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·综 述·

Ang-Tie 轴在血管和淋巴系统相关疾病中作用的研究进展

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摘 要: 形成血管和淋巴管内层的内皮细胞是脉管系统的重要组成部分，并参与血管和淋巴系统疾病的发病机制。内皮细胞上的血管生成素 (Angiopoietin，Ang)-具有免疫球蛋白和表皮生长因子同源性结构域的酪氨酸蛋白激酶 (Tyrosine kinase receptors with immunoglobulin and EGF homology domains，Tie) 轴是除了血管内皮生长因子受体途径外胚胎心血管和淋巴发育所必需的第二种内皮细胞特异性配体-受体信号传导系统。Ang-Tie 轴参与调节产后血管生成与重塑、血管通透性和炎症，以维持血管平衡，因此，该系统在许多血管和淋巴系统疾病中发挥重要的作用。针对近年来 Ang-Tie 轴在血管和淋巴系统相关疾病中作用的研究进展，文中系统论述了 Ang-Tie 轴在炎症诱导的血管通透性、血管重塑、眼部新生脉管、剪切应力反应、动脉粥样硬化和肿瘤血管生成和转移中的作用，并总结了涉及 Ang-Tie 轴的相关治疗性抗体、重组蛋白和小分子药物。

关键词: 血管生成素 1，血管生成素 2，酪氨酸激酶样受体 1，酪氨酸激酶样受体 2，血管内皮细胞，淋巴系统

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Advances of Angiopoietin-Tie axis in vascular and lymphatic system-related diseases

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Abstract: Endothelial cells that form the inner layers of both blood and lymphatic vessels are important components of the vascular system and are involved in the pathogenesis of vascular and lymphatic diseases. Angiopoietin (Ang)-Tie axis in endothelial cells is the second endothelium-specific ligand-receptor signaling system necessary for embryonic cardiovascular and lymphatic development in addition to the vascular endothelial growth factor receptor pathway. The Ang-Tie axis also maintains vascular homeostasis by regulating postnatal angiogenesis, vessel remodeling, vascular permeability, and inflammation. Therefore, the dysfunction of this system leads to many vascular and lymphatic diseases. In light of the recent advances on the role of the Ang-Tie axis in vascular and lymphatic system-related diseases, this review summarizes the functions of the Ang-Tie axis in inflammation-induced vascular permeability, vascular remodeling, ocular angiogenesis, shear stress response, atherosclerosis, tumor angiogenesis, and metastasis. Moreover, this review summarizes the relevant therapeutic antibodies, recombinant proteins, and small molecular drugs associated with the Ang-Tie axis.

Keywords: Angiopoietin1, Angiopoietin2, Tie1, Tie2, vascular endothelial cell, lymphatic system

形成血管和淋巴管内层的内皮细胞 (Endothelial cells，ECs) 是脉管系统的重要组成部分，调控新的血管和淋巴管的生成和生长、组织液稳态、血管通透性等。内皮细胞参与许多疾病的发生和发展，例如糖尿病、脓毒症、新生血管性眼病、癌症和动脉硬化，其特征是引起血管功能障碍、屏障破裂和血管生成过多或不足。在成人血管发育和新血管形成过程中，血管内皮生长因子 (Vascular endothelial growth factor，VEGF) 及其受体 (Vascular endothelial growth factor receptor，VEGFR) 系统在调节血管和淋巴管的生成中起重要角色[1]。在 VEGF-VEGFR 系统驱动血管生成阶段之后，血管生成素 (Angiopoietin，Ang) 及其具有免疫球蛋白和表皮生长因子同源性结构域的酪氨酸蛋白激酶 (Tyrosine kinase receptors with immunoglobulin and EGF homology domains，Tie) 系统形成了第二种内皮生长因子受体信号传导途径，在调节血管和淋巴管重塑的过程中起着关键的作用[2]。除此之外，Ang-Tie 轴在抑制内皮细胞凋亡，促进血管出芽、迁徙、趋化，维持血管稳定，抗血管渗漏和减轻局部炎症等方面也发挥重要的作用[3]。

1 Ang-Tie 轴组成及功能

Ang-Tie 轴包含血管生成素 (Ang1、Ang2 和 Ang4，Ang3 是小鼠体内 Ang4 的同源体) 及酪氨酸激酶样受体 (Tie1 和 Tie2)。Ang1 是 Tie2 的一种必需激动剂，主要由血管平滑肌细胞和血管周围细胞分泌，在肺、皮肤、肌肉、前列腺和卵巢等组织中也有表达，其表达受表皮生长因子、转化生长因子 (Transforming growth factor beta 2，TGFβ2) 等的调控[4]。Ang1 可诱导内皮细胞-内皮细胞 (EC-EC) 连接处形成 Tie 簇，增加血管稳定性 (特别是在血管生成过程之后)，抑制组织纤维化，并在抗血管生成治疗过程中调节血管正常化[5]。Ang2

由内皮细胞表达后，储存在细胞内 Weibel-Palade 小体中[6] (图 1)，但与 Ang1 相反，Ang2 是 Tie2 的自分泌环境依赖性激动剂或拮抗剂[7]。Ang2 作用于内皮细胞，增加内皮细胞渗透性，也作用于周细胞，引起周细胞从基底膜脱落，进而诱导血管渗漏、免疫或者癌细胞跨内皮细胞迁移。在正常生理条件下，Ang2 水平较低，但炎性和缺氧刺激会增加 Ang2 的表达，降低血管稳定，促进内皮细胞的活化、血管生成和重塑[8]。

Tie 是一种酪氨酸激酶样受体，包括 Tie1 和 Tie2，主要在血管和淋巴管的内皮细胞中表达，在某些造血细胞系中也有少量的表达[9]。Tie1 是孤儿受体，它在血管发育中发挥作用的机制也尚不明确，但研究表明 Tie1 可通过结合 Tie2 而行使其生物学功能[10-11]。另有文章报道白细胞衍生趋化因子 (Leukocyte cell-derived chemotaxin-2，LECT2) 为 Tie1 的功能性配体，并阐明了 LECT2/Tie1 信号通路在血管生成和肝纤维化进程中的重要作用和机制[12]。Tie2 与 Ang1 结合后发生自我磷酸化而激活，然后将信号传递给通路下游分子，激活磷脂酰肌醇 3-激酶-蛋白激酶 B (Phosphatidylinositol 3 kinase-protein kinase B，PI3K-Akt) 信号通路，促进内皮细胞维持血管壁的完整性和降低通透性，从而起到抑制炎症的作用[13] (图 1)。最近有研究发现 Tie2 介导的信号途径在视网膜血管新生中有关键作用，但其信号缺失对于出生后淋巴管的生长和重塑过程没有明显影响；而 Tie1 在调控淋巴管生长和重塑过程中起关键作用[14]。Ang-Tie 轴参与调控血管内皮细胞稳态，并与许多人类血管和淋巴系统相关疾病有关，使 Ang-Tie 轴成为血管和淋巴系统相关疾病治疗发展的一个有吸引力的靶标[15-16]。

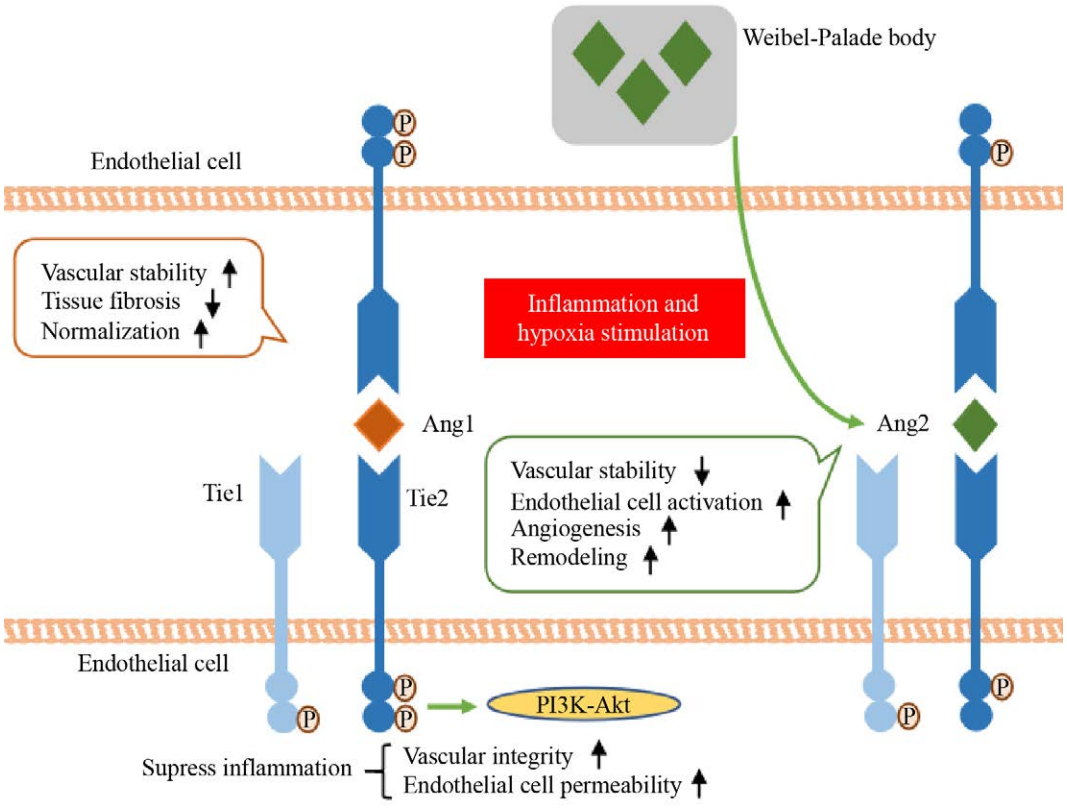

图 1　Ang-Tie 轴组成及其相互作用和功能[5]

Fig. 1　Components of Ang-Tie axis as well as their interactions and functions[5].

2 Ang-Tie 轴在血管和淋巴系统相关疾病中的作用

2.1 Ang-Tie 轴与炎症诱导的血管通透性和重塑

Ang1 可抑制多种炎症细胞因子和生长因子(如组胺、凝血酶和 VEGF) 诱导的细胞旁通透性升高[17-18]，使通透性降低，而 Ang2 与炎症细胞因子具有协同作用[19-20]，促进血管渗漏。Frye 等通过活体实验发现，当 Tie2 表达沉默时，可增加脂多糖 (Lipopolysaccharide，LPS) 诱导的肺血管通透性，提示 Tie2 可能对血管屏障功能起重要作用[21]。另外，Tie2 低表达的小鼠容易患埃博拉病毒引起的出血热[22]。Ang1 通过 Tie2 刺激多条下游信号传导途径的活性，有利于稳定内皮细胞接触点的血管内皮 (Vascular endothelial，VE)-钙粘蛋白以及维持皮质肌动蛋白细胞骨架[23-24] (图 2)。Ang1 还可以通过增加内皮糖化酶的形成直接降低基底微血管的通透性[25]。基于 Tie2 受体的存在和激活，Ang2 诱导其通透性的分子机制可分为 Tie2 依赖型和 Tie2 非依赖型[26]，其分子机制也归因于与细胞连接蛋白 (例如整合素蛋白和 VE-钙粘蛋白) 的相互作用。缺乏 *Ang2* 基因的小鼠在短期感染实验中无法引发炎症反应而重组 Ang2 的加入则重新触发炎症反应，表明 Ang2 对于引发炎症反应非常重要[27]。血清 Ang2 水平与炎性标志物 (如高敏 C 反应蛋白和白细胞计数) 呈正相关，因此 Ang2 也被视为炎性标志物[28]。

在慢性炎症期间，毛细血管到静脉的重塑扩大了血管区域，允许血浆渗漏和白细胞的迁移。有研究发现慢性肺炎支原体感染小鼠气道可导致血管内皮细胞 Ang2 升高和 Tie2 磷酸化水平的下降，但使用抗体 Anti-Ang2 (AZD5180，表 1) 可减少血管重塑、血管渗漏以及白细胞流入[29-32]。而使用重组 Ang1 蛋白 (COMP-Ang1，表 1) 也可阻止血管渗漏，其作用需要依赖周细胞的血小板衍化生长因子 (Platelet derived growth factor，PDGF)[33-34]。此外，在成年小鼠气管中，Ang1 的腺病毒载体诱导毛细血管向静脉的重构，产生无渗漏的血管扩大以及增加血流[35-36]。值得注意的是，相比小鼠皮肤中 VEGF 诱导的血管，Ang1 诱导的血管不渗漏，并增加了周细胞的包膜[37-38]。

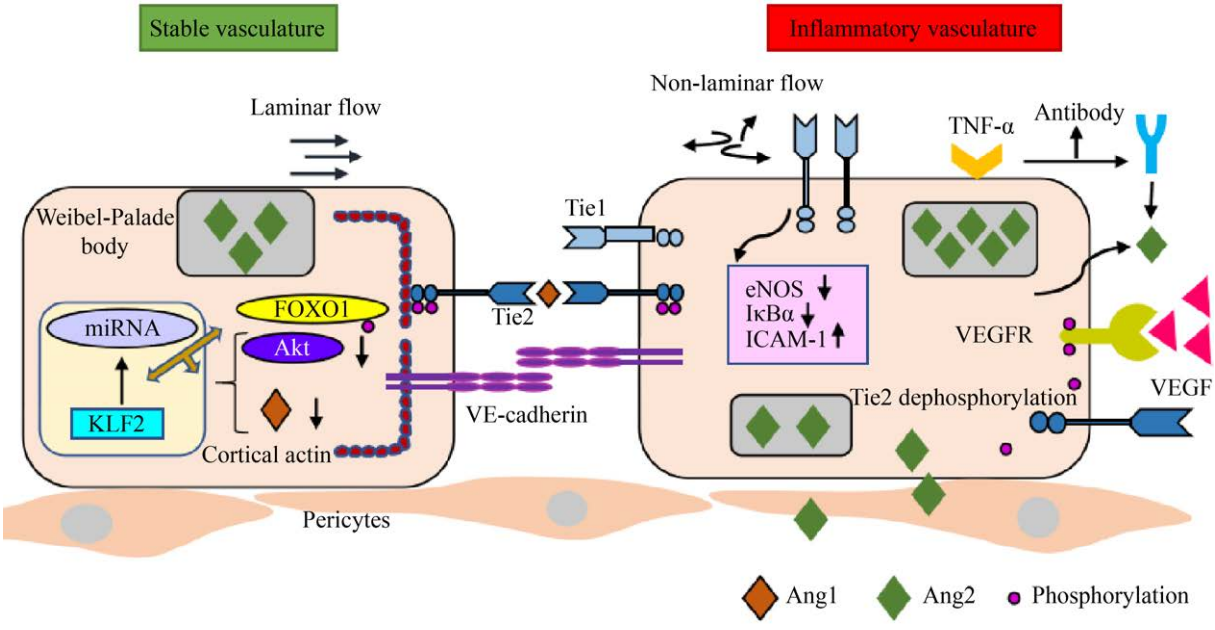

图 2 Ang-Tie 轴信号转导调节炎症中血管完整性的模型[4]

Fig. 2 A model illustrates how signal transduction in Ang-Tie axis regulates vascular integrity in inflammation[4].

在以内皮细胞活化和血管功能受损为特征的疾病中，Ang2 循环水平增加高于 Ang1，因此 Ang-Tie2 信号传导可能移向 Ang2[39-40]。Higgins 等研究发现在脓毒症小鼠模型的早期阶段，Ang1 浓度下降，Ang2 浓度升高，两者之间比值下降，也被认为是 Tie2 信号减少的外围指标，而 Tie2 信号紊乱又促进纤维蛋白过度沉积和无序血栓形成[41-44]。而经典标志物变化 (如血小板计数减少、D-二聚体升高) 均出现在后期。因此，这些结果提示 Ang1/Tie2 轴失调在时间上先于血小板和凝血因子的参与，Ang1/Tie2 轴的稳定在严重的脓毒症弥散性血管内凝血 (Disseminated intravascular coagulation，DIC) 发生前可能已被破坏。Alawo 等研究发现，可溶性 Tie2 (Soluble Tie2，sTie2) 浓度在一些心血管疾病中均有明显的升高[45]。然而，确定 sTie2 浓度的改变是否为严重疾病的原因或后果还是一个挑战。在疾病中，sTie2 浓度的升高是结合浓度同样升高的 Ang2 而起一种保护作用？还是和 Ang1 结合加剧 Ang1/Tie2 轴的失调？而且这过程是否还有其他蛋白参与等问题还未有定论。因此，明确 Ang1 和 sTie2 对凝血生成的影响，并分析疾病发生发展过程中 Ang1、Ang2 和 sTie2 的浓度关系，将有助于探寻识别早期 DIC 的标志物和理解 Ang1/Tie2 轴在对抗血栓形成中的作用。

在基因水平上，*Ang2* 基因转录的增加可能涉及转录因子 Forkhead box O1 (FOXO1)[45-46]，该转录因子在应激状态下与内皮细胞中的 Ang2 基因启动子结合，而减少 *Ang2* 基因剂量对小鼠肾脏和肺部损伤的影响[47] (图 2)。此外，重组 Ang1 (rhAng1，表 1) 可减轻脓毒症小鼠的血管并发症和急性炎症反应[48]，并保护大鼠心脏移植中内皮免受损伤，减轻炎症反应[49]。Han 等使用一种靶向 Ang2 单抗 (ABTAA，表 1) 可触发其聚集而激活 Tie2，可治疗炎症小鼠的炎症因子风暴、血管渗漏和稀疏，以及减轻器官损伤，从而提高存活率[50]。以上研究表明，Ang-Tie 轴在炎症诱导的血管重塑和通透性改变中发挥重要的作用 (图 2)。

表 1　Ang-Tie 轴相关的治疗性抗体、重组蛋白和小分子药物

Table 1　Therapeutic antibodies, recombinant proteins, and small molecule drugs associated with the Ang-Tie axis

Number	Compound	Type	Description	References
1	AZD5180	Ang2 antibody	The functional blocking antibody specifically neutralizes Ang2, which can reduce vascular remodeling, vascular leakage, and white blood cell influx	[30-31]
2	COMP-ANG1	Ang1 recombinant protein	Prevent vascular leakage; activate Tie2 activity; Tie2-mediated phosphorylation of PI3K/Akt and MAPK in human periodontal ligament cells enhances DNA synthesis and cell cycle progression	[33]
3	rhAng1	Ang1 recombinant protein	It has a direct anti-osmotic effect on the capillaries, protecting the body from systemic leakage and subsequently distributed shock	[48]
4	ABTAA	Antibodies that bind Ang2 and activate Tie2	Ang2 targeting antibody triggers Ang2 aggregation, which leads to the activation of Tie2, which is more effective than Ang2 neutralizing antibody in protecting the vascular system	[50]
5	AKB-9778	VE-PTP inhibitor	Activation of Tie2 by mediating inhibition of VE-PTP	[51]
6	MEDI3617	Ang2 antibody	Human tumor xenograft model that inhibits angiogenesis and tumor growth	[29]
7	3.19.3	Ang2 antibody	A potential new anti-angiogenesis therapy that can be used as a single drug or combined with chemotherapy or vascular endothelial growth factor inhibitors to treat cancer	[52]
8	L1-7(N)	Peptide-Fc fusion protein	Reduce blood vessel sprouting and inhibit tumor growth by selectively inhibiting Ang2	[53]
9	AdExTek	Soluble Tie2 recombinant protein	Inhibit tumor growth and the speed of metastasis	[54]
10	Regofinil	Targeting Tie2 and VEGFR small molecule inhibitors	Treatment of gastrointestinal stromal tumors and metastatic colorectal cancer	[55]
11	Rebatinib	Targeting Tie2 small molecule inhibitor	Combining paclitaxel in the treatment of advanced or metastatic solid tumors	[56]

2.2 Ang-Tie 轴与血流剪切应力和动脉粥样硬化

动脉粥样硬化是一种慢性炎症疾病，一般是先有炎性细胞和脂肪的累积，然后形成粥样斑块。炎性细胞促进斑块内新生血管形成，新生血管反过来诱导炎性细胞的聚集，增加了斑块不稳定性，导致出血和破裂[57]。动脉粥样硬化发生在动脉非层状的区域，主要在分叉处、主动脉的内曲处和分支处血液形成涡流，对内皮细胞造成低或振荡剪切应力。Franzoni 等实验结果初步表明，动脉交变流动的切应力导致内皮细胞损伤并促进慢性炎症，进而引起动脉粥样斑块的发生和发展[58]。与涡流相反，层流和高剪切应力保护其不发生动脉粥样硬化[59] (图 2)。

Tie1 表达受血流动力调控，在动脉粥样硬化血管壁龛中，非层流诱导 Tie1 表达，而在体外培养的内皮细胞中，层流则可下调 Tie1 的表达[60]。有研究结果显示，在条件性 *Tie1* 等位基因 *apoE* 不足型小鼠中，Tie1 表达的降低可减轻远端主动脉粥样硬化，并呈剂量依赖性，同时有内皮型一氧化氮合成酶 (Endothelial nitric oxide synthase，eNOS) 和核因子 κB 抑制蛋白 α (Inhibitor of nuclear factor kappa-B kinase subunit alpha，IκBα) 的增加和细胞间粘附分子 (Intercellular cell adhesion molecule-1，ICAM-1) 的表达减少 (图 2)，因此表明 Tie1 在动脉粥样硬化形成中有助于炎症性疾病的发生[60]。除了 Tie1，层流剪切刺激血管内皮蛋白酪氨酸磷酸酶 (Vascular endothelial protein tyrosine phosphatase，VE-PTP) 的亚细胞分布极化[61]，并通过转录因子 Kruppel 样因子 2 (Kruppel like factor 2，KLF2) 介导 miRNA 下调 Ang2 的表达[62]。在人体内，Ang2 高表达于非层流模式的动脉粥样硬化易发区，然而这与在动物模型中得到的结果相冲突[63]，因此 Ang2 在动脉粥样硬化发展中确切的作用还有待进一步阐明。

2.3 Ang1-Tie 轴与眼部新生血管和淋巴系统

眼部血管发育包括玻璃体和晶状体周围的胚胎透明血管的衰退以及在视网膜中脉管系统的形成。通过遗传学和对细胞因子等方面的研究表明，Ang-Tie 轴与视网膜新生血管性疾病 (如新生血管性老年黄斑病变 (Neovascular age-related macular degeneration，nAMD) 和息肉状脉络膜血管病变 (Polypoidal choroidal vasculopathy，PCV)的发病机理有关[64]。在基因水平，*Ang2* 基因上有 2 个单核苷酸多态性 (Single-nucleotide polymorphisms，SNPs)片段[65]和 *Tie2* 基因上的 SNP rs625767 片段一起与 nAMD 和 PCV 病变发生发展相关[66]。与对照组相比，nAMD 患者房水中 Ang2 水平升高，且与黄斑病变严重程度密切相关，但 Tie2 的激活可促进脉络膜毛细血管再生，从而减轻 nAMD 的病变[64]。

Ang1 和 Ang2 在淋巴系统中起激动剂配体的作用[67-68]，并且 Ang1/Ang2 以及 Tie2 基因条件性敲除小鼠在胚胎发育第 16.5 天后，都会导致角膜缘巩膜静脉窦 (Schlemm's canal，SC) 和淋巴毛细血管发育不良，从而在出生 21–28 d 后出现青光眼的临床特征，如高眼内压 (Intraocular pressure，IOP)、眼角膜炎、视网膜神经节变性和视力丧失，表明 Ang-Tie 轴中 Tie2 的失活参与了青光眼的发病机制[69-70]，而通过小分子抑制剂 (AKB-9778，表 1) 介导的 VE-PTP 抑制对 Tie2 的激活则可能为开角型青光眼和先天性青光眼提供潜在的治疗价值[51]。

3 Ang-Tie 轴在肿瘤血管生成和转移中的作用

3.1 Ang-Tie 轴与肿瘤血管生成

Ang-Tie 轴还涉及肿瘤的血管生成。Ang2 生物阻断制剂和 *Tie1* 的遗传缺失，通过减少肿瘤细胞增殖和内皮细胞发芽以及诱导血管衰退和内皮细胞凋亡来减少肿瘤血管生成和肿瘤生长，随着肿瘤血管周细胞覆盖率的增加，Ang2 阻断也促进了肿瘤血管表型的正常化[53]。研究表明一种 Ang2

抗体 (MEDI3617，表 1) 能够改善内皮细胞间连接并调节肿瘤基质的 Tie2 阳性促血管生成巨噬细胞，从而减少肿瘤细胞转移性的扩散和生长[71]。周细胞在肿瘤血管生成中起重要作用。研究发现[72]，缺氧肿瘤中的周细胞耗竭导致血管渗漏增加和转移率更高。周细胞耗竭后的肿瘤转录组学分析显示内皮细胞中 *Ang2* 基因转录增加，肿瘤中 Ang2 蛋白水平增加了 3 倍。而抑制 Ang2 可恢复血管稳定性，并降低周细胞衰竭小鼠的转移潜能[72]。

类肿瘤异位移植和原位小鼠肿瘤中，Ang2 抗体 (3.19.3，表 1) 和多肽-Fc 融合蛋白 (L1-7(N)，表 1) 选择性中和 Ang2 或 Ang1 与 Tie2 的相互作用，从而抑制肿瘤生长和血管生成[53,73-74]。这种抑制作用通过减少内皮细胞增殖和血管发芽、诱导细胞坏死、改善周细胞-内皮细胞的相互作用和血管退化实现。针对 VEGF 和 Ang2 在肿瘤血管生成方面的互补作用，已开展了大量的临床前研究，在一些临床前模型中，VEGF 抗体或者同时阻断 VEGF-trap 和 Ang2 的抗体 (3.19.3，表 1) 可以控制肿瘤生长和转移[75]。在某些肿瘤中，VEGF 靶向治疗的耐药性与治疗诱导 Ang2 表达有关，因此在这些肿瘤中，VEGF 靶向治疗与抑制 Ang2 相结合能克服这种耐药性。相反，阻断 Ang1 不能抑制肿瘤生长，但可阻止肿瘤血管正常化，表明在抗血管生成治疗中 Ang1 有助于血管的稳定性[76-77]。目前，对于针对 VGEF 和 Ang2 的双靶点药剂的剂量和给药时间研究不足[78]，因此，在临床试验中，对双抗血管增生疗法的剂量进行更为细致的研究，对于避免过度修剪血管和增加药物对肿瘤细胞的输送至关重要。

已有研究证明 *Tie* 基因的缺失能够抑制肿瘤生长和新血管形成[79-80]。与野生型小鼠生长的肿瘤相比，*Tie1* 基因缺陷小鼠的肿瘤体积更小，血管发芽较少，内皮细胞和肿瘤细胞凋亡增加，表明血管灌注减少以及退化的内皮细胞与肿瘤脉管系统中小血管纤维蛋白的沉积物有关系[80]。在 *Tie1* 基因缺陷型小鼠 VEGF 抗体疗法中，胞外可溶性 Tie2 重组蛋白 (AdExTek，表 1) 可进一步抑制肿瘤的生成[54-81]。重要的是，正常的脉管系统不受 *Tie1* 基因缺失的影响，表明 *Tie1* 基因缺失对肿瘤血管生成是不利的，但在正常的内皮细胞中却没有影响。

3.2 Ang-Tie 轴与肿瘤转移

对 Ang2 的阻断可能通过多种机制来抑制肿瘤转移。在小鼠模型中，Ang2 抗体 (MEDI3617，表 1) 可减少淋巴管的数量和人类肿瘤异种移植的淋巴结转移[82]。在血道转移过程中，血管内皮细胞形成一层屏障防止肿瘤细胞渗出，使用透射电子显微镜可以观察到阻断 Ang2 可改善肺毛细血管内皮细胞间的连接，从而减少肿瘤细胞从血液循环归巢于肺部[83]，此研究结果与 Ang2 抗体 (MEDI3617，表 1) 在体外可抑制肿瘤细胞跨内皮迁移的结果一致[84]。另一项研究发现 Ang2 抗体与小剂量规律化疗可减轻炎症和血管内皮反应而抑制肿瘤转移性生长，从而降低肿瘤促进的募集 $CCR2^{+}Tie2^{-}$转移相关的巨噬细胞和致瘤性骨髓源性髓样细胞[85]。与 Ang2 阻断剂相比，*Ang2* 基因的缺失对肿瘤生长的影响很小，但会导致肿瘤血管的特征改变，其特点是血管直径较窄，周细胞覆盖率较高。有趣的是，*Ang2* 基因缺陷小鼠结肠癌细胞的肺转移降低，而肝转移性增加。这些结果提示了器官特异性差异在通过 Ang2 调控肿瘤转移进展方面的作用，但其作用的分子机制还需进一步研究。研究人员认为 *Ang2* 基因靶向小鼠中肝转移增加可能涉及组织或转移微环境特异性上调 VEGF 非依赖性代偿性血管生成途径，如粒细胞集落刺激因子 (Granulocyte colony stimulating factor，G-CSF) 和趋化因子配体 1 (C-X-C motif chemokine ligand 1，CXCL1)[86]。Minami 等研究也发现，黑色素瘤、肺腺癌和肾癌细胞形成肺转移的机制与肿瘤来源的 VEGF 和 VEGF 依赖性钙调神经磷酸酶-活化 T 细胞核因子 (NFAT) 通路

在肿瘤生态位中的激活有关，使得活化 T-细胞核因子 1 (NFATc1) 蛋白与 *Ang2* 基因域结合，在转移微环境中调控 *Ang2* 基因的转录[87]。此外，目前一些通过抑制 Tie2 和其他酪氨酸激酶来达到治疗肿瘤转移的小分子抑制剂 (TKIs) 正在一期临床试验中。例如，瑞戈非尼 (Regorafenib，表 1) 可以靶向抑制 Tie2 和 VEGFR，用于治疗胃肠道间质瘤和转移性结直肠癌[55]；瑞巴替尼 (Rebastinib 或 DCC-2036，表 1) 也是一种 Tie2 小分子抑制剂[56]，目前也处于联合紫杉醇治疗晚期或转移性实体瘤的临床试验中 (美国临床试验编号：NCT03601897)。

4 总结与展望

Ang-Tie 轴参与调节血管和淋巴管的发育、维持血管稳态、抑制病理性的炎症和肿瘤血管生成反应。在许多人类疾病中 Ang2 的表达都上调，Tie1 也分别在动脉粥样硬化和肿瘤中促进促炎症和血管生成信号转导，并通过下调 Tie2 激活和上调 Ang2 使得 Ang-Tie 轴调控血管稳态在疾病中受到破坏。近年来，人们对 Ang-Tie 轴在血管和淋巴系统中的研究取得了显著进展，由于 Ang1 和 Ang2 分别介导血管的稳定性功能和不稳定性功能，炎症和心血管疾病中的 Ang-Tie 轴与血管渗漏和内皮功能障碍相关，因此越来越吸引研究人员的注意。一些研究机构和制药公司也围绕 Ang-Tie 轴寻找治疗血管相关疾病的新型治疗靶点，并开展了大量的基础和临床研究。相信未来随着人们对 Ang-Tie 轴在血管和淋巴疾病发病机制理解的不断深入，会有更多的新型研发药物成功应用于血管和淋巴疾病的治疗。

REFERENCES

[1] Jeltsch M, Leppänen VM, Saharinen P, et al. Receptor tyrosine kinase-mediated angiogenesis. Cold Spring Harb Perspect Biol, 2013, 5(9): a009183.

[2] Augustin HG, Koh GY, Thurston G, et al. Control of vascular morphogenesis and homeostasis through the angiopoietin-Tie system. Nat Rev Mol Cell Biol, 2009, 10(3): 165-177.

[3] Parikh SM. The angiopoietin-Tie2 signaling axis in systemic inflammation. J Am Soc Nephrol, 2017, 28(7): 1973-1982.

[4] Leligdowicz A, Richard-Greenblatt M, Wright J, et al. Endothelial activation: the ang/tie axis in sepsis. Front Immunol, 2018, 9: 838.

[5] Saharinen P, Eklund L, Alitalo K. Therapeutic targeting of the angiopoietin-Tie pathway. Nat Rev Drug Discov, 2017, 16(9): 635-661.

[6] Fiedler U, Scharpfenecker M, Koidl S, et al. The Tie-2 ligand angiopoietin-2 is stored in and rapidly released upon stimulation from endothelial cell Weibel-Palade bodies. Blood, 2004, 103(11): 4150-4156.

[7] Biel NM, Siemann DW. Targeting the Angiopoietin-2/Tie-2 axis in conjunction with VEGF signal interference. Cancer Lett, 2016, 380(2): 525-533.

[8] Eklund L, Kangas J, Saharinen. Angiopoietin-Tie signalling in the cardiovascular and lymphatic systems. Clin Sci (Lond), 2017, 131(1): 87-103.

[9] Teichert M, Milde L, Holm A, et al. Pericyte-expressed Tie2 controls angiogenesis and vessel maturation. Nat Commun, 2017, 8: 16106.

[10] Dalton AC, Shlamkovitch T, Papo N, et al. Constitutive association of Tie1 and Tie2 with endothelial integrins is functionally modulated by angiopoietin-1 and fibronectin. PLoS ONE, 2016, 11(10): e0163732.

[11] La Porta S, Roth L, Singhal M, et al. Endothelial Tie1-mediated angiogenesis and vascular abnormalization promote tumor progression and metastasis. J Clin Invest, 2018, 128(2): 834-845.

[12] Xu M, Xu HH, Lin Y, et al. LECT2, a ligand for tie1, plays a crucial role in liver fibrogenesis. Cell, 2019, 178(6): 1478-1492.e20.

[13] 吴晴, 李晓忠, 赵丽萍. Tie2 信号在血管炎中的抗炎作用. 国际免疫学杂志, 2019, 42(2): 185-189.
Wu Q, Li XZ, Zhao LP, et al. The anti inflammatory effect of Tie2 signal in vasculitis. Int J Immunol, 2019, 42(2): 185-189 (in Chinese).

[14] Chu M, Li TT, Shen B, et al. Angiopoietin receptor Tie2 is required for vein specification and maintenance via regulating COUP-TFⅡ. eLife, 2016, 5: e21032.
[15] Milam KE, Parikh SM. The angiopoietin-Tie2 signaling axis in the vascular leakage of systemic inflammation. Tissue Barriers, 2015, 3(1/2): e957508.
[16] Jongman RM, Zwiers P, Van De Sluis B, et al. Partial deletion of Tie2 affects microvascular endothelial responses to critical illness in a vascular bed and organ-specific way. Shock, 2019, 51(6): 757-769.
[17] Thurston G, Rudge JS, Ioffe E, et al. Angiopoietin-1 protects the adult vasculature against plasma leakage. Nat Med, 2000, 6(4): 460-463.
[18] Trieu M, Van Meurs M, Van Leeuwen AL, et al. Vasculotide, an angiopoietin-1 mimetic, restores microcirculatory perfusion and microvascular leakage and decreases fluid resuscitation requirements in hemorrhagic shock. Anesthesiology, 2018, 128(2): 361-374.
[19] Lee SJ, Lee CK, Kang S, et al. Angiopoietin-2 exacerbates cardiac hypoxia and inflammation after myocardial infarction. J Clin Invest, 2018, 128(11): 5018-5033.
[20] Gurnik S, Devraj K, Macas J, et al. Angiopoietin-2-induced blood-brain barrier compromise and increased stroke size are rescued by VE-PTP-dependent restoration of Tie2 signaling. Acta Neuropathol, 2016, 131(5): 753-773.
[21] Frye M, Dierkes M, Küppers V, et al. Interfering with VE-PTP stabilizes endothelial junctions *in vivo* via Tie-2 in the absence of VE-cadherin. J Exp Med, 2015, 212(13): 2267-2287.
[22] Thomson BR, Heinen S, Jeansson M, et al. A lymphatic defect causes ocular hypertension and glaucoma in mice. J Clin Invest, 2014, 124(10): 4320-4324.
[23] David S, Ghosh CC, Mukherjee A, et al. Angiopoietin-1 requires IQ domain GTPase-activating protein 1 to activate Rac1 and promote endothelial barrier defense. Arterioscler Thromb Vasc Biol, 2011, 31(11): 2643-2652.
[24] Hussain RM, Neiweem AE, Kansara V, et al. Tie-2/angiopoietin pathway modulation as a therapeutic strategy for retinal disease. Expert Opin Investig Drugs, 2019, 28(10): 861-869.
[25] Salmon AHJ, Neal CR, Sage LM, et al. Angiopoietin-1 alters microvascular permeability coefficients *in vivo* via modification of endothelial glycocalyx. Cardiovasc Res, 2009, 83(1): 24-33.
[26] Akwii RG, Sajib MS, Zahra FT, et al. Role of angiopoietin-2 in vascular physiology and pathophysiology. Cells, 2019, 8(5): 471.
[27] Fiedler U, Reiss Y, Scharpfenecker M, et al. Angiopoietin-2 sensitizes endothelial cells to TNF-α and has a crucial role in the induction of inflammation. Nat Med, 2006, 12(2): 235-239.
[28] Schuldt EA, Lieb W, Dörr M, et al. Circulating angiopoietin-2 and its soluble receptor Tie-2 concentrations are related to inflammatory markers in the general population. Cytokine, 2018, 105: 1-7.
[29] Leow CC, Coffman K, Inigo I, et al. MEDI3617, a human anti-angiopoietin 2 monoclonal antibody, inhibits angiogenesis and tumor growth in human tumor xenograft models. Int J Oncol, 2012, 40(5): 1321-1330.
[30] Tabruyn SP, Colton K, Morisada T, et al. Angiopoietin-2-driven vascular remodeling in airway inflammation. Am J Pathol, 2010, 177(6): 3233-3243.
[31] Le CTK, Laidlaw G, Morehouse CA, et al. Synergistic actions of blocking angiopoietin-2 and tumor necrosis factor-α in suppressing remodeling of blood vessels and lymphatics in airway inflammation. Am J Pathol, 2015, 185(11): 2949-2968.
[32] Gillen J, Richardson D, Moore K. Angiopoietin-1 and angiopoietin-2 inhibitors: clinical development. Curr Oncol Rep, 2019, 21(3): 22.
[33] Lim SS, Kook SH, Lee JC. COMP-Ang1 enhances DNA synthesis and cell cycle progression in human periodontal ligament cells via Tie2-mediated phosphorylation of PI3K/Akt and MAPKs. Mol Cell Biochem, 2016, 416(1/2): 157-168.
[34] Cahoon JM, Rai RR, Carroll LS, et al. Intravitreal AAV2. COMP-ang1 prevents neurovascular degeneration in a murine model of diabetic retinopathy. Diabetes, 2015, 64(12): 4247-4259.

[35] Cho CH, Kim KE, Byun J, et al. Long-term and sustained COMP-ang1 induces long-lasting vascular enlargement and enhanced blood flow. Circulat Res, 2005, 97(1): 86-94.

[36] Fujisawa T, Wang KQ, Niu XL, et al. Angiopoietin-1 promotes atherosclerosis by increasing the proportion of circulating $Gr1^+$ monocytes. Cardiovasc Res, 2017, 113(1): 81-89.

[37] Thurston G, Suri C, Smith K, et al. Leakage-resistant blood vessels in mice transgenically overexpressing angiopoietin-1. Science, 1999, 286(5449): 2511-2514.

[38] D'Apolito M, Santacroce R, Colia AL, et al. Angiopoietin-1 haploinsufficiency affects the endothelial barrier and causes hereditary angioedema. Clin Exp Allergy, 2019, 49(5): 626-635.

[39] Parikh SM, Mammoto T, Schultz A, et al. Excess circulating angiopoietin-2 may contribute to pulmonary vascular leak in sepsis in humans. PLoS Med, 2006, 3(3): e46.

[40] Melendez E, Whitney JE, Norton JS, et al. Systemic angiopoietin-1/2 dysregulation in pediatric sepsis and septic shock. Int J Med Sci, 2019, 16(2): 318-323.

[41] Higgins SJ, De CK, Kellum JA, et al. Tie2 protects the vasculature against thrombus formation in systemic inflammation. J Clin Invest, 2018, 128(4): 1471-1484.

[42] Ghosh CC, David S, Zhang RY, et al. Gene control of tyrosine kinase *TIE2* and vascular manifestations of infections. Proc Natl Acad Sci USA, 2016, 113(9): 2472-2477.

[43] Korhonen EA, Lampinen A, Giri H, et al. Tie1 controls angiopoietin function in vascular remodeling and inflammation. J Clin Investigat, 2016, 126(9): 3495-3510.

[44] Kim M, Allen B, Korhonen EA, et al. Opposing actions of angiopoietin-2 on Tie2 signaling and FOXO1 activation. J Clin Investigat, 2016, 126(9): 3511-3525.

[45] Alawo DOA, Tahir TA, Fischer M, et al. Regulation of angiopoietin signalling by soluble Tie2 ectodomain and engineered ligand tra. Sci Rep, 2017, 7: 3658.

[46] Idowu TO, Etzrodt V, Seeliger B, et al. Identification of specific Tie2 cleavage sites and therapeutic modulation in experimental sepsis. Elife, 2020, 9: e59520.

[47] Ghosh CC, Thamm K, Berghelli AV, et al. Drug repurposing screen identifies foxo1-dependent angiopoietin-2 regulation in sepsis. Crit Care Med, 2015, 43(7): e230-e240.

[48] David S, Park JK, Van Meurs M, et al. Acute administration of recombinant Angiopoietin-1 ameliorates multiple-organ dysfunction syndrome and improves survival in murine sepsis. Cytokine, 2011, 55(2): 251-259.

[49] Syrjälä SO, Tuuminen R, Nykänen AI, et al. Angiopoietin-2 inhibition prevents transplant ischemia-reperfusion injury and chronic rejection in rat cardiac allografts. Am J Transplant, 2014, 14(5): 1096-1108.

[50] Han S, Lee SJ, Kim KE, et al. Amelioration of sepsis by TIE2 activation-induced vascular protection. Sci Transl Med, 2016, 8(335): 335ra55.

[51] Shen JK, Frye M, Lee BL, et al. Targeting VE-PTP activates TIE2 and stabilizes the ocular vasculature. J Clin Invest, 2014, 124(10): 4564-4576.

[52] Brown JL, Cao ZA, Pinzon-Ortiz M, et al. A human monoclonal anti-ANG2 antibody leads to broad antitumor activity in combination with VEGF inhibitors and chemotherapy agents in preclinical models. Mol Cancer Therapeut, 2010, 9(1): 145-156.

[53] Hashizume H, Falcon BL, Kuroda T, et al. Complementary actions of inhibitors of angiopoietin-2 and VEGF on tumor angiogenesis and growth. Cancer Res, 2010, 70(6): 2213-2223.

[54] Lin PN, Buxton JA, Acheson A, et al. Antiangiogenic gene therapy targeting the endothelium-specific receptor tyrosine kinase Tie2. Proc Natl Acad Sci USA, 1998, 95(15): 8829-8834.

[55] Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet, 2013, 381(9863): 295-302.

[56] Harney AS, Karagiannis GS, Pignatelli J, et al. The

selective Tie2 inhibitor rebastinib blocks recruitment and function of Tie2^{Hi} macrophages in breast cancer and pancreatic neuroendocrine tumors. Mol Cancer Ther, 2017, 16(11): 2486-2501.

[57] 徐添添, 周建庆. 动脉粥样硬化斑块内血管新生的研究进展. 浙江医学, 2019, 41(4): 393-396.
Xu TT, Zhou JQ. Advances of angiogenesis in atherosclerotic plaque. Zhejiang Med J, 2019, 41(4): 393-396 (in Chinese).

[58] Franzoni M, Cattaneo I, Ene-Iordache B, et al. Design of a cone-and-plate device for controlled realistic shear stress stimulation on endothelial cell monolayers. Cytotechnology, 2016, 68(5): 1885-1896.

[59] Tabas I, García-Cardeña G, Owens GK. Recent insights into the cellular biology of atherosclerosis. J Cell Biol, 2015, 209(1): 13-22.

[60] Woo KV, Qu XH, Babaev VR, et al. Tie1 attenuation reduces murine atherosclerosis in a dose-dependent and shear stress-specific manner. J Clin Invest, 2011, 121(4): 1624-1635.

[61] Mantilidewi KI, Murata Y, Mori M, et al. Shear stress-induced redistribution of vascular endothelial-protein-tyrosine phosphatase (VE-PTP) in endothelial cells and its role in cell elongation. J Biol Chem, 2014, 289(10): 6451-6461.

[62] Tressel SL, Kim H, Ni CW, et al. Angiopoietin-2 stimulates blood flow recovery after femoral artery occlusion by inducing inflammation and arteriogenesis. Arterioscler Thromb Vasc Biol, 2008, 28(11): 1989-1995.

[63] Theelen TL, Lappalainen JP, Sluimer JC, et al. Angiopoietin-2 blocking antibodies reduce early atherosclerotic plaque development in mice. Atherosclerosis, 2015, 241(2): 297-304.

[64] Tang FY, Ng DS, Lam A, et al. Determinants of quantitative optical coherence tomography angiography metrics in patients with diabetes. Sci Rep, 2017, 7: 2575.

[65] Ma L, Brelen ME, Tsujikawa M, et al. Identification of *ANGPT2* as a new gene for neovascular age-related macular degeneration and polypoidal choroidal vasculopathy in the Chinese and Japanese populations. Invest Ophthalmol Vis Sci, 2017, 58(2): 1076-1083.

[66] Chen Q, Ma QK, Wu CM, et al. Macular vascular fractal dimension in the deep capillary layer as an early indicator of microvascular loss for retinopathy in type 2 diabetic patients. Invest Ophthalmol Vis Sci, 2017, 58(9): 3785-3794.

[67] Tanabe K, Wada J, Sato Y. Targeting angiogenesis and lymphangiogenesis in kidney disease. Nat Rev Nephrol, 2020, 16(5): 289-303.

[68] Varricchi G, Loffredo S, Galdiero MR, et al. Innate effector cells in angiogenesis and lymphangiogenesis. Curr Opin Immunol, 2018, 53: 152-160.

[69] Aspelund A, Tammela T, Antila S, et al. The Schlemm's canal is a VEGF-C/VEGFR-3-responsive lymphatic-like vessel. J Clin Invest, 2014, 124(9): 3975-3986.

[70] Thomson BR, Souma T, Tompson SW, et al. Angiopoietin-1 is required for Schlemm's canal development in mice and humans. J Clin Invest, 2017, 127(12): 4421-4436.

[71] Holopainen T, Saharinen P, D'Amico G, et al. Effects of angiopoietin-2-blocking antibody on endothelial cell-cell junctions and lung metastasis. J Natl Cancer Inst, 2012, 104(6): 461-475.

[72] Keskin D, Kim J, Cooke VG, et al. Targeting vascular pericytes in hypoxic tumors increases lung metastasis via angiopoietin-2. Cell Rep, 2015, 10(7): 1066-1081.

[73] Zhang Y, Chen F, Wang L. Metformin inhibits development of diabetic retinopathy through microRNA-497a-5p. Am J Transl Res, 2017, 9(12): 5558-5566.

[74] Yi QY, Deng G, Chen N, et al. Metformin inhibits development of diabetic retinopathy through inducing alternative splicing of VEGF-A. Am J Trans Res, 2016, 8(9): 3947-3954.

[75] Kienast Y, Klein C, Scheuer W, et al. Ang-2-VEGF-A CrossMab, a novel bispecific human IgG1 antibody blocking VEGF-A and Ang-2 functions simultaneously, mediates potent antitumor, antiangiogenic, and antimetastatic efficacy. Clin Cancer Res, 2013, 19(24): 6730-6740.

[76] Falcón BL, Hashizume H, Koumoutsakos P, et al. Contrasting actions of selective inhibitors of angiopoietin-1 and angiopoietin-2 on the normalization of tumor blood vessels. Am J Pathol,

2009, 175(5): 2159-2170.

[77] Coxon A, Bready J, Min H, et al. Context-dependent role of angiopoietin-1 inhibition in the suppression of angiogenesis and tumor growth: implications for AMG 386, an angiopoietin-1/2-neutralizing peptibody. Mol Cancer Ther, 2010, 9(10): 2641-2651.

[78] Fukumura D, Kloepper J, Amoozgar Z, et al. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. Nat Rev Clin Oncol, 2018, 15(5): 325-340.

[79] Singhal M, Gengenbacher N, La Porta S, et al. Preclinical validation of a novel metastasis-inhibiting Tie1 function-blocking antibody. EMBO Mol Med, 2020, 12(6): e11164.

[80] D'Amico G, Korhonen EA, Anisimov A, et al. Tie1 deletion inhibits tumor growth and improves angiopoietin antagonist therapy. J Clin Invest, 2014, 124(2): 824-834.

[81] 常双会. DCE-MRI 评价可溶性 Tie2 抗体抗 SCID 小鼠肺癌皮下移植瘤新生血管的疗效的研究[D]. 广州: 南方医科大学, 2010.
Chang SH. Evaluation of DCE-MRI of the Response of Pulmonary Carcinoma Xenografts in SCID mice to the Neovessels-Targeting Tie2 Agent[D]. Guangzhou: Southern Medical University, 2010 (in Chinese).

[82] Karaman S, Detmar M. Mechanisms of lymphatic metastasis. J Clin Invest, 2014, 124(3): 922-928.

[83] Nguyen DX, Bos D, Massagué J. Metastasis: from dissemination to organ-specific colonization. Nat Rev Cancer, 2009, 9(4): 274-284.

[84] Hakanpaa L, Sipila T, Leppanen VM, et al. Endothelial destabilization by angiopoietin-2 via integrin β1 activation. Nat Commun, 2015, 6: 5962.

[85] Srivastava K, Hu JH, Korn C, et al. Postsurgical adjuvant tumor therapy by combining anti-angiopoietin-2 and metronomic chemotherapy limits metastatic growth. Cancer Cell, 2014, 26(6): 880-895.

[86] Im JH, Tapmeier T, Balathasan L, et al. G-CSF rescues tumor growth and neo-angiogenesis during liver metastasis under host angiopoietin-2 deficiency. Int J Cancer, 2013, 132(2): 315-326.

[87] Minami T, Jiang SY, Schadler K, et al. The calcineurin-NFAT-angiopoietin-2 signaling axis in lung endothelium is critical for the establishment of lung metastases. Cell Rep, 2013, 4(4): 709-723.

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