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文献综述 REVIEW

肿瘤抗淋巴管生成研究进展

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Lymphangiogenesis in cancers: a therapy target

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Abstract
Tumor metastasis is a major cause of death among cancer patients. The lymphatic vasculature is an important route for the metastatic spread of cancer. Recent research has indicated that vascular endothelial growth factor C (VEGF-C), VEGF-D and VEGF receptor-3 (VEGFR-3) are closely related to tumor-induced lymphangiogenesis, tumor metastasis and prognosis. Numerous studies demonstrate that the VEGF-C/VEGF-D/VEGFR-3 signaling axis plays a leading role in the regulation of tumor lymphangiogenesis and is related to tumor metastasis and prognosis. It has been confirmed that inhibition of the VEGF-C/VEGF-D/VEGFR-3 signaling axis can exert anti-lymphangiogenic effect and thereby prevent tumor metastasis in animal models. In this paper we review the molecular biology of lymphangiogenesis, its relationship with cancer metastasis, and the clinical implications of inhibition of lymphangiogenesis.

Key Words: Lymphatic vasculature; Vascular endothelial growth factor; Molecular biology

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摘要
肿瘤转移是癌症患者的主要死因之一, 淋巴管转移是肿瘤转移的重要途径, 研究发现VEGF-C/VEGF-D/VEGFR-3与肿瘤淋巴管生成、肿瘤转移、肿瘤预后密切相关. 大量的研究证实VEGF-C/VEGF-D/VEGFR-3信号传导轴在调节肿瘤淋巴管生成中起主导作用, 临床病理研究也显示VEGF-C/VEGF-D/VEGFR-3与某些肿瘤转移、预后相关, 抑制VEGF-C/VEGF-D/VEGFR-3信号传导轴来抗肿瘤淋巴管生成, 从而阻止肿瘤转移已经广泛得在动物模型中得到证实. 近年通过抑制VEGF-C/VEGF-D/VEGFR-3信号系统来治疗肿瘤转移的研究已经开展, 本文就淋巴管生成分子生物学、淋巴管与肿瘤转移以及抗淋巴管生成三方面加以综述.

关键词: 淋巴管; 血管内皮生长因子; 分子生物学

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0 引言
肿瘤患者多数死于转移, 淋巴管是肿瘤转移的主要途径之一. 以前认为肿瘤通过周围既有的淋巴管转移, 通过研究的深入发现肿瘤可以诱导淋巴管生成促进转移, 一系列影响淋巴管生成的调控因子和受体也相继发现, 其中最主要的是血管内皮生长因子(vascular endothelial growth factor, VEGF)-C、VEGF-D及他们的受体血管内皮生长因子受体-3(vascular endothelial growth factor receptor-3), 许多动物模型和临床病理研究都提示其在肿瘤淋巴管生成和转移中起重要作用, 因此, 这些调控因子及其受体有望成为抑制淋巴管生成治疗肿瘤转移的靶向.

■背景资料
肿瘤转移是癌症患者的主要死因之一, 淋巴管转移是肿瘤转移的重要途径, 研究发现VEGF-C/VEGF-D/VEGFR-3与肿瘤淋巴管生成、肿瘤转移、肿瘤预后密切相关, 近年通过抑制VEGF-C/VEGF-D/VEGFR-3信号系统来治疗肿瘤转移的研究已经开展.

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抑制VEGF-C/VEGF-D/VEGFR-3信号传导轴来抗肿瘤淋巴管生成, 从而阻止肿瘤转移已经广泛得在动物模型中得到证实, 因此抗淋巴管生成有望成为肿瘤治疗手段之一.

1 淋巴管生成的分子生物学

1.1 VEGF-C/VEGF-D/VEGFR-3信号系统 VEGF-C、VEGF-D及他们的受体VEGFR-3是目前研究最深入的介导淋巴管生成的信号系统. VEGF-C和VEGF-D是分泌型的糖蛋白, 其前蛋白经过丝氨酸蛋白酶纤溶酶[1]和前蛋白转换酶(proprotein converting enzyme)家族的PC5、PC7[2]水解为成熟形式. 随着VEGF-C和VEGF-D的逐渐水解, 其对VEGFR-3的亲和力逐渐提高[3,4], 提示VEGF-C和VEGF-D的水解程度可能参与影响淋巴管生成的程度. VEGF-C和VEGF-D的成熟形式也能同时结合激活VEGFR-2促进血管生成, 但是他们对VEGFR-3的活性更强[3].

在成人VEGFR-3只表达于淋巴管内皮细胞[5], 作为受体酪氨酸激酶家族的成员, 与VEGF-C和VEGF-D结合后形成二聚体, 后者胞质的酪氨酸残基发生磷酸转移作用[6], 磷酸化是受体激酶活性调节和受体相互作用信号传导的重要步骤. 将分离培养的人淋巴管内皮细胞用抗体结合后发现VEGFR-3激活后可刺激细胞分化增殖[7], 而一些人类遗传性淋巴水肿疾病则于VEGFR-3基因突变有关[8].

大量的体内体外实验探索了VEGF-C和VEGF-D的作用. Makinen等[9]发现通过阻断VEGFR-3的活化可以阻止胚胎的淋巴管形成. Jeltsch等[10]和Veikkola等[11]通过转基因技术使小鼠皮肤表达VEGF-C和VEGF-D, 结果皮肤中出现淋巴管内皮细胞增殖, 而没有新生的血管. Karkkainen等[12]剔除小鼠的VEGF-C基因导致淋巴管内皮细胞不能出芽形成淋巴管系统, 导致小鼠胚胎时期死于水肿. Szuba等[13]在动物模型中用人重组VEGF-C治疗淋巴水肿, 结果发现VEGF-C促进淋巴管生成, 水肿得到改善. 上述研究结果提示, VEGF-C/VEGF-D/VEGFR-3在影响淋巴管生成中起重要作用, 因而也是抗淋巴管生成研究最多的治疗靶向.

1.2 淋巴管生成的其他影响因素 有研究[14]发现, VEGF-C和VEGF-D可以结合并激活表达于淋巴管内皮细胞的α9β1整合素, Huang等[15]剔除胚胎的α9亚单位引起淋巴管发育障碍而导致死亡, 提示α9β1整合素与淋巴管的发育和功能有关. 同源异型盒转录因子Prox1与淋巴管内皮细胞的表型改变密切相关, 剔除Prox1抑制了小鼠胚胎淋巴管出芽和延伸发育[16], 血管内皮细胞表达Prox1后表达了只在淋巴管内皮细胞的基因谱[17,18]. 据报道, 影响淋巴管生成的调控因子还有VEGF-A[19]、成纤维生长因子-2(fibroblast growth factor-2, FGF-2)[20], 血小板衍生因子(platelet derived growth factor–BB, PDGF-BB)[21]、促血管生成素受体(the angiopoietin receptor-2)的配体促血管生成素-1(Angiopoietin-1)[22]和肝细胞生长因子受体(c-Met)[23]. Schoppmann等[24]发现肿瘤相关的巨噬细胞表达VEGF-C, 与淋巴管生成、淋巴结转移有关.

2 淋巴管生成与肿瘤转移

2.1 淋巴管和肿瘤转移 肿瘤细胞转移至重要器官并继续增殖生长, 破坏器官结构、影响器官功能是肿瘤致死的原因之一. 淋巴道是肿瘤转移的重要途径, Sleeman等[25]认为, 肿瘤发展早期进入血管的肿瘤细胞因为血液中的血液动力学压力等一些因素而大多数被破坏, 而侵入淋巴道的肿瘤细胞可以继续增殖扩充先造成淋巴结转移, 最终通过胸导管进入血循环而远处转移, 因此淋巴结对于具备转移能力的肿瘤细胞起着选择和放大的作用, 淋巴结转移也可看作是肿瘤远处播散的“桥头堡”. Trarin等[26]给29位恶性腹水的患者实施腹腔静脉分流术, 虽然使含有肿瘤细胞的腹水进入了血循环, 但在最终15位患者尸解时却发现他们无一远处转移. 这提示我们淋巴管似乎在肿瘤转移中扮演特殊的角色.

2.2 VEGF-C/VEGF-D/VEGFR-3与肿瘤转移 以前认为肿瘤可以侵入周围既有的淋巴管发生转移, 不必生成新的淋巴管[27], 肿瘤内部是否存在淋巴管也曾经遭受质疑, 因为肿瘤不断生长扩张, 瘤体压力相对较大, 淋巴管不能延伸进入肿瘤内[28]. 随着研究的深入发现VEGFR-3活化后能诱导肿瘤淋巴管生成、促进肿瘤淋巴结转移, 肿瘤表达VEGF-C或VEGF-D促进淋巴管生成, 新生的淋巴管与周围的淋巴管相互连同, 肿瘤周围淋巴管密度的增加提高了肿瘤淋巴转移的机会. Skobe等[29]将人乳腺癌细胞种植到裸鼠体内, 发现VEGF-C的表达促进肿瘤内部淋巴管生成、肿瘤淋巴结转移和肺转移. 另一个乳腺癌动物模型中, VEGF-C促进肿瘤相关的淋巴管生长, 淋巴管内充满肿瘤细胞[30], 同时促进淋巴结转移[31]. Trojan等[32]发现VEGF-C在前列腺癌的表达高于良性前列腺增生(benign prostatic hyperplasia, BPH), 有淋巴结转移的前列腺癌高于无淋巴结转移. 在Mandriota等[33]建立的转基因小鼠模型中, 胰腺β细胞高表达VEGF-C的试验组比野生型对照组的胰岛有更广泛的淋巴管

生成, 当肿瘤被引入进胰岛后, 试验组发生了淋巴结转移, 而对照组则没有. 在一个异种移植物小鼠模型[34], 肿瘤细胞VEGF-D的表达促进瘤内淋巴管生成和淋巴结转移, 同时也促进血管生成和肿瘤生长, 提示水解后成熟型的VEGF-D也能结合激活VEGFR-2, 诱导血管生成; 试用中和性VEGF-D抗体封闭VEGFR-2和VEGFR-3能阻断肿瘤淋巴结转移[34,35], 这也是首个直接的证据表明可以预防肿瘤淋巴转移[28].

早期的研究都显示出肿瘤表达VEGF-C和VEGF-D跟淋巴结转移有关[27], VEGF-C的表达在肺癌、结直肠癌和前列腺癌中与淋巴结转移相关[36], 尽管到现在多数的研究结果如此, 但也有少数的报道与之不符. 神经母细胞瘤中VEGF-C和淋巴结转移无相关性[37], 肺癌中VEGF-D与淋巴结转移无相关性[38]. 早期未分化胃癌VEGF-C表达与淋巴结转移相关, 但在分化型胃癌却无相关性; 分化型胃癌中VEGF-D也显示与淋巴结转移无相关性[39]. T1和T2期口腔鳞癌VEGF-C表达与淋巴结转移相关, 但T3和T4期肿瘤却没有相关性[40]. 这些研究结果提示影响肿瘤淋巴管生成的因素可能比早先预料的复杂得多, 正如前文所述, 尚有其他因素同时影响淋巴管的生成, 因此在设计抗淋巴管生成的肿瘤治疗方法时, 这些影响因素也应加以考虑, 同时, 这些因素的影响程度也有待进一步研究.

2.3 VEGF-C/VEGF-D/VEGFR-3与肿瘤预后 回顾过去几年的临床病理研究可以看到VEGF-C、VEGF-D和VEGFR-3的表达跟患者预后相关. VEGF-C可能是卵巢癌和宫颈癌的预后危险因素[41,42]. RAA Mohammed等[43]一项对177例乳腺癌患者长达10年的随访研究发现, 肿瘤细胞表达VEGF-C与淋巴管密度、总体生存期和无病生存期相关, 但VEGF-D却未显示上述的相关性. 有两项研究研究显示VEGF-C与肺癌淋巴结转移无相关性, 却与预后差相关[44,45]. VEGF-D的表达水平与结直肠癌[46]、胰腺癌[47]、子宫内膜癌[48]和卵巢癌[49]的预后相关. Juttner等[50]报道同时表达VEGF-D和VEGFR-3是胃癌预后不良的独立危险因素.

然而, 同时也有少数不一致的报道. VEGF-C在神经母细胞瘤[37]、胰腺癌[47,51]和结直肠癌[52]中与预后未显示出相关性.

3 抗淋巴管生成作为肿瘤治疗的研究进展

3.1 动物模型中的抗淋巴管生成研究 从动物模型实验到人类肿瘤临床病理研究, 一系列的研究结果都显示VEGF-C/VEGF-D/VEGFR-3信号传导轴在肿瘤淋巴管生成和淋巴转移中起主导作用, 因此抑制VEGFR-3的活化, 使得以抑制转移为方法的肿瘤治疗成为可能, 在这点上, 已经有研究人员做了大量的工作. He等[53]将具有高度转移能力的人肺癌细胞株NCI-H460-LNM35通过转基因表达可溶性的VEGFR-3, 可溶性的VEGFR-3与肿瘤细胞VEGF-C结合, 抑制了内源性VEGFR-3的信号传导, 将处理过的肿瘤细胞种植到试验小鼠, 将未处理的肿瘤细胞种植到对照小鼠, 发现试验组小鼠相比对照组小鼠肿瘤内部少有淋巴管, 淋巴引流液也少有转移的肿瘤细胞, 将对照组小鼠用经过重组表达可溶性VEGFR-3的腺病毒处理后发现, 肿瘤淋巴结转移同样被限制. 在另一个动物模型中[54], 高度转移能力的乳腺癌细胞株MT-450表达可溶性VEGFR-3后, 小鼠的淋巴结专业和肺转移都被抑制. Lin等[55]发现小鼠黑素瘤模型中表达可溶性VEGFR-3的腺病毒能抑制淋巴结转移. 在一个小鼠乳腺癌模型[56]中siRNA介导的基因沉默抑制了VEGF-C的表达, 继而减少了淋巴管生成、淋巴结转移和肺转移.

3.2 抗淋巴管生成的实现方法 理论上有几种方法来阻断VEGFR-3依赖的肿瘤淋巴管生成. 应用可溶性的VEGFR-3结合VEGF-C和VEGF-D来抑制内源性VEGFR-3的活化已经在肿瘤动物模型中广泛开展[30,53-55], 目前还没有相关的临床试验的报道, 尚不清楚可溶性VEGFR-3结合VEGF-C/VEGF-D后是否同样可以抑制内源性VEGFR-2活化从而抑制血管生成. 类似的细胞表面受体可溶性制剂已经有药物用于临床, 比如可溶性肿瘤坏死因子受体p75和免疫球蛋白Fc段的融合蛋白依那西普(Enbrel)已经被FDA批准用于风湿性关节炎治疗.

另一种方法是用VEGF-C/VEGF-D/VEGFR-3的单克隆抗体来结合VEGFR-2/VEGFR-3[34,35,57,58]. 小鼠肿瘤动物模型中应用VEGF-D的单抗可以抑制血管生成、淋巴管生成和淋巴结转移[34]. VEGFR-3的单抗可以抑制成人的淋巴管再生[59], 其对于人类肿瘤的作用尚未见报道. VEGFR-3的单抗不能阻断VEGFR-2的激活, 但已有研究[60]报道了能同时结合VEGFR-2/VEGFR-3的双特异性抗体. 通过抑制肿瘤血管生成来治疗转移性结直肠癌的VEGF-A单抗贝伐单抗(avastin)既是此类药物.

第3种方法是利用小分子进到细胞内, 抑

■相关报道 近年已有报道通过抑制VEGF-C/VEGF-D/VEGFR-3信号系统来治疗肿瘤转移的研究.

■应用要点
通过抑制VEGF-C/VEGF-D/VEGFR-3信号传导轴来抗肿瘤淋巴管生成, 从而阻止肿瘤转移已经广泛得在动物模型中得到证实, 因此抗淋巴管生成有望成为肿瘤治疗手段之一.

制VEGFR-3酪氨酸激酶或抑制信号传导的环节, 他们包括BAY 43-9006[61]、CEP-7055[62]、PTK787/ZK222584[63]、MAE87、MAE106、MAZ51[64], 其中前三者已经进入临床试验. 目前尚无类似药物用于临床.

3.3 抗淋巴管生成的临床应用展望 目前掌握的淋巴管生成对于肿瘤转移的重要作用提示可以通过阻断VEGFR-3的活化来抑制转移, 虽然对于已有的转移可能无效, 但可以阻断新的淋巴管生成来抑制新的转移, 因此预防性的抑制肿瘤转移对于存在复发风险的肿瘤患者具有一定意义. 对于T1a期的前列腺癌, 外科手术的风险大于患者的获益而往往只是严密随访, 一定比例的患者会在期间出现危机生命的肿瘤转移, 有16%-25%的T1a期前列腺癌患者会在8-10年内发生上述情况[65], 因此对于类似生长缓慢的肿瘤长期应用预防性的抑制肿瘤转移的药物同样有重要意义.

大多数实体肿瘤的治疗方法采取手术局部切除, 然后根据敏感性给予化疗来预防控制复发和转移. 近年有研究术前应用化疗使肿瘤缩小易于手术, 或通过术前化疗来改善患者预后, 此时可应用抗淋巴管生成治疗联合常规化疗来改善预后、预防复发. 晚期无法切除的肿瘤仍是治疗的难题, 抗淋巴管生成治疗联合其他全身治疗也可用于这种情况.

抗淋巴管生成具有良好的应用前景, 为了更安全有效的用于临床治疗, Thiele等[66]在2006年提出4个需要进一步阐明的问题: (1)除VEGFR-3外, 其他同时参与影响肿瘤淋巴管生成的因素; (2)肿瘤发生发展过程中什么阶段VEGF-C/VEGF-D表达上调, 肿瘤淋巴管生成是否可逆; (3)抗淋巴管生成可能带来的副作用; (4)淋巴管在肿瘤转移中的作用.

4 结论

大量的研究证实肿瘤淋巴管生成和肿瘤转移相关, VEGF-C/VEGF-D/VEGFR-3信号传导轴在调节肿瘤淋巴管生成中起主导作用, 临床病理研究也显示VEGF-C/VEGF-D/VEGFR-3与某些肿瘤转移、预后相关. 抑制VEGF-C/VEGF-D/VEGFR-3信号传导轴来抗肿瘤淋巴管生成, 从而阻止肿瘤转移已经广泛得在动物模型中得到证实, 因此抗淋巴管生成有望成为肿瘤治疗手段之一, 而在真正实现有效安全的临床应用之前, 尚有许多问题有待解决.

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