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CXCR4与肿瘤的发生和发展

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[摘 要] 趋化因子受体-4 (chemokine receptor-4，CXCR4)属趋化因子家族，为G蛋白偶联的7次跨膜受体蛋白，基质细胞衍生因子-12是该受体的唯一配体。目前发现CXCR4在23种不同类型肿瘤中均有表达，与肿瘤细胞的增殖、侵袭、转移及预后密切相关，针对CXCR4靶向治疗可望成为肿瘤基因治疗研究的新热点。

[关键词] 趋化因子受体；肿瘤；CXCR4；CXCL12

Role of CXCR4 in the occurrence and development of tumors

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Abstract The chemokine receptor-4 (CXCR4) belongs to the large super-family of G-protein-coupled seven-span transmembrane receptors and stromal derived factor-12 is the only known ligand for CXCR4. It has been shown that CXCR4 expresses in malignant cells from 23 different types of cancer and plays an important role in tumor proliferation, invasion, metastasis and prognosis. Targeted therapeutic approaches against CXCR4 might attract great attention in gene therapy for cancers.

Key words chemokine receptor; tumor; CXCR4; CXCL12

趋化因子是细胞因子超家族成员中的一大类具有化学趋化作用的小分子蛋白，分子质量在8~17 kD(1 D=1 u)之间，在胚胎发育、血管生成、造血、动脉粥样硬化、炎症、肿瘤及艾滋病等多种生理及病理过程中发挥重要作用。目前已经发现至少50多种趋化因子和20种趋化因子受体。根据其分子结构中氨基酸区域上半胱氨酸残基的数量及空间排列不同分为C，CC，CXC和CX3C 4个亚家族，其中CXC超家族根据分子结构中第一个半胱氨酸的前面是否出现ELR构型又可分为ELR-CXC及非ELR-CXC。ELR-CXC趋化因子(CXCL1，2，3，5，6，7，8)是血管生成因子，而非ELR-CXC[除基质细胞衍生因子-12(stromal derived factor-12，CXCL12)外]为血管生成抑制因子。趋化因子的受体是G蛋白偶联受体，此受体有7个跨膜区，又称7次跨膜区受体超家族，目前通用命名方

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法为：受体末端用R表示，配体用L表示。

趋化因子受体-4(chemokine receptor-4，CXCR4)为G蛋白偶联的7次跨膜受体蛋白超家族的一员，其N端区域(胞外区)与配体结合，胞内区与G蛋白偶联，C端含丝氨酸/苏氨酸，可磷酸化而参与信号转导。CXCR4不仅正常表达于T/B淋巴细胞、单核细胞、巨噬细胞、中性粒细胞及嗜酸性粒细胞，在脑、肺、结肠、心、肾及肝等器官也有表达[1]。

CXCL12是由骨髓基质细胞及其他相关的间皮细胞和上皮细胞分泌的一种趋化蛋白，包括α和β 2种异构体，属于趋化因子CXC亚家族。CXCL12是CXCR4唯一的配体，能与CXCR4的N端特异性结合，与CXCR4的第2胞外环相互作用后启动下游信号通路形成CXCL12/CXCR4生物轴，并在维持胚胎发育、介导免疫及炎症反应、调控造血、诱导血管生成及肿瘤侵袭转移等多种生理和病理过程中发挥重要作用。

1 CXCR4在肿瘤中的表达

CXCR4是肿瘤细胞中最常见的趋化因子受体，在胃癌、肺癌、乳腺癌、前列腺癌及软组织肉瘤等肿瘤细胞中表达量均有增加。

Bai等[2]发现软骨肉瘤细胞CXCR4表达强于正常软骨细胞，在恶性程度高的软骨肉瘤中表达强于恶性程度低者。Ping等[3]发现$CD133^+$的胶质瘤干细胞高表达CXCR4，CXCL12在CXCR4作用下激活磷脂酰肌醇3激酶/丝苏氨酸蛋白激酶(phosphoinositide-3-kinase/ serine-threonine kinase，PI3K/Akt)信号通路促进VEGF的产生，导致血管形成和神经胶质瘤的生长。Dubrovska等[4]发现DU145和PC3两种前列腺癌细胞系中CXCR4表达上调。$CXCR4^+$的前列腺癌细胞系中干细胞因子CD44和CD133表达高于$CXCR4^-$的细胞系。CXCR4的表达与前列腺上皮内瘤变向前列腺癌发展以及骨转移相关[5]。Zhao等[6]发现胃癌组织中CXCR4表达显著高于正常胃黏膜，并与胃癌的分化程度和淋巴结转移相关。Nian等[7]在Lewis肺癌细胞中检测到CXCR4表达，未检测到C-kit，CD133和CD34等干细胞因子的表达，在$CXCR4^+$和$CXCR4^-$ Lewis肺癌细胞荷瘤小鼠模型上，发现$CXCR4^+$的Lewis肺癌细胞MMP9和VEGF mRNA表达显著高于$CXCR4^-$者，并且癌细胞增殖速度快，提示$CXCR4^+$的Lewis肺癌细胞可能具有肿瘤干细胞特性，可以促进肿瘤的生长。咽喉部鳞状细胞癌CXCR4过表达者血管密度高于低表达者，用shRNA抑制CXCR4表达，肿瘤组织中血管减少，抑制肿瘤生长[8]。Uchida等[9]应用CXCR4拮抗剂AMD3100治疗腺样囊腺癌荷瘤小鼠模型，结果发现涎腺癌肺转移率降低、存活率升高，提示CXCR4的表达与涎腺癌的转移有关。Ferrari等[10]研究发现：猫科动物乳腺癌转移灶CXCR4表达高于原发灶，CXCL12可显著提高培养的乳腺癌细胞的生长，而AMD3100能抑制肿瘤细胞增殖。这些结果提示CXCR4的表达参与肿瘤细胞增殖的调控。

2 CXCR4与肿瘤的侵袭及转移

转移是恶性肿瘤的重要生物学特征，Ying等[11]发现胃癌淋巴结转移灶中CXCR4和CXCL12表达高于正常胃黏膜。转移性前列腺癌细胞系CXCR4 mRNA表达高于原发瘤和正常前列腺组织[12]。有淋巴结转移的甲状腺癌CXCR4表达强于无淋巴结转移者，激活BRAF基因可以上调CXCR4在甲状腺癌中的表达[13]。Gahan等[14]发现肾透明细胞癌中CXCR4及CXCL12 mRNA表达高于正常肾组织，发生转移者高于未发生转移者。

Müller等[15]研究显示：荷瘤小鼠的乳腺癌转移瘤组织和淋巴结转移灶组织均高表达CXCR4 mRNA，使用CXCR4或CXCL12中和抗体均能抑制肿瘤的转移。抗-CXCR4抗体能抑制MDA-MB-231和MDA-MB-468乳腺癌细胞系的远处转移，敲除CXCR4能阻断肿瘤的转移[16]。Zhang等[17]发现转移的结直肠癌细胞$CD133^+/CXCR4^+$比原发部位高7倍，$CD133^+/CXCR4^+$细胞株比$CD133^+/CXCR4^-$细胞株侵袭能力强，发生转移的结直肠癌原发灶组织CXCR4表达高于未转移者。miRNA干扰能降低CXCR4的表达，敲除CXCR4能降低淋巴结、肝和肺转移，提示CXCR4表达与肿瘤的转移有关[18]。

3 CXCR4的表达与患者的预后

目前已知CXCR4在23种不同类型肿瘤中均有表达，是肿瘤细胞表达最为普遍的趋化因子受体，与预后相关[19]。Li等[20]对肾透明细胞癌进行回顾性分析，应用免疫组织化学技术检测CXCR4在肾透明细胞癌中的表达，发现高表达CXCR4提示预后更差。高表达CXCR4的前列腺癌局部复发率及远处转移率高于低表达者[21]。Sekiya等[22]对卵巢透明细胞癌进行回顾性分析，应用免疫组织化

学技术检测CXCR4在卵巢透明细胞癌中的表达，显示高表达CXCR4的患者5年生存率和无病生存率均低于低表达者。Parker等[23]发现CXCR4表达水平、肿瘤分期和分级可作为乳腺癌患者5年总体生存率的独立预测指标。高表达CXCR4的乳腺癌患者总体生存率和5年无病生存率低于低表达者，高表达者复发率高[24]。乳腺癌骨转移者的原发瘤细胞CXCR4在胞质和胞核中共同表达，提示可能会发生骨转移[25]。Otsuka等[26]认为CXCR4高表达与IV期非小细胞肺癌患者低生存率有关。CXCR4/SDF-1α高表达与胃癌的浸润深度、淋巴结转移及5年生存率有关，提示高表达者可能预后不良[27]。Zhang等[17,28]研究显示结直肠癌高表达CXCR4$^+$者生存率较低。

然而，Ma等[29]发现骨肉瘤CXCR4阳性表达与转移没有相关性，与肿瘤预后无关；Mirisola等[30]也未发现乳腺癌CXCR4表达与生存率有关。上述研究结果提示在不同的肿瘤类型中，CXCR4/CXCL12轴的激活与患者的预后存在差异。

4 CXCR4表达与肿瘤治疗

目前认为CXCR4小分子抑制剂能阻断CXCR4或CXCR4/CXCL12的相互作用，抑制肿瘤细胞的增殖、侵袭和转移。AMD3100最初是在抗HIV的抗体中发现，之后被发现是CXCR4强有力的选择性抑制剂[31]。AMD3100联合化学治疗(化疗)药物可以诱导胶质母细胞瘤细胞凋亡，抑制该肿瘤细胞增殖[32]。在多发性骨髓瘤、非霍奇金淋巴瘤以及非血液系统肿瘤的治疗中，AMD3100也有作用[33]。Uchida等[34]应用AMD3100治疗发生肺转移的涎腺癌小鼠模型，结果显示小鼠的存活率得到提升。D'Alterio 等[35]将黑素瘤细胞注入表达CXCR4$^+$小鼠体内并分成实验组和空白对照组，实验组用AMD3100治疗10 d，空白对照组未作处理，在第19天取出两组肺组织，结果发现实验组肺转移率低于对照组。Parameswaran等[36]应用CXCR4拮抗剂AMD11070和AMD3100处理3种急性淋巴细胞白血病细胞系，发现使用AMD11070的细胞系CXCR4表达显著低于使用AMD3100的细胞系，联合使用CXCR4拮抗剂和长春新碱处理的肿瘤细胞再生能力低于单独使用者，同时发现荷瘤小鼠的存活率显著提升。Spinello等[37]发现急性髓性白血病CXCR4表达水平与miRNA-146a负相关，上调miRNA表达后，CXCR4表达降低。联合使用AMD3100和阿糖胞苷对白血病细胞的抑制作用强于单独使用阿糖胞苷。体外实验[4]发现中和性抗CXCR4抗体可以抑制DU145前列腺癌细胞系微球体的生长。AMD3100对CD44$^+$/CD133$^+$前列腺癌干细胞的抑制作用比传统化疗药的效果好，两者联合使用抑制效果更明显。Ping等[3]发现AMD3100治疗能显著减小胶质瘤的体积并降低血管密度；进一步研究发现AMD3100并不直接杀死肿瘤细胞，而是通过使肿瘤CXCL12/CXCR4轴发生紊乱进而抑制小鼠体内胶质细胞瘤的分化。Domanska等[38]发现AMD3100可以增强前列腺癌对多西他赛的敏感性。

Fahham等[39]发现在体内外CXCR4拮抗剂BKT140均可抑制非小细胞肺癌的生长，化疗药物与BKT140联合使用可以更有效地抑制非小细胞肺癌的增殖。Manu等[40]提出白花丹素是CXCR4受体的新型受体阻滞剂，能下调乳腺癌和胃癌细胞CXCR4蛋白的表达。Liang等[41]发现MSX-122可抑制功能性CXCR4，阻断肿瘤的转移。RNA干扰能有效地下调癌细胞CXCR4的表达从而抑制肿瘤浸润与转移[42-43]。Wang等[44]将CXCR4-RNAi质粒转染到肾透明细胞癌细胞系中，发现CXCR4表达下降，细胞增殖能力降低，CXCR4-shRNA同样可以增加肿瘤细胞的死亡率。

由于CXCR4也表达于多种免疫细胞、血管内皮细胞以及干细胞等正常细胞中，当与化疗药物联合使用时，针对CXCR4的抗肿瘤治疗可能会引起一些临床不良反应，例如CXCR4拮抗剂会动员正常造血干细胞，从而增加细胞毒性药物对正常造血源性细胞的毒性作用。

5 展 望

CXCR4在多种肿瘤的发生和发展中具有重要作用，开发稳定有效且不良反应较小的CXCR4拮抗药物将成为肿瘤治疗研究的新热点；基于CXCR4的基因治疗有广阔的前景，这将为肿瘤的治疗开辟新的途径。

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