恶性黑色素瘤中应用组织芯片及免疫组化技术发现,在转移性黑色素瘤组(52 例)与发育异常的痣(52 例)相比,Bim 表达明显降低(P<0.001),转移性黑色素瘤组与原发黑色素瘤未转移组(159 例)相比也明显低表达(P<0.001);在 159 例原发性黑色素瘤中发现,Bim 表达与患者年龄、性别、肿瘤大小、肿瘤部位及有无溃疡形成无相关性；生存分析发现患者 Bim 表达与 5 年生存率相关,Bim 表达阴性、弱阳性、阳性及强阳性的患者 5 年生存率分别为 39%、66%、78%和 81%，证明 Bim 低表达与恶性黑色素瘤的进展以及较差的 5 年存活率及总生存期相关。Yuan 等[19]在结肠癌组织标本中行免疫组化染色研究发现,Bim 在结肠癌组织中阳性率为 62.7%,明显低于正常肠黏膜组织表达阳性率(90.0%),Bim 表达与肿瘤的分化、淋巴结转移、TNM 分期及 P-gp 表达相关(P<0.05),而且 Bim 低表达与肿瘤的晚分期及不良预后相关。Sinicrope 等[20]对 431 例结肠癌患者进行免疫组化染色评分,Bim 高表达组与低表达组相比明显有更好的无病生存期(disease-free survival,DFS)及 OS (5 年 DFS:64.5% *vs* 53%,P=0.0225; OS:71.5% *vs* 66.7%, P=0.0334),Cox 回归分析显示 Bim 是 DFS 与 OS 独立的影响因素。因此,Bim 低表达可能在这些肿瘤的发病机制中发挥着一定的作用。

一些微小 RNA 也是通过影响 Bim 表达来调控肿瘤的发生及发展。研究证实,miR-17-92 可抑制促凋亡蛋白 Bim 及肿瘤抑制基因 PTEN 的表达[21, 22]。其他的研究发现,miR-106b-25 也可通过抑制 Bim 表达在食管癌发生中发挥重要作用[23]。

3 Bim 作为肿瘤治疗的靶点

在对不同癌症治疗的反应中，尤其在靶向治疗中,Bim 发挥着关键作用。在靶向治疗中,许多药物阻断肿瘤主要的生存信号途径，最终发挥作用于促凋亡蛋白和抗凋亡蛋白的水平。Bim 在传递死亡信号中发挥着重要的作用,促进细胞 DNA 损伤。大量证据表明,通过对 Bim 基因的干预导致其蛋白表达上调,可更有效地导致肿瘤细胞凋亡率的增加。

3.1 组蛋白脱乙酰酶抑制剂

在肿瘤细胞中,组蛋白脱乙酰酶抑制剂(histone deacetylase inhibitor,HDACI)可通过 E2F1 依赖机制导致 Bim 表达上调[24]。在小儿白血病患者中,组蛋白脱乙酰酶抑制剂可以逆转 Bim 低表达,从而恢复糖皮质激素治疗的敏感性 [25]。在人白血病细胞中,HDACI 可显著性增强 BH3 类似物 ABT-737 的抗肿瘤作用，这种效应与其诱导 Bim 表达上调相关[26]。此外,Gilardini 等[27]在胰腺癌的研究中发现,组蛋白脱乙酰酶抑制剂 Trichostatin A (TSA) 及 Valproic Acid (VPA)可导致胰腺癌细胞系中 Bim 表达水平上调,同时 Mcl-1 表达水平降低,进而导致细胞色素 C 释放及 Caspase 3 的激活,诱导细胞发生凋亡。在对激素耐受性前列腺癌的研究中，组蛋白脱乙酰酶抑制剂 PXD101 与多西他赛联合应用可显著性减少 Mcl-1 及 Bcl-xl 的表达，同时增加 Bid、Bik 及 Bim 表达,促进肿瘤细胞及凋亡动物移植瘤体积缩小[28]。这些研究结果证明 HDACI 通过影响 Bim 的表达达到其抗肿瘤效应。

3.2 蛋白酶体抑制剂

蛋白酶体在细胞内稳态中起关键作用。蛋白酶体抑制剂,如硼酸硼替佐米(Velcade)或不可逆的蛋白酶体抑制剂 Carfilzomib(PR-171)等,可选择性作用于蛋白酶体,引起蛋白质积累,从而导致蛋白毒性应激。基础研究表明蛋白酶体抑制剂可选择性作用

于恶性转化的细胞，调控多种凋亡相关蛋白的表达，如 Bim 及 MCL-1 等，导致 Bim 蛋白在恶性转化细胞中的积累，诱导细胞发生凋亡[29]。研究发现，组蛋白脱乙酰酶抑制剂与蛋白酶体抑制剂联合应用可引发滑膜肉瘤细胞过度内质网应激，导致促凋亡相关蛋白 Bim、BIK 激活，同时抗凋亡蛋白 Bcl-2 磷酸化失活，诱发细胞凋亡，抑制小鼠滑膜肉瘤移植瘤的生长[30]。此外，在肝癌及结肠癌等多种肿瘤中，蛋白酶体抑制剂也可以通过上调 Bim 蛋白表达促进细胞凋亡，发挥抗肿瘤作用[31,32]。因此蛋白酶体抑制剂的抗肿瘤治疗效果与 Bim 蛋白表达状态相关。

3.3 MEK1/2 抑制剂

Ras/Raf/MEK/ERK 途径的异常激活是癌症中最常见的机制之一，已成为药物干预的主要靶点。选择性作用于此通路的药物很多，如法尼基转移酶抑制剂、HMG-CoA 还原酶抑制剂（他汀类）、Raf 抑制剂和 MEK1/2 抑制剂[33-37]。MEK1/2 抑制剂阻止 ERK1/2 的磷酸化，可作用于许多下游靶点，包括细胞周期蛋白 D1(cyclin D1)，β-连环蛋白(β-catenin)和 Ets 转录因子(Ets transcription factors)等，在许多肿瘤如黑色素瘤、结肠癌、肺癌及卵巢癌等肿瘤中发挥抗肿瘤作用[38-41]。Ras/Raf/MEK/ERK 通路在调节 Bim 表达及功能中也起到关键的作用，ERK1/2 可诱导 Bim 蛋白的磷酸化导致其在蛋白酶体降解，因此阻断该过程则导致 Bim 积累，引起细胞凋亡增多[42]。除了直接调节 Bim 蛋白的丰度外，抑制 MEK1/2 也可以影响 Bim 和其他 Bcl-2 家族成员之间的相互作用而导致细胞凋亡变化[43]。

3.4 BH3-类拟物 BH3-Mimetics

目前已经研发出多种 BH3 类似物（例如 ABT-737、Obatoclax、ABT-199、ch282-5 及 AT-101），这些类似物可以不同程度干扰多结构域抗细胞凋亡分子的功能，如 Bcl-2，Bcl-XL 和 MCL-1 等[44,45]。但是，在对慢性淋巴细胞白血病细胞的药物实验中发现，MCL-1 蛋白水平的高低不是决定 ABT-737 药物活性的惟一因素，Bim 表达在 ABT-737 引起细胞死亡的过程中也发挥着关键作用[46]。此外，在存在 B-RAF 基因突变的肿瘤中，MEK1/2 抑制剂和 BH3-模拟物 ABT-737 联合应用可诱导细胞死亡，这个过程中 Bim 蛋白也发挥着重要的作用[47]。

3.5 受体酪氨酸激酶

受体酪氨酸激酶 (receptor tyrosine kinases, RTKs) 抑制剂可以通过调节 Bcl-2 家族成员相互作用(例如 BAD 或 Bim)来调控细胞死亡，因此提出了一个可能性，即这种抑制剂可以通过 BH3 类似物来增强其抗肿瘤功效。事实上，在肺癌细胞，ABT-737 通过调控 BCL-2/BAX 之间的比例，已显示出增强 EGFR 抑制剂活性的作用[48]。EGFR 抑制剂与 ABT-737 联用也可在肺癌细胞中上调 Bim 蛋白表达，增强其抗肿瘤作用[49,50]。在 BCR/ABL +白血病中应用 Bcr/Abl 激酶抑制剂的治疗过程中，Bim 在介导细胞死亡中起关键作用。一般认为，Bcr/Abl 通过 FOXO3a 调节 Bim 转录，因此作为 Bcr/Abl 激酶抑制剂也调控 Bim 的转录[51]。

3.6 PI3K 抑制剂

在 PI3K 突变的肿瘤中，Bim 表达状态也可预测肿瘤对 PI3K 抑制剂的反应[52]。在神经母细胞瘤细胞中应用 PI3K 抑制剂(如 PI103)后，可增加促凋亡蛋白(如 Bim)与抗凋亡蛋白的比例，导致细胞凋亡[53]。但是，在肿瘤化疗中未检测到 Bim 表达状态与化疗反应的相关性，提示在靶向治疗手段中，Bim 表达状态对治疗效果起到较为重要的作用。

总的来说，这些研究结果表明 Bim 不仅在肿瘤发生中发挥着重要的作用，而且在肿瘤细胞的生物学行为以及对治疗的疗效方面也发挥着重要的调节作用。此外，大量的证据表明，在肿瘤的治疗尤其是在阻滞信号通路的靶向治疗中，Bim 表达状态是治疗疗效的决定因素。由于可以在多个水平调控 Bim 表达状态(例如表观遗传、转录、翻译和翻译后)，因此也存在许多增加其表达的切入点。这些可能包括：(1)增强其转录：通过调节 FOXO3a 途径；(2)减少其降解：通过阻断其在 ERK1/2 或 AKT 依赖性位点处的磷酸化；(3)通过干扰蛋白酶体降解等。在未来，我们可以设计理想的靶向药物合理组合，通过上调 Bim 的表达来增强抗肿瘤效果。

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