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文献综述 REVIEW

B7-H1与胃肠道肿瘤

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Role of B7-H1 in gastrointestinal cancer

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Abstract

Immune evasion is a hallmark of cancer. Although cancer cells have been shown to be able to be recognized by T cells, host immune system fails to develop effective antitumor activity and tumor control. B7-H1, an immune inhibitory molecule, plays an important role in the immune evasion process. B7-H1 inhibits T cell immunity during immune priming and effector phases and is also implicated in intrinsic proliferation, apoptosis and migration of tumor cells. Targeting B7-H1 using blockade antibodies has generated immense antitumor activity in preclinical tumor models. Durable response for a variety of tumor types was also documented in clinical trials. Thus, B7-H1 targeted immune therapy offers a new line of tumor treatment. Gastrointestinal cancer is one of the leading causes of tumor morbidity. However, traditional therapy has not been able to effectively improve survival. This review will focus on the role of B7-H1 in immune evasion and the latest progression of the B7-H1 blockade immune therapy in gastrointestinal cancer.

Key Words: B7-H1; Immune evasion; Gastrointestinal cancer

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摘要

恶性肿瘤发生发展过程中会产生突变蛋白, 可作为抗原而被免疫系统识别. 然而机体往

背景资料
B7-H1是新近发现的B7抑制性共刺激分子家族的一员, 被认为是免疫调控的检查点(immune checkpoint). 由肿瘤疫苗等正向刺激肿瘤免疫, 到阻断免疫负调控节点, 是近年来肿瘤免疫研究的重大转变.

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研发前沿
针对B7-H1的阻断性抗体已被美国批准应用于晚期膀胱癌的治疗. 在胃肠道肿瘤患者中的临床试验结果显示出安全性, 以及不同亚群的肿瘤对治疗的反应有显著差异. 如何进行正确的疗效预测, 是目前研究的热点.

往难以产生有效控制肿瘤的免疫反应, 即形成所谓肿瘤的免疫逃逸状态. B7-H1是表达在免疫和肿瘤细胞中的B7家族分子, 被发现是维持免疫逃逸的重要机制. B7-H1作为共刺激分子, 能够在T细胞免疫起始和效应阶段下调抗肿瘤免疫反应; 又参与调节肿瘤细胞自身增殖、凋亡和侵袭等生物学行为. 阻断B7-H1, 在临床前肿瘤模型和临床试验中显现出巨大的抗肿瘤效应. B7-H1阻断可能为胃肠道肿瘤提供新的治疗途径. 本文就B7-H1参与肿瘤免疫逃逸的机制及在胃肠道肿瘤中的研究进展作一综述.

关键词: B7-H1; **免疫逃逸**; **胃肠道肿瘤**

核心提示: B7-H1在肿瘤组织中高表达, 可抑制特异性T细胞应答效应和诱导T细胞凋亡, 形成肿瘤免疫逃逸状态. B7-H1还参与调节肿瘤细胞自身增殖、凋亡和侵袭等生物学行为. B7-H1阻断性单克隆抗体, 在临床试验中显现出巨大的抗肿瘤效应.

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0 引言

免疫逃逸是恶性肿瘤的标志性特征之一[1]. 尽管肿瘤能够产生被免疫系统识别的新生抗原, 有效的免疫应答与肿瘤控制却很少自然发生. 以激发正向肿瘤免疫应答为目的的免疫治疗手段, 如肿瘤抗原疫苗、树突状细胞疫苗和T细胞过继疗法尚未在实际应用中取得良好效果[2,3]. 近年理念的主要转变在于, 认识到肿瘤能够诱导形成抑制性免疫微环境, 而治疗应针对这种免疫抑制机制而开展[4]. 其中B7同源物1(B7 homolog 1, B7-H1)是B7共刺激分子家族的一员, 能够抑制T细胞免疫应答, 是T细胞免疫反应的“免疫检查点”[5]. B7-H1在免疫起始和效应阶段抑制T细胞活化. 阻断B7-H1的单克隆抗体在临床前模型和临床试验中展现出对多种晚期肿瘤的治疗效应, 有着巨大的应用前景[6].

胃肠道肿瘤是我国常见的肿瘤类型, 尤其是胃癌和结直肠癌, 发病率高, 晚期患者预后差[7,8]. 传统的治疗手段, 即手术和放化疗是主流方案, 然而对患者生存率的提高作用仍然有限[9,10]. B7-H1免疫疗法的出现, 为胃肠道肿瘤的治疗提供了新的途径. 本文将就B7-H1参与免疫逃逸的机制以及在胃癌和结直肠癌中的研究进展作一综述.

1 B7-H1参与免疫负调节

1.1 B7-H1的表达 *B7-H1*基因最初由对B7共刺激家族成员B7-1和B7-2的同源搜索而得到克隆, 表达一个含290个氨基酸的Ⅰ型跨膜蛋白. 其mRNA在心脏、骨骼肌、胎盘和肺广泛表达, 而蛋白质在正常组织中几乎无表达, 仅单核细胞来源的谱系组成性表达[11]. 但在多种肿瘤, 如肺、结肠、卵巢、黑色素瘤和胃癌组织中B7-H1广泛表达[12]. 干扰素γ(interferon γ, IFN-γ)是B7-H1表达的强诱导剂[11,13]. 研究认为, 肿瘤B7-H1的高表达代表了肿瘤对抗瘤免疫的适应性反应. 将黑色素瘤细胞种植在免疫功能健全小鼠皮下, 肿瘤细胞的B7-H1表达不久后即发生上调; 而种植在$CD8^+$ T细胞剔除或IFN-γ缺陷的小鼠中, B7-H1表达没有变化[14]. 黑色素瘤组织中, B7-H1阳性的肿瘤细胞总是与浸润的淋巴细胞相近, 且局部检测到IFN-γ的表达[15]. 这些结果提示, 肿瘤发展过程中, 先有$CD8^+$ T细胞浸润, 然后肿瘤微环境中IFN-γ上调了肿瘤B7-H1表达.

肿瘤中B7-H1的表达的预后价值有待探讨. 如果B7-H1代表了对预先存在的抗肿瘤活动的适应, 另一方面也提示抗肿瘤活性在早期则可能起到保护作用. 对56例转移性黑色素瘤患者的分析显示B7-H1表达的患者生存率较高[15]. 然而另一项研究中, B7-H1表达则是黑色素瘤患者预后不良的独立因素[16]. 一项包含了胃癌、结直肠癌和食管癌共2993例患者的Meta分析指出, 50%的肿瘤表达B7-H1, 是预后的危险因素[17].

1.2 B7-H1调节T细胞应答起始 尽管最初的研究显示B7-H1可以刺激T细胞增殖, 之后的大部分研究缺乏这种效应[12]. *B7-H1*基因敲除小鼠体内树突状细胞(dendritic cell, DC)和T细胞都显示较正常水平升高的刺激和活化能力, 还有自身免疫病的出现, 支持B7-H1起免疫抑制作用的观点[18]. 抗原提呈阶段, 在成熟DC上表达的B7-H1可为T细胞活化提供共抑

制性信号. B7-H1的受体之一, 程序死亡受体1(programmed cell death 1, PD-1)在T细胞活化早期即有表达. 成熟DC B7-H1与PD-1结合后, 可下调T细胞表面受体(T cell receptor, TCR)在T细胞膜上的表达水平. 阻断B7-H1的作用后, DC刺激产生高反应性的、高增殖的T细胞[19]. 这项研究提示B7-H1在应答起始即可限制T细胞活化程度. 小鼠膀胱癌模型中, 转染入DC小干扰RNA来沉默B7-H1的表达, 能够使DC分泌高水平白介素12(interleukin 12, IL-12), 降低IL-10分泌, 增强DC刺激T细胞增殖的效应. 经此种DC刺激得到的细胞毒性T细胞(cytotoxic T cell, CTL)分泌更多的IFN-γ, 具有更强的细胞毒作用[20].

B7-H1的刺激有助于调节性T细胞(regulatory T cell, Treg)的产生[21]. B7-H1缺陷的抗原提呈细胞较正常抗原提呈细胞在转化生长因子β(translational growth factor β, TGF-β)作用下诱导Treg产生的能力下降. PD-L1(-/-)PD-L2(-/-) Rag(-/-)小鼠接受初始T细胞输注后, 相较Rag(-/-)小鼠转化为Treg的细胞数目降低了10倍[22]. TGF-β本身可上调B7-H1的表达, 进而诱导Treg的产生, 说明TGF-β与B7-H1具有协同作用[23].

B7-H1与T细胞PD-1结合后, 可诱导T细胞失能[24]. 用单克隆抗体阻断DC上B7-H1, 甚至可以重新激活失能T细胞, 使其活化增殖[25]. 这对于DC疫苗为基础的免疫疗法有重要意义.

1.3 B7-H1调节T细胞应答效应阶段 肿瘤抗原激发的免疫应答反应, 最终由效应细胞来完成. CTL是主要的效应细胞. 通过TCR识别特异性主要组织相容性复合体-抗原肽复合物, 在合适的共刺激信号和细胞因子作用下, CTL分泌颗粒酶、穿孔素和利用Fas配体杀伤肿瘤细胞. 大量研究证明, 肿瘤细胞高表达B7-H1, 而活化的T 细胞表达PD-1, B7-H1通过PD-1向效应T细胞传递抑制性信号. PD-1是一个免疫抑制性受体, *PD-1*基因敲除小鼠出现狼疮样肾炎、关节炎等自身免疫病的表型[26]. B7-H1与PD-1结合后, 可直接抑制TCR信号转导, 引起T细胞增殖和IL-2和IFN-γ的分泌水平下降[13].

B7-H1还可诱导T细胞凋亡. 体外实验中, 肿瘤细胞与抗原特异性$CD8^+$ T细胞克隆共培养, $CD8^+$ T细胞凋亡率在表达B7-H1的肿瘤细胞刺激下明显升高. 2C T细胞能够特异识别P815肿瘤细胞, 将活化的2C T细胞过继转移至种植有转染表达B7-H1的P815肿瘤小鼠和种植有不表达B7-H1的P815肿瘤小鼠, 前者缺乏2C T细胞的初始扩增现象, 且8 h后2C T细胞凋亡率明显升高[12].

肿瘤组织虽然发生$CD8^+$ T细胞浸润, 但其分泌细胞因子、细胞毒功能与正常效应T细胞相比却处于抑制状态, 类似于慢性感染中的耗竭状态(T cell exhaustion)[27,28]. T细胞耗竭指在长期抗原刺激下, T细胞逐渐丧失效应功能和增殖能力. B7-H1/PD-1通路在慢性感染中引起T细胞耗竭已有大量研究. 慢性粒细胞性白血病中B7-H1/PD-1通路已被证明导致了肿瘤特异性CTL的耗竭状态[29].

B7-H1可以限制效应性T细胞向记忆性T细胞转化. 抗原免疫后, B7-H1缺陷的小鼠相较野生型小鼠$CD8^+$ T细胞增殖增加, 出现保护性$CD8^+$ T细胞记忆. 机制研究表明, 激活的$CD8^+$ T细胞接受B7-H1的刺激后, 发生了凋亡[30]. 此外, T细胞表达B7-H1对自身存活具有促进作用. B7-H1阴性的$CD8^+$ T细胞转移疗法不能起到对肿瘤的抑制作用[31]. B7-1是新近发现的B7-H1的另一受体, 与B7-H1结合后可双向抑制T细胞增殖和功能, 为B7-H1的作用又增添了一层复杂性[32].

2 B7-H1参与调节肿瘤细胞生物学行为

在众多的实验体系中, B7-H1阳性的肿瘤细胞能够抵抗CTL的杀伤作用, 阻断B7-H1能增强杀伤效应. 对这种现象的解释之一是B7-H1阳性的细胞抑制了T细胞功能. 然而将B7-H1阳性和B7-H1阴性的肿瘤细胞与CTL共培养, CTL选择性杀伤B7-H1阴性的细胞, 提示T细胞功能并未明显受损[33]. 另外的解释是B7-H1可以作为受体向肿瘤细胞传递保护性信号. 尽管B7-H1胞浆区仅含有30个氨基酸, 没有已知的功能模体,研究仍证实这种信号确实存在. PD-1刺激B7-H1引起的信号, 抵抗了CTL的杀伤以及Fas配体和药物诱导的凋亡作用[34,35]. 我们课题组发现B7-H1还可向胃癌干细胞内传递促增殖信号[36]. 在胰腺癌细胞中过表达B7-H1, S期细胞减少, G_1和G_2期细胞比例增加[37]. 敲低结肠癌细胞中的B7-H1表达, 细胞迁移和侵袭能力下降[38]. B7-H1可促进肿瘤上皮间充质转

相关报道
一般认为, B7-H1与程序死亡受体1(programmed cell death 1, PD-1)结合后, 通过PD-1向T细胞内传递抑制性信号. Azuma等报道, B7-H1还可作为受体, 向肿瘤细胞内传递抗凋亡信号, 提示B7-H1本身参与肿瘤生物学行为的调节.

创新盘点

本文综述了B7-H1在肿瘤免疫中的研究进展, 同时以胃肠道肿瘤为重点, 论述了B7-H1阻断治疗的临床应用价值.

化的发生[39]. 多柔比星处理乳腺癌细胞, 能够通过蛋白激酶B(protein kinase B, PKB/AKT)促使B7-H1由膜表面向核内的转位; 抑制AKT, 转位减少, 细胞凋亡增加, 提示B7-H1可能有新颖的核内作用[40].

B7-H1的表达受到多条细胞生长信号通路的调节. 磷酸酶-张力蛋白类似物基因(phosphatase and tensin homolog, *PTEN*)是重要的抑癌基因. PTEN缺失可导致B7-H1表达上调[41,42]. 非小细胞肺癌中表皮生长因子受体激活或突变可通过p-ERK1/2/p-c-Jun上调B7-H1表达[43]. 肺癌中, 棘皮动物微管相关蛋白4-间变性淋巴瘤酶融合基因(echinoderm microtubule protein like 4-anaplastic lymphoma kinase, *EML4-ALK*)是一个重要的癌基因. *EML4-ALK*融合基因阳性的细胞系显示出更高的B7-H1的表达水平. 抑制ALK, MEK/ERK或PI3K-AKT通路, B7-H1表达随之受到抑制. 肺癌组织标本中B7-H1表达与EML4-ALK表达成正相关[44]. 这些研究提示癌基因信号通路与B7-H1表达存在内在联系, 可能为联合靶向药物与免疫治疗提供理论依据.

3 抗B7-H1单克隆抗体在胃肠道肿瘤中的应用

B7-H1在肿瘤免疫中的作用研究迅速催生了阻断B7-H1能够用于治疗肿瘤的假设, 抗B7-H1单克隆抗体已开展多项针对各种肿瘤的临床试验.

BMS-936559, B7-H1阻断性单抗, Ⅰ期试验纳入207例晚期肿瘤患者, 包括18例结直肠癌和7例胃癌患者. 结直肠癌患者中未出现客观反应, 而胃癌病例未进入效应分析. 在黑色素瘤患者中, 客观反应率在3 mg剂量最高为29%. 许多其他患者观察到疾病稳定(24 wk时比例为12%-41%). 毒性作用大多数为1、2级, 糖皮质激素可缓解. 9%的患者出现3或4级治疗相关毒性反应. 免疫相关的不良反应包括红疹、甲低、肝炎、肾上腺功能不足和重症肌无力等[45].

MPDL3280A, B7-H1阻断性单抗, Ⅰ期试验中175例晚期肿瘤患者参与效应评价, 包括6例结直肠癌患者和1例胃癌患者. 毒性作用包括疲劳、高血糖和肿瘤溶解综合征. 共32例出现客观反应. 1例胃癌患者出现客观反应, 最终30 wk后进展; 1例结直肠癌患者出现客观反应, 48 wk停药后反应持续[46].

MEDI4736, B7-H1阻断性单抗, Ⅰ期试验初步结果显示毒性作用在耐受范围内, 胃肠道肿瘤中已出现客观反应[47].

从以上初步结果来看, 首先, B7-H1阻断抗体的安全性是可靠的. 相较于其他免疫检查点抑制剂, 如CTLA-4和PD-1单克隆抗体, 严重的免疫相关毒性, 如肺炎、结肠炎少见. 然而其自有独特的毒性作用, 在用于治疗胃肠道肿瘤时要予以考虑, 如内分泌毒性、胃肠道毒性和肝毒性; 其次, 肿瘤反应率在胃肠道患者中相对偏低. 如何准确预测肿瘤反应是研究的方向. Pembrolizumab, 一个PD-1阻断性单克隆抗体, 在错配修复缺陷的结直肠癌患者的反应率达到40%(4/10)而在错配修复正常的患者反应率为0(0/18)[48]. 这凸显了不同亚群肿瘤患者对治疗反应的差异性. 错配修复患者被认为带有更多突变蛋白, 因而更容易被免疫系统攻击. 而且微卫星不稳定性与B7-H1表达上调相关[49]. 错配修复缺陷、B7-H1高表达及其他可能的疗效预测指标是研究的热点. 虽然反应率偏低, 一部分患者出现了持久的反应和肿瘤控制, 这是有别于传统疗法的特点. 此外, 临床观察到肿瘤在免疫治疗初期, 反应不明显, 甚至影像学上有进展, 之后肿瘤才缩小. 这种独特的反应模式对标准疗效评价系统提出了挑战[50]. 目前已有许多临床试验考虑免疫检查点阻断抗体与其他药物联用, 如两种免疫检查点阻断抗体联用, 免疫检查点阻断抗体与靶向药物联用等, 可能是未来临床应用的方向[51].

4 结论

B7-H1是T细胞的重要共抑制分子, 与受体结合后, 直接抑制T细胞活化, 促进初始T细胞向Treg分化, 还可促进T细胞凋亡. 除了免疫抑制作用, B7-H1参与调节肿瘤细胞的增殖、存活和迁移行为, 促进上皮间充质转化的发生. 阻断B7-H1的单克隆抗体在临床试验中显现出良好的安全性与抗肿瘤作用, 在胃肠道肿瘤中的应用前景巨大. 对肿瘤患者进行正确的亚群分析, 有助于预测疗效; 将B7-H1阻断抗体与其他疗法连用, 可能为胃肠道肿瘤开辟新的治疗途径.

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■应用要点

B7-H1阻断抗体已在临床试验中显现出针对多种肿瘤包括胃肠道肿瘤的有效性，对B7-H1的研究有助于进一步明确机制和筛选疗效预测的标志.

名词解释

免疫逃逸: 肿瘤在发生发展过程中会产生肿瘤相关或特异抗原, 从而诱发免疫系统识别, 产生抗肿瘤免疫反应, 以致清除肿瘤. 然而多种免疫抑制成分和机制, 如MHC I类分子的低表达, 调节性T细胞、骨髓来源的抑制性T细胞、IL-10, TGF-β、B7-H1等导致的免疫应答效应减弱, 无法抑制肿瘤生长, 即形成肿瘤免疫逃逸;

免疫检查点: 指活化T细胞的表面分子CTLA-4和PD-1与配体结合后, 能抑制T细胞免疫应答, 维持免疫耐受, 避免正常组织的免疫损伤. 肿瘤细胞可利用免疫检查点逃脱杀伤.

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同行评价

文章选题恰当, 针对B7-H1在肿瘤中的研究进展展开论述, 抓住热点, 条理清晰, 应用文献新颖, 有较高的学术价值.

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