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· 评述与综述 ·

白细胞介素-8与肿瘤免疫逃逸

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摘　要：IL-8 是趋化因子 CXC 家族的一员，是一种多细胞来源的细胞因子，在细胞的多种炎症反应中起调节作用，并且在自身免疫性疾病中也发挥重要作用。IL-8 通过与细胞膜上的 CXC 趋化因子受体 CXCR1 和 CXCR2 相互作用，激活偶联的 G 蛋白，由 G 蛋白进一步激活 PLC、AC、PLD、PI3K、JAK2 及 Ras 等信号分子，从而调控基因表达、细胞增殖和分化、细胞代谢、细胞运动及血管生成等多种细胞生命过程。IL-8 在多种恶性肿瘤细胞中表达量升高，其高表达与肿瘤细胞增殖、迁移、侵袭、血管生成及上皮间充质转化有密切联系。肿瘤免疫逃逸是肿瘤细胞产生和转移过程中的主要特征之一，肿瘤细胞可以通过多种机制使得人体免疫系统无法对其进行正常的识别和攻击，从而导致肿瘤细胞在体内存活，并且不断增殖和转移，而肿瘤细胞、免疫细胞以及肿瘤微环境中其他相关组分均可以促进肿瘤免疫逃逸。IL-8 作为一种炎性趋化因子，已被证明在肿瘤免疫逃逸中具有重要作用，其可通过诱导肿瘤细胞 PD-L1 表达、抑制肿瘤细胞凋亡、促进肿瘤细胞 EMT 进程、促进肿瘤微环境血管生成、招募免疫抑制性细胞等五个方面介导肿瘤免疫逃逸。IL-8 中和抗体和 CXCR1/2 拮抗剂在抗肿瘤治疗方面已经显示出较好的治疗效果。

关键词：IL-8；免疫逃逸；肿瘤微环境
中图分类号：R730.3　　**文献标志码：**A

Interleukin-8 and tumor immune escape

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Abstract: IL-8 is a multicellular cytokine which belongs to the CXC family of chemokines and plays regulatory roles in various inflammatory responses and autoimmune diseases. After binding to CXCR1 and CXCR2, which are members of the transmembrane G-protein coupled receptor family, IL-8 activates the G protein and downstream molecules, such as PLC, AC, PLD, PI3K, JAK2 and RAS, to regulate gene expression, cell proliferation and differentiation, cell metabolism, cell movement and angiogenesis. IL-8 is over-expressed in various tumors, which is closely related to proliferation, migration, invasion, angiogenesis and EMT of tumors. Tumor immune escape is one critical step in malignant progression of tumors. Tumors develop numerous strategies to escape immune surveillance to proliferate and metastasize. All of the tumor cells, immunosuppressive cells and inflammatory factors within tumor microenvironment facilitate tumor immune escape. As an inflammatory chemokine, IL-8 has been proved to play an important role in tumor immune escape by inducing the expression of PD-L1 in tumor cells, promoting the EMT and angiogenesis, inhibiting the apoptosis of tumor cells and recruiting immunosuppressive cells. IL-8 neutralizing antibodies and CXCR1/2 antagonists have shown certain anti-tumor effects.

Key words: IL-8; immune escape; tumor microenvironment

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肿瘤微环境 (tumor microenvironment, TME) 是肿瘤细胞和间质组织细胞之间复杂的动态相互作用网络，其主要由肿瘤细胞、免疫细胞、成纤维细胞、内皮细胞、细胞外基质以及多种多样的细胞因子构成 [1]。肿瘤的发生主要依赖于肿瘤细胞的产生和肿瘤微环境从抗肿瘤型向促肿瘤型的转变，抗肿瘤型肿瘤微环境抑制肿瘤的发生发展，促肿瘤型肿瘤微环境促进肿瘤的发生发展 [2-3]。肿瘤细胞可以通过与基质细胞和免疫细胞相互作用，或者通过分泌可溶性细胞因子，摆脱宿主的免疫识别和攻击，抑制宿主的免疫应答，使肿瘤微环境转化成有利于肿瘤发展迁移的微环境，从而使得肿瘤细胞在体内不断增殖发展，即肿瘤细胞免疫逃逸 [4]。最初，人们发现白细胞介素 8 (interleukin-8, IL-8) 作为一种细胞趋化因子，对中性粒细胞具有趋化作用。现在，越来越多的证据表明，IL-8 在肿瘤炎性微环境中作为一种促癌因子发挥重要作用。本文就肿瘤炎性微环境中重要的促癌因子 IL-8 及其在肿瘤免疫逃逸中的作用机制进行综述。

1 IL-8及其受体

1.1 IL-8

IL-8 最初作为中性粒细胞的趋化因子被发现并被提纯，其蛋白质结构由 1 个 N 环、3 个 β 折叠和 1 个 C 端的 α 螺旋组成，属于趋化因子 CXC 家族，因此也被称为趋化因子 CXCL8 [5-6]。后续研究表明，除了趋化中性粒细胞，IL-8 还可以诱导中性粒细胞形状改变、释放溶酶体酶类、诱导呼吸爆发并促进中性粒细胞黏附分子的表达 [7]。人类的 IL-8 编码基因定位于 4q13.3，含有 4 个外显子和 3 个内含子，约 3.1 kb [8]。该基因经翻译后，形成一个有 99 个氨基酸残基的前体，经不同蛋白酶水解 N 端的引导序列后，形成 4 种相对分子质量不同的 IL-8，其中由 72 个氨基酸残基组成的 IL-8 活性最强 [9]。IL-8 是一种多细胞来源的细胞因子，单核细胞、巨噬细胞、中性粒细胞、淋巴细胞、血管内皮细胞、皮肤成纤维细胞、角质细胞和肝细胞等都可以产生 IL-8 [10-13]。作为调节炎症反应的重要介质，IL-8 对炎症反应、免疫应答及创伤愈合等多种过程具有重要的调节作用，并且在自身免疫性疾病、代谢性疾病、生殖病理生理等多种病理环境中发挥重要作用。研究表明，在肝癌、结直肠癌、乳腺癌、胃癌、肺癌和食道肿瘤等多种恶性肿瘤细胞中也发现 IL-8 高表达，表明 IL-8 在肿瘤的发生和发展中发挥着重要的调控作用 [14-16]。

1.2 IL-8受体

IL-8 通过与细胞膜上的 CXC 趋化因子受体 1 (CXC chemokine receptor 1, CXCR1) 和 CXC 趋化因子受体 2 (CXC chemokine receptor 2, CXCR2) 相互作用，从而发挥其生物学功能。CXCR1 和 CXCR2 最早于 1991 年被克隆分离，属于 G 蛋白偶联受体家族 [17-18]。CXCR1 和 CXCR2 有 77% 的序列同源性，且以类似的亲和力与 IL-8 相结合 [17-18]。它们结构相似，均由 α- 螺旋穿过细胞膜形成 7 个跨膜区，有 3 个胞膜外环和 3 个胞浆环；N 端位于膜外，C 端位于膜内；C 端含有丝氨酸和苏氨酸残基，作为受体调节的磷酸化位点。而 CXCR1 与 CXCR2 的不同在于，二者具有不同的糖基化修饰 [19]。CXCR1 与 CXCR2 主要在中性粒细胞、$CD8^+$ T 细胞、肥大细胞、成纤维细胞、内皮细胞等细胞中表达 [20-22]。

IL-8 与受体 CXCR1/2 结合后，可激活与受体 CXCR1/2 偶联的 G 蛋白。G 蛋白是由 α、β 和 γ 三个亚基组成的异三聚体，在无活性状态下，G 蛋白的 α 亚基与 GDP 结合。CXCR1/2 与配体结合后，诱导 G 蛋白 α 亚基的 GDP 与 GTP 发生交换，从而使得 α 亚基与 β 和 γ 亚基形成的异二聚体发生解离 [23]。解离的 α-GTP 亚基与 β-γ 亚基可以通过激活磷脂酶 C (phospholipase C, PLC)、磷脂酰肌醇 3 激酶 (phosphatidylinositol 3 kinase, PI3K)、腺苷酸环化酶 (adenylate cyclase, AC) 等蛋白从而调控不同的细胞活动 [24-26]。当相应的细胞活动完成时，CXCR1/2 会通过同源脱敏和异源脱敏等多种途径迅速脱敏 [27]。例如，由 G- 蛋白偶联受体激酶 (G-protein coupled receptor kinase, GRK) 介导 CXCR1/2 发生磷酸化后，β- 抑制蛋白 1/2 (β-arrestin 1/2) 通过与磷酸化后的 CXCR1/2 结合，终止 G 蛋白效应，并刺激网格蛋白和转录因子激活蛋白 -2 (transcription factor activator protein-2, AP-2) 等蛋白，激活内吞机制，进而介导 CXCR1/2 内化，使得 CXCR1/2 信号脱敏 [28-31]。

1.3 IL-8-CXCR1/CXCR2信号通路的作用

IL-8 与其受体 CXCR1/2 结合后，主要通过以下几种信号途径发挥生理效应 (图 1)。(1) IL-8 与 CXCR1/2 结合后，激活偶联的 G 蛋白，由 G 蛋白进一步激活 PLC，PLC 进一步作用于质膜上的磷脂酰肌醇 -4,5- 二磷酸 (phosphatidylinositol 4,5-bisphosphate, PIP2)，使其水解为三磷酸肌醇 (inositol-1,4,5-triphosphate, IP3) 和二酰甘油 (diacylglycerol, DAG)。其中，DAG 进一步激活蛋白激酶 C (protein kinase C,

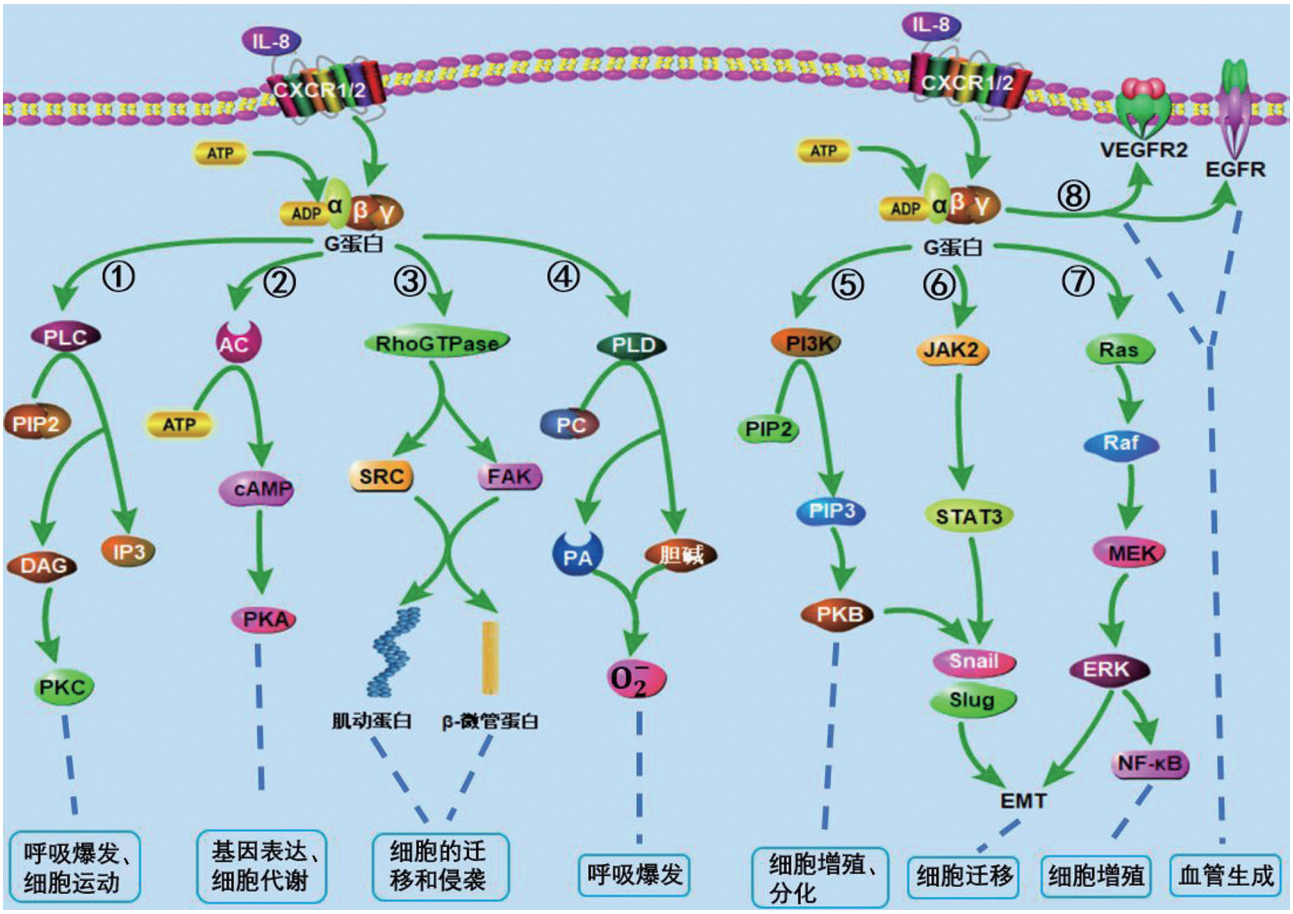

图1　IL-8-CXCR1/CXCR2信号通路的作用

PKC)，PKC 可进一步激活多种蛋白，引起呼吸爆发，影响细胞骨架的运动和巨噬细胞抗原 -1 (macrophage associated antigen-1, Mac-1) 介导的细胞黏附等 [32-34]；而 IP3 可以通过刺激内质网的膜蛋白引起钙离子波动，进而调节多种钙调蛋白的活性 [35]。(2) IL-8 可以通过激活 G 蛋白进而激活腺苷酸环化酶 (AC)，而 AC 可以通过将 ATP 转化为环磷酸腺苷 (cyclic AMP, cAMP) 引起 cAMP 浓度的升高，进而激活蛋白激酶 A (protein kinase A, PKA)。PKA 可以通过改变多种蛋白的活性，进而影响多种细胞代谢进程 [36]。(3) IL-8 通过与 CXCR1/2 结合，激活 RhoGTPase 家族成员，诱导 Src 蛋白激酶和黏着斑激酶 (focal adhesion kinase, FAK) 等多种蛋白激酶的活化，从而诱导肌动蛋白和 β- 微管蛋白重新定位，以促进细胞的迁移和侵袭 [37-40]。(4) IL-8 与 CXCR1/2 结合后，通过 G 蛋白激活磷脂酶 D (phospholipases D, PLD)，PLD 将磷脂酰胆碱 (phosphatidylcholine, PC) 转化为磷脂酸 (phosphatidic acid, PA) 和胆碱，进而激活氧合酶，生成超氧阴离子，从而刺激中性粒细胞的呼吸爆发 [41-42]。(5) IL-8 与 CXCR1/2 结合后激活 G 蛋白，在 G 蛋白的介导下，PI3K 将 PIP2 转化为磷脂酰 -3,4,5- 三磷酸 (phosphatidylinositol 3,4,5-trisphosphate, PIP3)，然后由 PIP3 激活蛋白激酶 B (protein kinase B, PKB)，而 PKB 可以通过激活多种蛋白进而产生多种细胞应答。例如，PKB 可以通过促进哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR)、基质金属蛋白酶 9 (matrix metalloprotein 9, MMP-9) 等的表达，并抑制半胱氨酸天冬氨酸蛋白酶 -3 (caspase-3) 等的表达，导致细胞出现增殖分化异常 [43-45]。PKB 还可以促进 Snail 蛋白和锌指转录因子 Slug 蛋白的表达，使得肿瘤细胞发生上皮间充质转化 (epithelial-mesenchymal transition, EMT)，提高肿瘤细胞的浸润性 [46]。(6) IL-8 与 CXCR1/2 结合后，可通过 G 蛋白激活 JAK2 蛋白，进而通过 JAK2/STAT3/Snail 信号通路激活细胞的 EMT 进程 [47]。(7) IL-8 通过与 CXCR1/2 结合激活 G 蛋白，活化的 G 蛋白进而依次激活 Ras、Raf 和 MEK 蛋白，最终激活细胞外调节蛋白激酶 (extracellular regulated protein kinases, ERK)，影响细胞增殖、细胞运动等多种细胞反应 [48-49]。例如，

IL-8 可通过 Raf 激活 ERK，进而促进核因子 -κB (nuclear factor kappa-B, NF-κB) 的激活，对细胞增殖分裂和分化的进程产生影响 [50]；此外，还可以通过 ERK 的激活促进细胞的 EMT 进程 [51]。(8) IL-8 与 CXCR1/2 结合后，CXCR1/2 通过 Src 激酶介导的受体磷酸化反式激活血管内皮生长因子受体 2 (vascular endothelial growth factor receptor 2, VEGFR2)[52]；或者通过NF-κB途径诱导血管内皮生长因子(vascular endothelial growth factor, VEGF) 的表达，进而刺激 VEGFR2 的活化 [53]。而且，CXCR1/2 还可以通过受体磷酸化反式激活表皮生长因子受体 (epithelial growth factor receptor, EGFR)，共同介导内皮细胞迁移和毛细血管形成，促进肿瘤生长 [54-55]。

2 肿瘤微环境下的肿瘤免疫逃逸

免疫系统在肿瘤的发生和发展中发挥着复杂的作用。免疫编辑学说提出，免疫系统和肿瘤细胞之间的相互关系可以分成 3 个阶段，包括免疫清除、免疫平衡和免疫逃逸 [56]。在肿瘤免疫逃逸阶段，肿瘤细胞可以通过多种机制使得人体免疫系统无法对其进行正常的识别和攻击，从而导致肿瘤细胞在体内存活，并且不断增殖和转移 [56]。在肿瘤微环境中，肿瘤细胞、免疫细胞和各种细胞因子对肿瘤细胞的免疫逃逸均有影响 [57]。

2.1 肿瘤细胞引起的肿瘤免疫逃逸

肿瘤细胞可以通过多种途径调节自身基因表达，进而促进自身免疫逃逸。(1) 肿瘤表面主要组织相容性复合体 (major histocompatibility complex, MHC) 的表达降低。在大多数肿瘤细胞中，MHC 类分子通常低表达甚至不表达 [58]。由于缺少抗原呈递，T 淋巴细胞不能正常活化，无法对肿瘤细胞形成有效杀伤 [59]。(2) 肿瘤细胞抑制自身凋亡。肿瘤细胞可以促进抗凋亡基因 *API5* 的表达，通过 FGFR1/PKCδ/ERK 途径引起促凋亡因子 BIM 不断降解，使得细胞凋亡受到抑制 [60]；肿瘤细胞也可通过下调 Fas 的表达，逃脱免疫系统介导的细胞凋亡 [61]。(3) 肿瘤细胞抗原调变 (antigenic modulation)。肿瘤细胞可以通过 DNA 甲基化等途径使抗原基因表达沉默，从而导致免疫逃逸 [62]。(4) 肿瘤细胞共刺激信号缺乏。肿瘤细胞中 B7 家族分子 B7-1 (CD80)、B7-2 (CD86) 表达量极低，相反还高表达 B7-H1 (PD-L1)、B7-H3、B7-H4、B7-H6 等负刺激分子，抑制共刺激因子提供的第二信号，进而抑制 T 细胞的活化，促进肿瘤的免疫逃逸 [63-66]。

2.2 免疫细胞与肿瘤免疫逃逸

肿瘤微环境中聚集了大量的抑制性免疫细胞，它们不仅不会攻击肿瘤细胞，反而会抑制其他免疫细胞的免疫应答，促进肿瘤细胞的免疫逃逸。(1) 调节性 T 细胞 (regulatory T cells, Tregs)。肿瘤细胞可以通过趋化因子招募 Tregs，而且肿瘤微环境中的转化生长因子 -β (transforming growth factor-β, TGF-β)、白细胞介素 10 (interleukin-10, IL-10) 等细胞因子可以促进 Tregs 的增殖 [67]。Tregs 可以通过多种途径抑制免疫应答，例如：① Tregs 可以通过分泌 TGF-β、IL-10 等免疫抑制因子抑制效应 T 细胞 (effector T cells) 和自然杀伤细胞 (natural killer cells, NK 细胞) 的增殖 [68]；② Tregs 也可以通过分泌颗粒酶 B 和穿孔蛋白杀死效应 T 细胞和 NK 细胞 [69]；③ Tregs 还可以抑制抗原呈递细胞的呈递作用，抑制免疫细胞应答 [70]。(2) 髓源性抑制细胞 (myeloid-derived suppressor cells, MDSCs)。在肿瘤微环境中，白细胞介素 1β (interleukin-1β, IL-1β)、白细胞介素 6 (interleukin-6, IL-6) 和前列腺素 E2 (prostaglandin E2, PGE2) 等炎症因子可以募集 MDSCs[71]，而 MDSCs 可以通过多种途径抑制免疫应答，例如：① MDSCs 可以通过分泌 IL-10 和 TGF-β 诱导 Tregs 的产生，间接抑制免疫反应 [72]；② MDSCs 可以通过摄取精氨酸和高表达精氨酸酶，消耗 T 细胞活化所必需的精氨酸来抑制其活化 [73]；③ MDSCs 可以通过半胱氨酸剥夺来抑制 T 细胞的活化 [74]；④ MDSCs 也可以通过高表达诱导型一氧化氮合酶 (inducible nitric oxide synthetase, iNOS) 产生 NO，从而诱导 T 细胞凋亡 [75]。

除了上述的 Tregs、MDSCs 等免疫抑制性细胞可以在肿瘤微环境中发挥免疫抑制作用，免疫系统中的巨噬细胞、中性粒细胞等免疫细胞在肿瘤微环境中也具有免疫抑制作用。例如，肿瘤相关巨噬细胞 (tumor associated macrophages, TAMs) 可以通过分泌 IL-10、TNF-α 和 INF-γ 诱导肿瘤细胞 B7-H4 的表达，进而抑制效应 T 细胞的细胞毒性，或者通过释放 EGF 与肿瘤细胞释放的 CSF-1 相互作用，促进肿瘤细胞的迁移 [76-77]。而肿瘤相关中性粒细胞 (tumor-associated neutrophils, TANs) 可以通过产生血管生长因子促进血管生长，为肿瘤迁移形成通道，或者通过分泌胶原酶 - IV、乙酰肝素酶和人中性粒细胞弹性蛋白酶降解细胞外基质，进而促进肿瘤免疫逃逸 [78-80]。TANs 也可以通过分泌精氨酸酶消耗精氨酸，使得 T 细胞饥饿，抑制 T 淋巴细胞的免疫

活性，或者通过分泌 CCL17 招募 Tregs 等免疫抑制细胞，形成免疫抑制微环境[81-82]。

2.3　肿瘤微环境其他组分与免疫逃逸

在肿瘤微环境中，肿瘤细胞和基质细胞可分泌 TGF-β、IL-4、IL-6、COX-2、IL-10、VEGF 等大量的免疫抑制性因子和炎症因子，进而通过招募免疫抑制性细胞、促进免疫细胞凋亡、促进血管生成等多种途径，形成免疫抑制性肿瘤微环境，促进肿瘤发生发展[83-86]。细胞因子在不同环境下的作用可能有所不同，存在肿瘤特异性[87]。而且，肿瘤细胞会通过代谢重编程增强有氧糖酵解，增加葡萄糖的摄取和消耗，产生大量乳酸，形成酸性缺氧环境，进而抑制免疫细胞的正常代谢[88]。甚至在肿瘤微环境中，血小板自身的 MHC-Ⅰ会转移到肿瘤细胞上，使得肿瘤细胞获得假正常表型，干扰免疫细胞的识别[89]。

3　IL-8介导的肿瘤免疫逃逸

前文第一部分提到 IL-8 是一种多细胞来源的细胞因子，单核细胞、巨噬细胞、中性粒细胞、淋巴细胞、血管内皮细胞、皮肤成纤维细胞、角质细胞和肝细胞等都可以产生 IL-8。肿瘤细胞及肿瘤微环境中的肿瘤相关成纤维细胞、肿瘤相关巨噬细胞等多种细胞都表达 IL-8，但到底哪一种细胞来源的 IL-8 起主要作用，目前尚无定论[90-93]。例如，2019 年的一项研究发现，在胃癌肿瘤微环境中，IL-8 的主要来源是微环境中的巨噬细胞[94]；而同一年另有研究发现，网膜组织来源的 IL-8 在胃癌腹膜转移发生发展的过程中发挥了重要作用[95]。此外，2016 年的一项研究发现，肿瘤相关成纤维细胞来源的 IL-8 可以促进黑色素瘤细胞的迁移和侵袭[96]。研究表明，IL-8 在肿瘤细胞的免疫逃逸中也发挥重要作用，主要在诱导 PD-L1 表达、抑制肿瘤细胞凋亡、促进肿瘤细胞 EMT 进程、促进肿瘤微环境血管生成、招募免疫抑制性细胞等方面发挥重要作用，具体阐述如下 (图 2)。

3.1　诱导PD-L1的表达

IL-8 可以通过作用于肿瘤细胞影响肿瘤细胞表面 PD-L1 的表达，诱导 $CD8^+$ T 细胞凋亡，从而抑制 T 细胞抗肿瘤免疫应答。在胃癌组织中，胃癌间充质干细胞可以通过分泌 IL-8 激活肿瘤细胞的 STAT3 通路和 AKT/mTOR 通路，共同上调 c-Myc 的表达，进而激活肿瘤细胞 PD-L1 的表达，抑制效

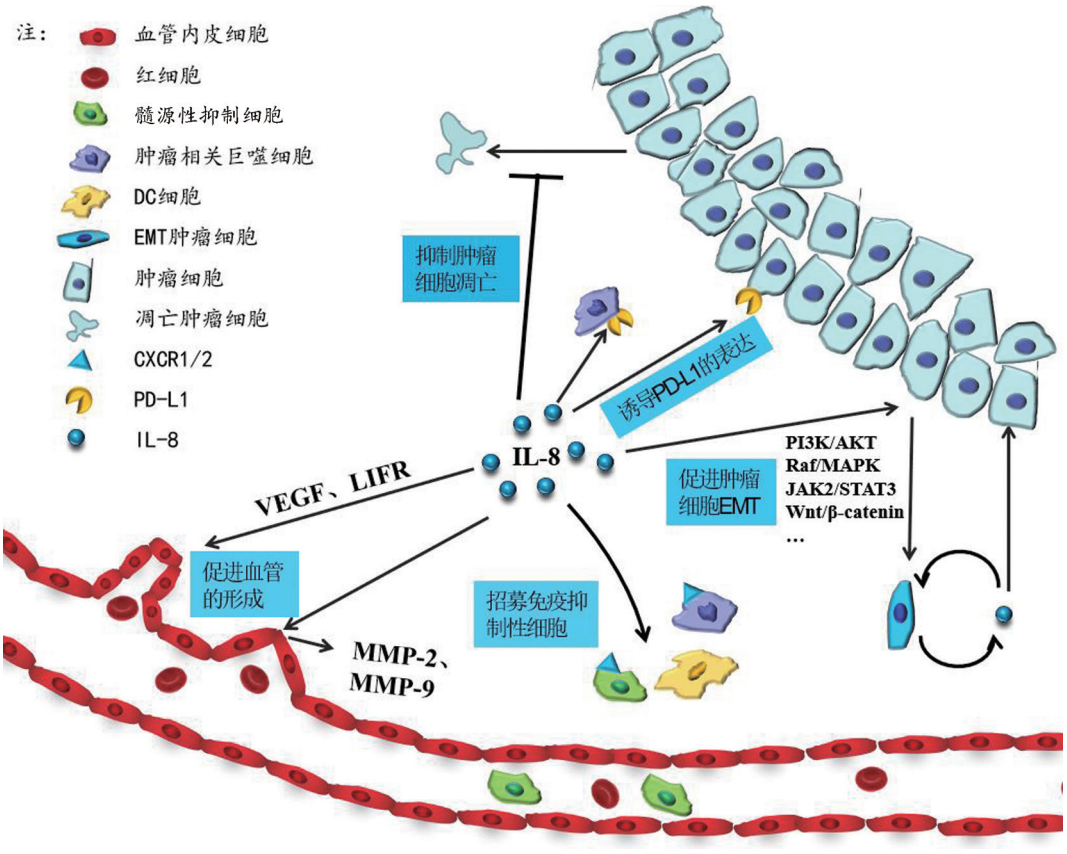

图2　IL-8在肿瘤免疫逃逸中的作用

应 T 细胞的免疫应答，达到促进肿瘤细胞免疫逃逸的目的 [97]。在非小细胞肺癌和黑色素瘤中，IL-8 可以作为指示分子，其水平的变化能反映和预测抗 PD-1 治疗的疗效 [98]。2019 年的一项研究表明，胃癌肿瘤微环境中巨噬细胞来源的 IL-8 可以诱导肿瘤相关巨噬细胞 PD-L1 的表达，诱导 T 细胞凋亡，进而抑制效应 T 细胞的免疫应答，形成免疫抑制微环境，促进肿瘤细胞免疫逃逸 [94]。

3.2 抑制肿瘤细胞凋亡

IL-8 可以通过抑制肿瘤细胞凋亡来提高肿瘤细胞的免疫耐受，进而促进肿瘤细胞免疫逃逸。例如，IL-8 可以通过提高多药耐药基因 MDR1 以及 bcl-2 和 bcl-xl 等多种凋亡抑制蛋白基因的表达，或者下调 caspase-3 的表达等多种方式，抑制肿瘤细胞凋亡，进而促进肿瘤细胞对奥沙利铂、顺铂、紫杉醇、5-氟尿嘧啶等多种化疗药物的耐药性 [99-101]。IL-8 也可以通过降解细胞周期调节蛋白 CDK1，抑制核纤层蛋白磷酸化引起的核退化，进而抑制细胞凋亡。IL-8 还可以通过上调 MUC1 黏蛋白，阻止 caspase 依赖性和非依赖性凋亡，保护肿瘤细胞免受细胞毒效应引发的细胞凋亡，促进肿瘤细胞的免疫逃逸 [102-103]。鉴于 IL-8 在肿瘤微环境中具有促进肿瘤细胞抗凋亡和提高肿瘤细胞耐药性的作用，靶向 IL-8 及其受体有望成为逆转肿瘤细胞耐药的新策略。

3.3 促进肿瘤细胞上皮间充质转化

在肿瘤细胞发生 EMT 的过程中，肿瘤细胞波形蛋白表达水平升高，而 E- 钙黏蛋白表达水平降低，从而使肿瘤细胞丧失细胞极性和细胞间连接，增强了迁移和侵袭的特性 [104-105]。一旦上皮肿瘤细胞发生了 EMT，便会进一步产生 IL-8 等促进 EMT 的细胞因子，通过自分泌反馈回路维持间充质状态，并且诱导邻近肿瘤细胞也发生 EMT [106]。IL-8 可以通过 PI3K/AKT、Raf/MAPK 和 JAK2/STAT3 等多种途径，激活 Snail、Twist、Slug 等 EMT 相关转录因子，促进肿瘤细胞 EMT，进而促进肿瘤免疫逃逸，这些在第一部分中已详细叙述。另外，IL-8 作为 Wnt/β-catenin 的上游调节因子，可以通过诱导肿瘤细胞 Wnt 通路的激活，抑制 β-catenin 的降解，进而诱导肿瘤细胞发生 EMT [107]。IL-8 也可以通过和 MMPs 相互协同，共同诱导肿瘤细胞的 EMT 进程 [108]。

3.4 促进血管的形成

大量实验研究表明，在黑色素瘤、卵巢癌等多种癌症中，IL-8 与肿瘤血管生成有关 [109-110]，甚至可能是肿瘤血管生成所必需的 [111]。IL-8 可以作为缺氧诱导因子 -1 的代偿途径，由 NF-κB 介导，刺激 VEGF 的表达，促进血管生长 [112]；也有报道称，IL-8 促进血管生成与 VEGF 无关，而是参与了白血病抑制因子受体 (leukemia inhibitory factor receptor, LIFR) 诱导的血管生成 [100,113]。IL-8 也可以通过促进内皮细胞 bcl-xl 高表达，同时降低 bax 表达，进而抑制内皮细胞凋亡，促进内皮细胞增殖、迁移，提高其成管能力，促进血管形成 [114]。IL-8 还可以通过增强内皮细胞 MMP-2、MMP-9 表达，使其降解细胞外基质，促进内皮细胞的迁移，进而促进血管生成 [115]。另外，也有证据表明，IL-8 可以通过 CXCR2 激活细胞 EGFR/AKT/NF-κB 途径，进而促进血管生成 [110]。

3.5 招募免疫抑制性细胞

如第二部分所述，肿瘤微环境中存在多种免疫抑制性细胞，可促进肿瘤细胞的免疫逃逸。研究表明，IL-8 对 MDSCs、TAMs 等多种免疫抑制性细胞均有一定的招募作用。Asfaha 等 [116] 通过将 IL-8 编码基因导入小鼠发现，IL-8 可以通过募集 MDSCs 加速结肠癌和胃癌的发生。IL-8 对 MDSCs 的招募作用可能与 MDSCs 上 CXCR1 和 CXCR2 高表达有关，而 CXCR2 又是 MDSCs 转移所必需的，因此 IL-8 可能通过浓度梯度对 MDSCs 进行招募 [111,117]。也有证据表明，IL-8 可通过 TGF-β 介导的 Smad2/3 信号转导，将 MDSCs 诱导到食管鳞癌的肿瘤微环境中 [118]。而且，IL-8 和 IL-6 可以通过影响造血细胞分化，增加肿瘤微环境中 MDSCs 的数量。IL-8 可以通过动员癌症患者骨髓中的造血祖细胞，使它们通过血液循环被肿瘤微环境中的 IL-6 诱导分化为 MDSCs [111]。在肿瘤微环境中，IL-8 也可以招募 TAMs。例如，张明杰教授发现，在胰腺癌小鼠模型中，$CXCR1/2^{+}CD68^{+}$ 巨噬细胞较正常组明显偏多，认为可能是肿瘤来源的 IL-8 通过 CXCL8-CXCR1/2 轴将 TAMs 募集到肿瘤中，以促进胰腺癌细胞免疫逃逸 [119]。也有研究表明，IL-8 对于 TAMs 的招募机理可能与 PI3K/AKT 通路有关 [120]。此外，肿瘤细胞来源的 IL-8 可以通过吸引树突状细胞 (dendritic cells, DCs)，使其长期暴露于 IL-8 微环境中，造成 DCs 对于体内迁移的敏感性降低，从而形成免疫抑制肿瘤微环境，促进肿瘤细胞的免疫逃逸 [109]。

4 抗IL-8/CXCR1/2信号通路在肿瘤治疗中的作用

基于 IL-8/CXCR1/2 在肿瘤发生发展中的关键

作用，IL-8 中和抗体和 CXCR1/2 拮抗剂的研究已陆续展开，并且显示出了较好的抗肿瘤效果。例如，研究发现，IL-8 的中和抗体 ABX-IL8 可以抑制黑素瘤细胞的 MMP-2 启动子活性和胶原酶活性，进而抑制肿瘤血管的生成，也发现 ABX-IL8 在体外可以直接抑制血管内皮细胞形成毛细血管样网络。肿瘤血管生成的抑制会进一步造成肿瘤细胞的凋亡，抑制肿瘤的发生和转移 [121]。一种新型的全人源单克隆抗体 HuMax-IL8 经Ⅰ期临床试验被证实安全且耐受性良好。研究表明，在三阴性乳腺癌中，HuMax-IL8 可以削弱肿瘤细胞的间充质特性，减少肿瘤部位 MDSCs 募集，还可以增强乳腺癌细胞对 NK 细胞和特异性 T 细胞介导的细胞裂解的易感性，有助于免疫系统介导的细胞杀伤，目前正在研究评估其和多西紫杉醇等其他肿瘤疗法的组合疗效 [122]。研究人员还研制了多种 CXCR1/2 拮抗剂。例如，Reparixin 是一种 CXCR1/2 拮抗剂，其处理卵巢癌细胞后，卵巢癌细胞的 E- 钙黏蛋白水平升高，导致 EMT 活性降低，卵巢癌细胞的迁移受到抑制 [107]。Reparixin 处理晚期肝癌细胞后，肝癌细胞的干细胞特性受到抑制，并且对索拉非尼的敏感性显著增加 [123]。采用 CXCR2 的另一种抑制剂 AZ13381758 处理胰腺癌细胞后发现，AZ13381758 增强了 T 细胞的滤过，引起 T 细胞积聚，进而可诱导基质重塑，增强吉西他滨等药物的有效性 [124]。在结肠癌小鼠异种移植瘤中，CXCR1/2 的别构拮抗剂 SCH527123 处理可抑制肿瘤生长和血管生成，并提高肿瘤细胞对奥沙利铂治疗的敏感性 [125]。

5 展望

研究发现，肿瘤衍生的细胞因子 IL-8 作为循环肿瘤细胞的引诱剂，可以诱导 $CXCR1/2^{+}$ 肿瘤细胞向 IL-8 高表达部位迁移和定植；而如果将肿瘤细胞中的 CXCR1/2 敲除，这种现象就会消失。而且，IL-8 可以通过募集中性粒细胞，使其分泌更多的 IL-8，这种级联效应有助于转移前炎性微环境的形成，从而为肿瘤细胞归巢做准备。因此，IL-8 分子可能在肿瘤发生和转移的整个过程中均具有重要作用，其在肿瘤发生前期，通过促进血管生成并且抑制肿瘤细胞凋亡，促进肿瘤的发生和生长。IL-8 还可以通过促进肿瘤细胞 EMT，在促进肿瘤细胞转移的过程中发挥重要作用。最后，IL-8 通过趋化中性粒细胞使其向转移灶聚集，进而分泌更多的 IL-8，诱导肿瘤细胞的定植归巢。目前，IL-8 中和抗体和 CXCR1/2 拮抗剂在抗肿瘤治疗方面显示出较好的治疗效果，但是 IL-8 在肿瘤免疫逃逸过程中的具体分子机制仍存在争议，特别是 IL-8 对于免疫抑制性细胞的招募机制尚未阐明。此外，肿瘤微环境是一个极其复杂的动态相互作用网络，包括多种细胞和细胞因子，因此，在肿瘤发生发展这个复杂的病理过程中，确认 IL-8 在此反应通路中所处的位置显得尤为重要。推动 IL-8 在肿瘤发生发展过程中的相关分子机理的研究，对于抗癌药物的开发和肿瘤免疫疗法的改进均具有重要意义。

[参 考 文 献]

[1] Wu T, Dai Y. Tumor microenvironment and therapeutic response. Cancer Lett, 2017, 387: 61-8

[2] Li D, Jiao W, Liang Z, et al. Variation in energy metabolism arising from the effect of the tumor microenvironment on cell biological behaviors of bladder cancer cells and endothelial cells. Biofactors, 2020, 46: 64-75

[3] Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science, 2011, 331: 1565-70

[4] Ryu D, Kim SJ, Hong Y, et al. Alterations in the transcriptional programs of myeloma cells and the microenvironment during extramedullary progression affect proliferation and immune evasion. Clin Cancer Res, 2020, 26: 935-44

[5] Waugh DJ, Wilson C. The interleukin-8 pathway in cancer. Clin Cancer Res, 2008, 14: 6735-41

[6] Rajarathnam K, Clark-Lewis I, Sykes BD. 1H NMR solution structure of an active monomeric interleukin-8. Biochemistry, 1995, 34: 12983-90

[7] Matsushima K, Baldwin ET, Mukaida N. Interleukin-8 and MCAF: novel leukocyte recruitment and activating cytokines. Chem Immunol, 1992, 51: 236-65

[8] Mukaida N, Shiroo M, Matsushima K. Genomic structure of the human monocyte-derived neutrophil chemotactic factor IL-8. J Immunol, 1989, 143: 1366-71

[9] Brat DJ, Bellail AC, Van Meir EG. The role of interleukin-8 and its receptors in gliomagenesis and tumoral angiogenesis. Neuro Oncol, 2005, 7: 122-33

[10] Peveri P, Walz A, Dewald B, et al. A novel neutrophil-activating factor produced by human mononuclear phagocytes. J Exp Med, 1988, 167: 1547-59

[11] Strieter RM, Kunkel SL, Showell HJ, et al. Monokine-induced gene expression of a human endothelial cell-derived neutrophil chemotactic factor. Biochem Biophys Res Commun, 1988, 156: 1340-5

[12] Kwon OJ, Au BT, Collins PD, et al. Tumor necrosis factor-induced interleukin-8 expression in cultured human airway epithelial cells. Am J Physiol, 1994, 267: L398-405

[13] Wanninger J, Neumeier M, Weigert J, et al. Adiponectin-stimulated CXCL8 release in primary human hepatocytes is regulated by ERK1/ERK2, p38 MAPK, NF-κB, and STAT3 signaling pathways. Am J Physiol Gastrointest

Liver Physiol, 2009, 297: G611-8
[14] Xu H, Zeng Y, Liu L, et al. PRL-3 improves colorectal cancer cell proliferation and invasion through IL-8 mediated glycolysis metabolism. Int J Oncol, 2017, 51: 1271-9
[15] Benoy IH, Salgado R, Van Dam P, et al. Increased serum interleukin-8 in patients with early and metastatic breast cancer correlates with early dissemination and survival. Clin Cancer Res, 2004, 10: 7157-62
[16] Li W, Lin S, Li W, et al. IL-8 interacts with metadherin promoting proliferation and migration in gastric cancer. Biochem Biophys Res Commun, 2016, 478: 1330-7
[17] Holmes WE, Lee J, Kuang WJ, et al. Structure and functional expression of a human interleukin-8 receptor. Science, 1991, 253: 1278-80
[18] Murphy PM, Tiffany HL. Cloning of complementary DNA encoding a functional human interleukin-8 receptor. Science, 1991, 253: 1280-3
[19] Murdoch C, Finn A. Chemokine receptors and their role in inflammation and infectious diseases. Blood, 2000, 95: 3032-43
[20] Liewert I, Ehrig K, Alban S. Effects of fucoidans and heparin on reactions of neutrophils induced by IL-8 and C5a. Carbohydr Polym, 2017, 165: 462-9
[21] Namba S, Nakano R, Kitanaka T, et al. ERK2 and JNK1 contribute to TNF-α-induced IL-8 expression in synovial fibroblasts. PLoS One, 2017, 12: 182-23
[22] Ju L, Zhou Z, Jiang B, et al. Autocrine VEGF and IL-8 promote migration via Src/Vav2/Rac1/PAK1 signaling in human umbilical vein endothelial cells. Cell Physiol Biochem, 2017, 41: 1346-59
[23] Damaj BB, McColl SR, Mahana W, et al. Physical association of Gi2α with interleukin-8 receptors. J Biol Chem, 1996, 271: 12783-9
[24] Wu Y, Wang S, Farooq SM, et al. A chemokine receptor CXCR2 macromolecular complex regulates neutrophil functions in inflammatory diseases. J Biol Chem, 2012, 287: 5744-55
[25] Knall C, Worthen GS, Johnson GL. Interleukin 8-stimulated phosphatidylinositol-3-kinase activity regulates the migration of human neutrophils independent of extracellular signal-regulated kinase and p38 mitogen-activated protein kinases. Proc Natl Acad Sci USA, 1997, 94: 3052-7
[26] Hall DA, Beresford IJ, Browning C, et al. Signalling by CXC-chemokine receptors 1 and 2 expressed in CHO cells: a comparison of calcium mobilization, inhibition of adenylyl cyclase and stimulation of GTPγS binding induced by IL-8 and GROα. Br J Pharmacol, 1999, 126: 810-8
[27] Richardson RM, Pridgen BC, Haribabu B, et al. Differential cross-regulation of the human chemokine receptors CXCR1 and CXCR2. Evidence for time-dependent signal generation. J Biol Chem, 1998, 273: 23830-6
[28] Barlic J, Khandaker MH, Mahon E, et al. β-arrestins regulate interleukin-8-induced CXCR1 internalization. J Biol Chem, 1999, 274: 16287-94
[29] Yang W, Wang D, Richmond A. Role of clathrin-mediated endocytosis in CXCR2 sequestration, resensitization, and signal transduction. J Biol Chem, 1999, 274: 11328-33
[30] Raghuwanshi SK, Su Y, Singh V, et al. The chemokine receptors CXCR1 and CXCR2 couple to distinct G protein-coupled receptor kinases to mediate and regulate leukocyte functions. J Immunol, 2012, 189: 2824-32
[31] Kirchhausen T, Bonifacino JS, Riezman H. Linking cargo to vesicle formation: receptor tail interactions with coat proteins. Curr Opin Cell Biol, 1997, 9: 488-95
[32] Richardson RM, Ali H, Pridgen BC, et al. Multiple signaling pathways of human interleukin-8 receptor A. Independent regulation by phosphorylation. J Biol Chem, 1998, 273: 10690-5
[33] Nasser MW, Marjoram RJ, Brown SL, et al. Cross-desensitization among CXCR1, CXCR2, and CCR5: role of protein kinase C-ε. J Immunol, 2005, 174: 6927-33
[34] Takami M, Terry V, Petruzzelli L. Signaling pathways involved in IL-8-dependent activation of adhesion through Mac-1. J Immunol, 2002, 168: 4559-66
[35] Wu D, LaRosa GJ, Simon MI. G protein-coupled signal transduction pathways for interleukin-8. Science, 1993, 261: 101-3
[36] Zimmermann S, Wagner C, Muller W, et al. Induction of neutrophil chemotaxis by the quorum-sensing molecule N-(3-oxododecanoyl)-L-homoserine lactone. Infect Immun, 2006, 74: 5687-92
[37] Lee LF, Louie MC, Desai SJ, et al. Interleukin-8 confers androgen-independent growth and migration of LNCaP: differential effects of tyrosine kinases Src and FAK. Oncogene, 2004, 23: 2197-205
[38] Cohen-Hillel E, Yron I, Meshel T, et al. CXCL8-induced FAK phosphorylation via CXCR1 and CXCR2: cytoskeleton- and integrin-related mechanisms converge with FAK regulatory pathways in a receptor-specific manner. Cytokine, 2006, 33: 1-16
[39] Feniger-Barish R, Yron I, Meshel T, et al. IL-8-induced migratory responses through CXCR1 and CXCR2: association with phosphorylation and cellular redistribution of focal adhesion kinase. Biochemistry, 2003, 42: 2874-86
[40] McFarlane S, Seaton A, Chacko A, et al. 45 POSTER focal adhesion kinase is a key signalling intermediate in interleukin-8 promoted chemotaxis and adhesion of prostate cancer cells to bone marrow endothelium. EJC Suppl, 2006, 4: 18
[41] L'Heureux GP, Bourgoin S, Jean N, et al. Diverging signal transduction pathways activated by interleukin-8 and related chemokines in human neutrophils: interleukin-8, but not NAP-2 or GROα, stimulates phospholipase D activity. Blood, 1995, 85: 522-31
[42] Sozzani S, Agwu DE, Ellenburg MD, et al. Activation of phospholipase D by interleukin-8 in human neutrophils. Blood, 1994, 84: 3895-901
[43] Zheng H, Liu JF. Studies on the relationship between P13K/AKT signal pathway-mediated MMP-9 gene and lung cancer. Eur Rev Med Pharmacol Sci, 2017, 21: 753-9
[44] Hermida MA, Dinesh Kumar J, Leslie NR. GSK3 and its

interactions with the PI3K/AKT/mTOR signalling network. Adv Biol Regul, 2017, 65: 5-15
[45] Bhowmik T, Gomes A. NKCT1 (purified Naja kaouthia protein toxin) conjugated gold nanoparticles induced Akt/mTOR inactivation mediated autophagic and caspase 3 activated apoptotic cell death in leukemic cell. Toxicon, 2016, 121: 86-97
[46] Okui G, Tobiume K, Rizqiawan A, et al. AKT primes snail-induced EMT concomitantly with the collective migration of squamous cell carcinoma cells. J Cell Biochem, 2013, 114: 2039-49
[47] Fu XT, Dai Z, Song K, et al. Macrophage-secreted IL-8 induces epithelial-mesenchymal transition in hepatocellular carcinoma cells by activating the JAK2/STAT3/Snail pathway. Int J Oncol, 2015, 46: 587-96
[48] Knall C, Young S, Nick JA, et al. Interleukin-8 regulation of the Ras/Raf/mitogen-activated protein kinase pathway in human neutrophils. J Biol Chem, 1996, 271: 2832-8
[49] Roskoski R Jr. ERK1/2 MAP kinases: structure, function, and regulation. Pharmacol Res, 2012, 66: 105-43
[50] Yu Z, Ye S, Hu G, et al. The RAF-MEK-ERK pathway: targeting ERK to overcome obstacles to effective cancer therapy. Future Med Chem, 2015, 7: 269-89
[51] Zhang H, Sun JD, Yan LJ, et al. PDGF-D/PDGFRβ promotes tongue squamous carcinoma cell (TSCC) progression via activating p38/AKT/ERK/EMT signal pathway. Biochem Biophys Res Commun, 2016, 478: 845-51
[52] Petreaca ML, Yao M, Liu Y, et al. Transactivation of vascular endothelial growth factor receptor-2 by interleukin-8 (IL-8/CXCL8) is required for IL-8/CXCL8-induced endothelial permeability. Mol Biol Cell, 2007, 18: 5014-23
[53] Martin D, Galisteo R, Gutkind JS. CXCL8/IL8 stimulates vascular endothelial growth factor (VEGF) expression and the autocrine activation of VEGFR2 in endothelial cells by activating NFκB through the CBM (Carma3/Bcl10/Malt1) complex. J Biol Chem, 2009, 284: 6038-42
[54] Kyriakakis E, Cavallari M, Pfaff D, et al. IL-8-mediated angiogenic responses of endothelial cells to lipid antigen activation of iNKT cells depend on EGFR transactivation. J Leukoc Biol, 2011, 90: 929-39
[55] Schraufstatter IU, Trieu K, Zhao M, et al. IL-8-mediated cell migration in endothelial cells depends on cathepsin B activity and transactivation of the epidermal growth factor receptor. J Immunol, 2003, 171: 6714-22
[56] Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science, 2011, 331: 1565-70
[57] Jiang X, Wang J, Deng X, et al. Role of the tumor microenvironment in PD-L1/PD-1-mediated tumor immune escape. Mol Cancer, 2019, 18: 10
[58] Garrido F, Ruiz-Cabello F, Aptsiauri N. Rejection versus escape: the tumor MHC dilemma. Cancer Immunol Immunother, 2017, 66: 259-71
[59] Yoshihama S, Roszik J, Downs I, et al. NLRC5/MHC class I transactivator is a target for immune evasion in cancer. Proc Natl Acad Sci USA, 2016, 113: 5999-6004
[60] Noh KH, Kim SH, Kim JH, et al. API5 confers tumoral immune escape through FGF2-dependent cell survival pathway. Cancer Res, 2014, 74: 3556-66
[61] Tan S, Xu M, Ke B, et al. IL-6-driven FasL promotes NF-κBp65/PUMA-mediated apoptosis in portal hypertensive gastropathy. Cell Death Dis, 2019, 10: 748
[62] DuPage M, Mazumdar C, Schmidt LM, et al. Expression of tumour-specific antigens underlies cancer immunoediting. Nature, 2012, 482: 405-9
[63] Schlecker E, Fiegler N, Arnold A, et al. Metalloprotease-mediated tumor cell shedding of B7-H6, the ligand of the natural killer cell-activating receptor NKp30. Cancer Res, 2014, 74: 3429-40
[64] Chen C, Qu QX, Shen Y, et al. Induced expression of B7-H4 on the surface of lung cancer cell by the tumor-associated macrophages: a potential mechanism of immune escape. Cancer Lett, 2012, 317: 99-105
[65] Botti G, Scognamiglio G, Cantile M. PD-L1 immuno-histochemical detection in tumor cells and tumor microenvironment: main considerations on the use of tissue microarrays. Int J Mol Sci, 2016, 17: 43-7
[66] Wang L, Kang FB, Shan BE. B7-H3-mediated tumor immunology: friend or foe? Int J Cancer, 2014, 134: 2764-71
[67] Campbell DJ. Control of regulatory T cell migration, function, and homeostasis. J Immunol, 2015, 195: 2507-13
[68] Rodriguez GM, Galpin KJC, McCloskey CW, et al. The tumor microenvironment of epithelial ovarian cancer and its influence on response to immunotherapy. Cancers (Basel), 2018, 10: 242
[69] Facciabene A, Motz GT, Coukos G. T-regulatory cells: key players in tumor immune escape and angiogenesis. Cancer Res, 2012, 72: 2162-71
[70] Rochman Y, Spolski R, Leonard WJ. New insights into the regulation of T cells by γ_c family cytokines. Nat Rev Immunol, 2009, 9: 480-90
[71] Ostrand-Rosenberg S, Sinha P. Myeloid-derived suppressor cells: linking inflammation and cancer. J Immunol, 2009, 182: 4499-506
[72] Huang B, Pan PY, Li Q, et al. Gr-1$^+$CD115$^+$ immature myeloid suppressor cells mediate the development of tumor-induced T regulatory cells and T-cell anergy in tumor-bearing host. Cancer Res, 2006, 66: 1123-31
[73] Bronte V, Zanovello P. Regulation of immune responses by L-arginine metabolism. Nat Rev Immunol, 2005, 5: 641-54
[74] Srivastava MK, Sinha P, Clements VK, et al. Myeloid-derived suppressor cells inhibit T-cell activation by depleting cystine and cysteine. Cancer Res, 2010, 70: 68-77
[75] Kumar V, Patel S, Tcyganov E, et al. The nature of myeloid-derived suppressor cells in the tumor microenvironment. Trends Immunol, 2016, 37: 208-20
[76] Chen C, Qu QX, Shen Y, et al. Induced expression of B7-H4 on the surface of lung cancer cell by the tumor-

associated macrophages: a potential mechanism of immune escape. Cancer Lett, 2012, 317: 99-105
[77] Coffelt SB, Hughes R, Lewis CE. Tumor-associated macrophages: effectors of angiogenesis and tumor progression. Biochim Biophys Acta, 2009, 1796: 11-8
[78] Nozawa H, Chiu C, Hanahan D. Infiltrating neutrophils mediate the initial angiogenic switch in a mouse model of multistage carcinogenesis. Proc Natl Acad Sci USA, 2006, 103: 12493-8
[79] Welch DR, Schissel DJ, Howrey RP, et al. Tumor-elicited polymorphonuclear cells, in contrast to "normal" circulating polymorphonuclear cells, stimulate invasive and metastatic potentials of rat mammary adenocarcinoma cells. Proc Natl Acad Sci USA, 1989, 86: 5859-63
[80] Sun Z,Yang P. Role of imbalance between neutrophil elastase and α 1-antitrypsin in cancer development and progression. Lancet Oncol, 2004, 5: 182-90
[81] Rotondo R, Barisione G, Mastracci L, et al. IL-8 induces exocytosis of arginase 1 by neutrophil polymorphonuclears in nonsmall cell lung cancer. Int J Cancer, 2009, 125: 887-93
[82] Mishalian I, Bayuh R, Eruslanov E, et al. Neutrophils recruit regulatory T-cells into tumors via secretion of CCL17--a new mechanism of impaired antitumor immunity. Int J Cancer, 2014, 135: 1178-86
[83] Wu M, Chen X, Lou J, et al. TGF-β1 contributes to $CD8^+$ Treg induction through p38 MAPK signaling in ovarian cancer microenvironment. Oncotarget, 2016, 7: 44534-44
[84] Ito SE, Shirota H, Kasahara Y, et al. IL-4 blockade alters the tumor microenvironment and augments the response to cancer immunotherapy in a mouse model. Cancer Immunol Immunother, 2017, 66: 1485-96
[85] Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nat Rev Clin Oncol, 2018, 15: 234-48
[86] Landskron G, De la Fuente M, Thuwajit P, et al. Chronic inflammation and cytokines in the tumor microenvironment. J Immunol Res, 2014, 2014: 145-85
[87] Lippitz BE. Cytokine patterns in patients with cancer: a systematic review. Lancet Oncol, 2013, 14: 218-28
[88] Koppenol WH, Bounds PL, Dang CV. Otto Warburg's contributions to current concepts of cancer metabolism. Nat Rev Cancer, 2011, 11: 325-37
[89] Placke T, Örgel M, Schaller M, et al. Platelet-derived MHC class I confers a pseudonormal phenotype to cancer cells that subverts the antitumor reactivity of natural killer immune cells. Cancer Res, 2012, 72: 440-8
[90] Liu Q, Li A, Tian Y, et al. The CXCL8-CXCR1/2 pathways in cancer. Cytokine Growth Factor Rev, 2016, 31: 61-71
[91] Underwood PW, Zhang DY, Cameron ME, et al. Nicotine induces IL-8 secretion from pancreatic cancer stroma and worsens cancer-induced cachexia. Cancers (Basel), 2020, 12: 329
[92] Tong H, Ke JQ, Jiang FZ, et al. Tumor-associated macrophage-derived CXCL8 could induce ERα suppression via HOXB13 in endometrial cancer. Cancer Lett, 2016, 376: 127-36
[93] Cioni B, Nevedomskaya E, Melis MHM, et al. Loss of androgen receptor signaling in prostate cancer-associated fibroblasts (CAFs) promotes CCL2- and CXCL8-mediated cancer cell migration. Mol Oncol, 2018, 12: 1308-23
[94] Lin C, He H, Liu H, et al. Tumour-associated macrophages-derived CXCL8 determines immune evasion through autonomous PD-L1 expression in gastric cancer. Gut, 2019, 68: 1764-73
[95] Kersy O, Loewenstein S, Lubezky N, et al. Omental tissue-mediated tumorigenesis of gastric cancer peritoneal metastases. Front Oncol, 2019, 9: 1267
[96] Jobe NP, Rösel D, Dvořánková B, et al. Simultaneous blocking of IL-6 and IL-8 is sufficient to fully inhibit CAF-induced human melanoma cell invasiveness. Histochem Cell Biol, 2016, 146: 205-17
[97] Sun L, Wang Q, Chen B, et al. Gastric cancer mesenchymal stem cells derived IL-8 induces PD-L1 expression in gastric cancer cells via STAT3/mTOR-c-Myc signal axis. Cell Death Dis, 2018, 9: 928
[98] Sanmamed MF, Perez-Gracia JL, Schalper KA, et al. Changes in serum interleukin-8 (IL-8) levels reflect and predict response to anti-PD-1 treatment in melanoma and non-small-cell lung cancer patients. Ann Oncol, 2017, 28: 1988-95
[99] Kuai WX, Wang Q, Yang XZ, et al. Interleukin-8 associates with adhesion, migration, invasion and chemosensitivity of human gastric cancer cells. World J Gastroenterol, 2012, 18: 979-85
[100] Ning Y, Manegold PC, Hong YK, et al. Interleukin-8 is associated with proliferation, migration, angiogenesis and chemosensitivity *in vitro* and *in vivo* in colon cancer cell line models. Int J Cancer, 2011, 128: 2038-49
[101] Wang Y, Qu Y, Niu XL, et al. Autocrine production of interleukin-8 confers cisplatin and paclitaxel resistance in ovarian cancer cells. Cytokine, 2011, 56: 365-75
[102] Hamilton DH, Huang B, Fernando RI, et al. WEE1 inhibition alleviates resistance to immune attack of tumor cells undergoing epithelial-mesenchymal transition. Cancer Res, 2014, 74: 2510-9
[103] David JM, Hamilton DH, Palena C. MUC1 upregulation promotes immune resistance in tumor cells undergoing brachyury-mediated epithelial-mesenchymal transition. Oncoimmunology, 2016, 5: 111-38
[104] Scheel C, Eaton EN, Li SH, et al. Paracrine and autocrine signals induce and maintain mesenchymal and stem cell states in the breast. Cell, 2011, 145: 926-40
[105] Okui G, Tobiume K, Rizqiawan A, et al. AKT primes snail-induced EMT concomitantly with the collective migration of squamous cell carcinoma cells. J Cell Biochem, 2013, 114: 2039-49
[106] Fu XT, Dai Z, Song K, et al. Macrophage-secreted IL-8 induces epithelial-mesenchymal transition in hepatocellular carcinoma cells by activating the JAK2/STAT3/Snail pathway. Int J Oncol, 2015, 46: 587-96
[107] Wen J, Zhao Z, Huang L, et al. IL-8 promotes cell migration through regulating EMT by activating the Wnt/

β-catenin pathway in ovarian cancer. J Cell Mol Med, 2020, 24: 1588-98
[108] Bie Y, Ge W, Yang Z, et al. The crucial role of CXCL8 and its receptors in colorectal liver metastasis. Dis Markers, 2019, 2019: 8023460
[109] Yung MM, Tang HW, Cai PC, et al. GRO-α and IL-8 enhance ovarian cancer metastatic potential via the CXCR2-mediated TAK1/NFκB signaling cascade. Theranostics, 2018, 8: 1270-85
[110] Tobin RP, Jordan KR, Kapoor P, et al. IL-6 and IL-8 are linked with myeloid-derived suppressor cell accumulation and correlate with poor clinical outcomes in melanoma patients. Front Oncol, 2019, 9: 1223
[111] Wu S, Singh S, Varney ML, et al. Modulation of CXCL-8 expression in human melanoma cells regulates tumor growth, angiogenesis, invasion, and metastasis. Cancer Med, 2012, 1: 306-17
[112] Martin D, Galisteo R, Gutkind JS. CXCL8/IL8 stimulates vascular endothelial growth factor (VEGF) expression and the autocrine activation of VEGFR2 in endothelial cells by activating NFκB through the CBM (Carma3/Bcl10/Malt1) complex. J Biol Chem, 2009, 284: 6038-42
[113] Wu HX, Cheng X, Jing XQ, et al. LIFR promotes tumor angiogenesis by up-regulating IL-8 levels in colorectal cancer. Biochim Biophys Acta Mol Basis Dis, 2018, 1864: 2769-84
[114] Pecci A, Scholz A, Pelster D, et al. Progestins prevent apoptosis in a rat endometrial cell line and increase the ratio of bcl-XL to bcl-XS. J Biol Chem, 1997, 272: 11791-8
[115] Li A, Dubey S, Varney ML, et al. IL-8 directly enhanced endothelial cell survival, proliferation, and matrix metalloproteinases production and regulated angiogenesis. J Immunol, 2003, 170: 3369-76
[116] Asfaha S, Dubeykovskiy AN, Tomita H, et al. Mice that express human interleukin-8 have increased mobilization of immature myeloid cells, which exacerbates inflammation and accelerates colon carcinogenesis. Gastroenterology, 2013, 144: 155-66
[117] Highfill SL, Cui Y, Giles AJ, et al. Disruption of CXCR2-mediated MDSC tumor trafficking enhances anti-PD1 efficacy. Sci Transl Med, 2014, 6: 237ra67
[118] Li P, Chen X, Qin G, et al. Maelstrom directs myeloid-derived suppressor cells to promote esophageal squamous cell carcinoma progression via activation of the Akt1/RelA/IL8 signaling pathway. Cancer Immunol Res, 2018, 6: 1246-59
[119] Zhang M, Huang L, Ding G, et al. Interferon γ inhibits CXCL8-CXCR2 axis mediated tumor-associated macrophages tumor trafficking and enhances anti-PD1 efficacy in pancreatic cancer. J Immunother Cancer, 2020, 8: e000308
[120] Xuan W, Qu Q, Zheng B, et al. The chemotaxis of M1 and M2 macrophages is regulated by different chemokines. J Leukoc Biol, 2015, 97: 61-9
[121] Huang S, Mills L, Mian B, et al. Fully humanized neutralizing antibodies to interleukin-8 (ABX-IL8) inhibit angiogenesis, tumor growth, and metastasis of human melanoma. Am J Pathol, 2002, 161: 125-34
[122] Bilusic M, Heery CR, Collins JM, et al. Phase I trial of HuMax-IL8 (BMS-986253), an anti-IL-8 monoclonal antibody, in patients with metastatic or unresectable solid tumors. J Immunother Cancer, 2019, 7: 240
[123] Kahraman DC, Kahraman T, Cetin-Atalay R. Targeting PI3K/Akt/mTOR pathway identifies differential expression and functional role of IL8 in liver cancer stem cell enrichment. Mol Cancer Ther, 2019, 18: 2146-57
[124] Steele CW, Karim SA, Leach JDG, et al. CXCR2 inhibition profoundly suppresses metastases and augments immunotherapy in pancreatic ductal adenocarcinoma. Cancer Cell, 2016, 29: 832-45
[125] Ha H, Debnath B, Neamati N. Role of the CXCL8-CXCR1/2 axis in cancer and inflammatory diseases. Theranostics, 2017, 7: 1543-88