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· 转化医学 ·

肿瘤中血管生成信号通路相关药物临床转化研究现状

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[摘 要] 血管生成在肿瘤发生、增殖、侵袭和转移的全程中都扮演着重要角色,以肿瘤血管生成信号通路中的关键分子为靶点开发抗肿瘤药物是目前药物研发的热点。肿瘤相关的血管生成信号通路包括 VEGF/VEEFR、血管生成素及其受体、血小板源生长因子及其受体、Delta-like Ligand/Notch、成纤维细胞生长因子及其受体、肝细胞生长因子及其受体、转化生长因子及其受体、内皮素系统等。与肿瘤血管生成通路相关的药物中,贝伐单抗(bevacizumab)、索拉非尼(sorafenib)、舒尼替尼(sunitinib)等药物已经获得 FDA 的批准,在直肠癌、肾癌、非小细胞肺癌、肝癌、胃肠间质瘤等肿瘤患者中取得了良好效果,数十种尚未被 FDA 批准的抗血管生成药物也正在全球进行各期临床试验。本文总结肿瘤血管生成信号通路的基础研究及其相关药物临床转化的研究进展。

[关键词] 肿瘤;血管生成;信号转导;抗肿瘤药物;临床试验;转化医学
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Research progress of clincal translation on signal pathway and relevant drugs in tumor angiogenesis

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[**Abstract**] Angiogenesis plays an important role in almost all aspects of tumor biology, including the occurrence, proliferation, progression and metastasis. Accordingly, inhibition of tumor angiogenesis through targeting key molecules in the signal pathways involved in angiogenesis has become a subject of extensive and intensive research in the field of anti-tumor drug development. Amongst these molecules are VEGF/VEGFR, Angiopoietin(Ang)/Tie, platelet derived growth factor, fibroblast growth factor, Delta-like Ligand(DLL4)/Notch, transforming growth factor β, hepatocyte growth factor, and endothelin. A few drugs, such as bevacizumab, sorafinib and sunitinib, targeting angiogenic molecules have been approved by FDA and their clinical use has generated satisfactory results in treating colorectal cancer, renal cell carcinoma, non small cell lung cancer, hepatocellular carcinoma and gastrointestinal stroma tumor; dozens of unapproved drugs in this class are under evaluation in clinical trials. This article aims to review recent advances in both bench-top and translational research on essential signal pathways involved in tumor angiogenesis.

[**Key words**] angiogenesis; tumor; signal pathway; clinical trails; translation medicine
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血管生成在肿瘤的生长过程中发挥着重要作用,1971 年 Folkman[1]第一次提出了肿瘤血管生成的概念,认为肿瘤的生长、增殖均与血管生成密切相关。随后的几十年中,以血管生成为靶点,开发了多种药物,其中一些已经在临床应用。目前大部分药物都是针对血管内皮生长因子(vascular endothelial growth factor, VEGF)及其受体(VEGFR)的信号通路设计的,其他一些与血管生成相关的通路也相继被发现,并有相关药物正在研究。血管生成信号通路的转化研究无疑是转化医学中最为成功的范例之一。本文就血管生成信号网络的机制及以其为靶点的药物研发和临床转化现状作一总结。

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1 肿瘤相关的血管生成信号通路

1.1 VEGF/VEGFR

VEGF 家族成员包括 VEGF-A、-B、-C、-D 和血小板生长因子,通常 VEGF 指的是 VEGF-A。VEGFR 包括 VEGFR-1、VEGFR-2 和 VEGFR-3。VEGF-A 可结合于 VEGFR-1 和 VEGFR-2。目前研究认为,VEGR-A/VEGFR-2 途径是介导肿瘤血管生成的关键通路。VEGF-A 与内皮细胞表面的 VEGFR-2 结合后,激活下游的 PI3K/AKT、p38/MAPK 和 PLCr/MAPK 途径,使得内皮细胞迁移和增殖,产生大量蛋白酶,增加血管渗透性。VEGFR-1 与 VEGF-A 结合后可以阻止其与 VEGFR-2 的结合,所以 VEGFR-1 参与了血管生成途径的负性调节[2]。

1.2 血管生成素及其受体(angiopoietin, Ang/Tie)

Ang /Tie 通路不直接作用于肿瘤细胞,而是通过介导肿瘤细胞和内皮细胞相互作用间接影响肿瘤细胞的生物学行为[3]。人类 Ang 家族有 Ang-1、Ang-2 和 Ang-4,其受体均为内皮细胞特异性酪氨酸激酶受体 Tie-2。Ang-1 表达于很多成熟组织,与 Tie2 结合后受体自身磷酸化,使得内皮细胞与周细胞之间连接加速,维持血管稳定和成熟[4]。Ang-2,主要表达于新生血管,与 Ang-1 竞争结合 Tie2,使血管去稳定化[5]。但是 Ang-2 的作用与 VEGF-A 的存在与否相关,在 VEGF-A 存在时,促使血管生成增加;无 VEGF-A 时,通过促进内皮细胞死亡和血管退化发挥作用,所以 Ang 在促血管生成和抗血管生成两方面发挥着复杂的作用[6]。

1.3 血小板源生长因子(platelet derived growth factor,PDGF)及其受体(PDGFR)

PDGF 家族有四个成员,PDGF-A、-B、-C-、D,可以形成5 种二聚体,分别是 PDGF-AA、-AB、-BB、-CC 和-DD。PDGFR 有两个亚型,PDGF-a 和 PDGF-β,因此可以形成三种二聚体,PDGF-aa、-aβ 和-ββ。目前只发现了三种有功能的组合形式即 PDGF-AA/PDGDR-aa, PDGF-CC/PDGFR-aa 和 PDGF-BB/PDGFR-ββ。PDGFR 与 PDGF 结合形成二聚体后,在胞内的酪氨酸残基位点发生自身磷酸化,并激活下游的磷脂酰肌醇 3 激酶(PI3K)、Ras-有丝分裂原激活蛋白激酶(Ras-MAPK)和 PLCγ 信号通路。PDGFR-a 与器官发育有关,而且通过募集表达 VEGF 的成纤维细胞,间接在肿瘤的血管生成中发挥作用[7]。PDGFR-β 表达于周细胞,在内皮细胞不表达,所以该通路促进肿瘤生长的机制是通过募集周细胞使肿瘤血管成熟,而不是增加肿瘤血管数量或密度。阻断 VEGFR 通路,可使早期不成熟的血管缺少周细胞的覆盖,但是对大血管、周细胞覆盖良好的血管没有影响;而阻断 PDGFR-β 通路后,抑制的是成熟血管,使得周细胞彼此分离,从而达到破坏肿瘤血管的目的[8-9]。

1.4 Delta-like Ligand (DLL4)/Notch

DLL4/North 通路决定哪些内皮细胞能被激活,而另外一些则不被激活。DLL1、DLL3、DLL4、Jagged1 和 Jagged2 都是 Notch 受体的配体。在这些配体中,DLL4 是最受关注的,因为它表达于肿瘤血管内皮细胞,而在正常血管的内皮细胞中表达非常微弱。DLL4 是个跨膜配体,它在肿瘤血管中的表达受 VEGF-A 的调节。VEGF-A 可以上调 DLL4 的表达,上调的 DLL4 与邻近细胞的 Notch 配体结合,从而负反馈调节 VEGFR-2 的表达[10],所以 DLL4/Notch 通路可以认为是对 VEGF 通路的负反馈调节系统。Notch 受体是单跨膜受体,该家族成员包括 Notch1、Notch2、Nothc3 和 Notch4。阻断 DLL4/Notch 信号通路后可增加血管生成,促进尖端细胞形成、分支,增加血管密度,介导化疗耐药[11]。

1.5 成纤维细胞生长因子(fibroblast growth factor, FGF)及其受体(FGFR)

FGF 属于肝素结合生长因子,这个家族包括 23 个成员,即 FGF1 ~ FGF23。在这个家族中,FGF1 和 FGF2 是研究得最多的,两者能诱导内皮细胞增殖和迁移,促进血管生成[12-13]。FGFR 家族有 5 个成员,其中 FGFR1 ~ FGFR4 结构上高度保守,为单跨膜的酪氨酸激酶受体,其胞外部分均含 3 个 Ig 样结构域(I-Ⅲ),其中Ⅱ-Ⅲ构成了配体结合位点。第 5 个成员 FGFR5 与 FGF 有高度亲和力,但是胞内部分缺少酪氨酸激酶结构域,所以其作用尚不明确。阻断该通路,在多种荷瘤动物模型和细胞模型中都显示出抑制肿瘤生长的效果[14-15]。。

1.6 肝细胞生长因子(hepatocyte growth factor, HGF)及其受体(C-met)

HGF 受体由 α 亚基和 β 亚基形成异二聚体,是 C-met 基因编码的蛋白产物,其胞外区可识别并结合 HGF,胞内部位具有酪氨酸激酶活性,是多种信号分子相互作用的结合部位。HGF 与内皮细胞表面的 c-Met 受体结合,激活受体酪氨酸激酶,使 α 亚基磷酸化,激活血管内皮细胞并引起血管内皮细胞的增殖和迁移,参与肿瘤新生血管的生成。体外实验中使用 c-Met 的抑制剂可以抑制直肠癌细胞的增殖。通过基因敲除或 RNA 干扰的方法可以抑制多种肿瘤细胞的生长和侵袭特性[16-17]。

1.7　转化生长因子 β(transforming growth factor β, TGF-β)及其受体

TGF-β 是一种多功能的细胞因子,有Ⅰ型和Ⅱ型两类受体。激活素受体样激酶(activin receptor like kinase, AIK)是 TGF-β 的Ⅰ型受体。Smad 是 TGF-β 的胞浆递质,参与 TGF-β 的信号传导。Alk1 和 Alk5 分别是两类不同的Ⅰ型受体,Alk1 与配体结合后,使得 Smad1/5/8 磷酸化,诱导内皮细胞增殖和迁移,参与新生血管形成;Alk5 与配体结合后,激活 Smad2/3,拮抗 ALKl 信号通路的作用,抑制增殖、网络形成和管状血管形成以及诱导细胞凋亡[18]。内皮细胞的最终活化状态依赖于 2 种信号通路的平衡。体外和体内实验都发现,Alk1 基因敲除后,可以明显减少血管形成,肿瘤细胞的生长和转移潜能,成为被关注的靶向肿瘤的策略之一。Endoglin 是参与 TGF-β 通路的辅助性受体,只在血管内皮细胞表达,使 TGF-β 高效地与受体结合。研究发现 endoglin 可以直接作用于病理性的血管生成,在多种人类实体瘤中发现,其表达水平与微血管密度和不良预后相关[19]。

1.8　内皮素系统(endothelin, ET)

ET 家族包括三个成员:ET-1、ET-2 和 ET-3,与两类 G 蛋白受体 ET_AR 和 ET_BR 结合后参与肿瘤细胞的增殖、抗凋亡和基质重塑,是介导肿瘤进展的重要因子。ET 家族中 ET-1 是研究最为深入的,它可以直接刺激内皮细胞、血管平滑肌细胞、成纤维细胞和周细胞的增殖从而参与肿瘤组织中的血管新生。因此,选择性阻断 ET-1 及其受体成为抗肿瘤药物研发的策略,并有多种药物已经进入临床试验阶段[20]。

2　肿瘤血管生成信号通路相关药物的临床转化

2.1　已获 FDA 批准药物的临床使用现状

血管生成对肿瘤的发生、侵袭和转移,几乎全程都起着至关重要的作用,所以以血管生成为靶点的药物一直是药物研发的热点。至今 FDA 批准上市的抗肿瘤血管生成药物大部分都以 VEGF/VEGFR 通路为靶点,如前所述的贝伐单抗、索拉非尼,舒尼替尼,帕唑帕尼、阿柏西普和阿西替尼。表 1 中总结了目前被 FDA 批准应用于临床的抗血管药物名称、靶点、适应证及获批时间。

贝伐单抗,人源化的 VEGFA 抗体,是第一个被批准用于临床的抗血管生成靶向药物。在临床使用中,贝伐单抗作为单药使用未见明确的疗效,所以都是与细胞毒药物联合应用。在晚期初治的结直肠癌Ⅲ期临床实验中,贝伐单抗与标准化疗方案联合应用改善了总生存期,这是抗血管药物第一次在肿瘤患者中被证实了生存获益(15.6 个月 *vs* 20.3 个月)[21],正是基于该研究的结果,FDA 批准了贝伐单抗在晚期结直肠癌中的应用。同样基于大宗临床试验的结果,FDA 批准贝伐单抗联合卡铂、紫杉醇用于局部晚期、复发或转移的非鳞非小细胞肺癌的一线治疗[22],联合干扰素 α 用于晚期肾细胞癌的一线治疗[23]。

表 1　已获 FDA 批准的靶向 VEGF/VEGFR 的药物

Tab. 1　Durgs targeting VEGF/VEGFR approved by FDA

Target	Drug	Indication	Action date
VEGF-A	Bevacizumab	CRC[21]	2004
		NSCLC[22]	
		RCC[23]	
	Aflibercept	CRC[24]	2012
	Sorafenib	RCC[25]	2005
		HCC[26]	
VEGFRs/ PDGFRs	Sunitinib	RCC[27]	2006
		GIST[28]	
	Pazopanib	Soft-tissue sarcoma[29]	2009
		RCC[30]	
VEGFR-1,2,3	Axitinib	RCC[31]	2012

阿柏西普,又称 VEGF-trap,是可溶性的 VEGF 的 VEGFA 受体,是由人的 VEGFR1 和 VEGFR2 的胞外区域融合到人的 Ig 的 Fc 段组合成的融合蛋白,通过纯化和结合循环中的 VEGFA 发挥作用。在晚期结直肠癌患者的Ⅲ期临床研究中,FOLFIRI 联合阿柏西普与 FOLFIRI 方案相比,明显改善了患者的 OS 和 PFS。基于该结果, 2012 年 FDA 批准该药用于晚期结直肠癌的二线治疗[24]。目前,阿柏西普在非小细胞肺癌、前列腺癌、卵巢癌中正在进行Ⅲ期临床试验。

靶向 VEGFR、FDGFR 等的多靶点激酶抑制剂索拉非尼、舒尼替尼、帕唑帕尼分别在 2005、2006 和 2009 年获批用于晚期肾细胞癌的治疗。舒尼替尼目前批准用于伊马替尼治疗后进展的胃肠间质瘤和初治的晚期肾细胞癌。在复治的晚期乳腺癌中[32],舒尼替尼单药应用实现了 11% 的客观缓解率,常见

的副反应为轻至中度的发热,这一结果在另外一个Ⅱ期临床试验也得到了证实[33],但是在后续的Ⅲ期试验[34]的结果并不支持舒尼替尼的单药应用。在复治的晚期非小细胞肺癌中,舒尼替尼单药应用缓解率达到 11.1%[35],表现了良好的应用前景。目前,舒尼替尼在胆管癌、子宫内膜癌和尿道上皮癌中分别进行单药应用的Ⅱ期临床试验。

2.2 尚未送 FDA 审批药物的临床试验进展

目前,数十种尚未被 FDA 批准的抗血管药物仍在全球范围内进行各期临床试验,并且有部分药物已经进入到Ⅲ期,表 2 总结了目前正在进行临床试验的抗血管药物生成的设计靶点、进行试验的瘤别、试验方案以及主要的研究结果。

表 2 抗血管生成药物临床试验研究汇总(尚未获得 FDA 批准)

Tab. 2 The summary of drugs targeting angiogenesis in clinical trails (unapproved by FDA)

Target	Drug	Indication	Main result	Schedule
VEGFRs/ PDGFRs	Cediranib	CRC Ⅲ[36]	PFS 8.6 *vs* 8.3 months	Folfox/Capox *vs* Cediranib/placebo
		RCC Ⅱ[37]	PFS 12.1 *vs* 2.8 months	Cediranbi *vs* placebo
	Telatinib	Advanced solid tumors Ⅰ[38]	Clinical benefits was observed. Cardiac toxicity needs further investigation	Telatinib + irinotecan + capecitabine
		CRC Ⅰ[39]	41% tumor shrinkage, no PR	Telatinib
	Linfanib	NSCLC Ⅱ[40]	Median progression-free rate at 16 weeks 33.1%, ORR 5%	Linfanib
		Hepatocellular carcinoma Ⅱ[41]	Estimated progression-free rate at 16 weeks 31.8%, ORR 9.1%	Linfanib
		CRC Ⅲ[42]	Median PFS 5.6 *vs* 4.2 months	Vatalanib + FOLFOX *vs* Vatalanib + placebo
	Vatalanib	CRC Ⅲ[43]	No survival benefit, identification of potential population	Vatalanib + FOLFOX *vs* Vatalanib + placebo
		NSCLC Ⅱ[44]	DCR at 12 weeks 35% *vs* 37%	Vatalanib(QD *vs* TDD)
	Motesanib	NSCLC Ⅲ[45]	No OS benefit	Carboplatin + paclitaxel + Motesanib/placebo
		Breast cancer Ⅱ[46]	No ORR benefit	Bevacizumab + paclitaxel + Motesanib/placebo
		Ovarian/fallopian tube and primary peritoneal carcinomas Ⅱ[47]	Early closure forserious central nervous system toxicity	Motesanib
VEGFRs/ FGFRs	Brivanib	Hepatocellular carcinoma Ⅲ[48]	No OS benefit ORR 10% *vs* 2%	Brivanib/placebo
		CRC Ⅲ[49]	No OS benefit, positive effects on PFS and ORR	Cetuximab + Brivanib/placebo
VEGFRs/ PDGFRs/ FGFRs	BIBF-1120	Ovarian cancer Ⅱ[50]	PFS rate at 36 weeks 16.3% *vs* 5.0%	BIBF-1120/placebo
		CRC Ⅱ[51]	No ORR benefit	BIBF-1120 followed by afatinib
		NSCLC Ⅱ[52]	No difference in efficacy	BIBF-1120 250 mg b.i.d *vs* 150 mg b.i.d.
Ang1/ Ang2	AMG-386	CRC Ⅱ[53]	No PFS benefit	AMG-386/placebo
		Gastro-oesophageal cancer Ⅱ[54]	Median PFS 4.2, 4.9, and 5.2 months	Cisplatin + capecitabine + AMG-386(10 mg/kg)/AMG-386(5 mg/kg)/placebo
		RCC Ⅱ[55]	No PFS benefit	Sorafenib + AMG-386/placebo
Ang2	CVX-060	Advanced solid tumors Ⅰ	NCT00879684*(Unreported)	CVX-060

续表 2

Target	Drug	Indication	Main result	Schedule
VEGFR/TIE2	CEP-11981	Advanced solid tumors Ⅰ	NCT00875264 *(unreported)	CEP-11981
DLL4	REGN421	Advanced solid tumors Ⅰ	NCT00871559 recruiting	REGN421
		Advanced solid tumors Ⅰ	NCT00744562 *(unreported)	REGN421
	OMP-21M18	NSCLC Ⅰ	NCT01189968 Recruiting	OMP-21M18
		Pancreatic cancer Ⅰ	NCT01189929 recruiting	OMP-21M18
Notch	MK0752	Advanced solid tumors Ⅰ[56]	Clinical benefit was observed, toxicity was schedule dependent	MK0752
	ARQ-197	Germ cell tumor Ⅱ[57]	No single-agent activity was observed	ARQ-197
		Hepatocellular carcinoma Ⅱ[58]	Prolongation on TTP	ARQ 197/placebo
c-Met/VEGFR	XL-184	Prostate cancer Ⅱ[59]	ORR at 2 weeks 5%, improvement in PFS,	XL-184/placebo
		Thyroid carcinoma	NCT00704730 Active, not recruiting	XL-880
	XL-880	Gastric cancer Ⅱ[60]	No single-agent efficacy was observed	XL-880
		RCC Ⅱ[61]	Elevated ORR withmanageable toxicity profile	
ALK1	PF-03446962	Malignant pleural mesothelioma Ⅱ	NCT01486368 recruiting	PF-03446962
		Advanced solid tumors Ⅰ	NCT00557856 * (Unreported)	PF-03446962
	ACE-041	RCC Ⅱ	NCT01727336 recruiting	ACE-041/ Axitinib
Endoglin	TRC-105	Advanced solid tumors Ⅰ[62]	Clinical activity was observed with a safety profile	TRC-105
ET-1	Bosentan	Melanoma Ⅱ[63]	No benefit in TTP	Dacarbazine + Bosentan/placebo
ETsR	Atrasentan	Prostate cancer Ⅲ[64]	No improvement in PFS、OS	Docetaxel + Atrasentan/placebo
		Ovarian cancer Ⅰ/Ⅱ[65]	Schedule is feasible with indication of prolonged survival	Pegylated liposomal doxorubicin + Atrasentan
	Zibotentan	Prostate cancer Ⅲ[66]	No improvement in OS	Docetaxel + Atrasentan/placebo
		Ovarian cancer Ⅱ[67]	No improvement in PFS	Paclitaxel + carboplatin + Zibotentan/placebo
		NSCLC Ⅱ[68]	No improvement in PFS	Pemetrexed + Atrasentan/placebo

CR: Colorectal cancer; NSCLC: Non small cell lung cancer; RCC: Renal clear carcinoma; PFS: Progression-free survival; ORR: Objective Response Rate; OS: Overall survival; PR: Partial Response; SD: Stable disease; TTP: Time to progression; DCR: Disease control rate.
" * " The clinical trails result is not available until the article writing, so the Clinical Trials goverment Identifier were provided

Vatalanib 抑制 VEGFR1、VEGFR2、VEGFR3 和 PIGFR-β,是备受关注的多靶点小分子激酶抑制剂之一。在晚期结直肠癌患者中进行的的两个Ⅲ期临床试验[42-43]都没有达到主要的研究终点,目前认为可能是由于抑制 PIGFR-β 通路影响了血管正常化的形成,从而削弱了与化疗药物联合的协同效应[69]。然而在晚期复发非小细胞肺癌中,Vatalanib 单药应用却表现了不错的效果,两个剂量的治疗组的客观缓解率分别为 35% 和 37%。因此 Vatalanib 在肿瘤患者中的应用还有待分析更多的研究结果。目前,在晚期乳腺癌、胰腺癌、胶质母细胞瘤,前列腺癌,间皮瘤等多中肿瘤患者中进行Ⅰ和Ⅱ临床试验。

BIBF-1120 是第一个三重靶点(VEGFR, PIGFR, FGFR)的口服激酶抑制剂, Ⅰ期临床的药物安全谱仅显示了剂量限制性的肝脏转氨酶升高。在一线化疗后行 BIBF-1120 维持治疗的卵巢癌患者中观察到疾病进展明显延迟,治疗组与安慰剂组相比,36 周时无病疾病进展的比例为 16.3% 和 5.0%[50]。在一线或二线化疗后进展的非小细胞肺癌患者口服 BIBF-1120 治疗的Ⅱ期临床中,药物安全性良好,疾病控制率达到 46%,250 mg bid 与 150 mg bid 两个剂量组的疗效没有明显差异[52]。目前在非小细胞肺癌一线治疗进展的患者进行培美曲塞联合 BIBF-1120 或安慰剂的Ⅲ期临床研究。

AMG-386 是 Ang1/2 的中和性受体,通过阻断 Ang 与 Tie2 的结合发挥作用、在晚期实体瘤患者中

进行的Ⅰ期[70]临床试验结果显示,药物的主要不良反应为疲劳和周围性水肿,并且显示了一定的抗肿瘤效果。在复发的卵巢癌患者中进行的Ⅱ期临床试验,AMG-386 联合紫杉醇与单药紫杉醇相比,明显提高客观缓解率,延长了 PFS[71]。但是在乳腺癌、胃食管癌的研究中未看到生存获益,在肾细胞癌中没有看到客观缓解率的提高。最近在分析药物剂量与客观反应的关系时,发现 AUC ≥ 9.6 mg h/ml 的的患者,PFS 为 8.1 月,明显长于 AUC < 9.6 mg h/ml 组患者的 5.7 月,而安慰剂组患者为 4.6 月,提示在后续的研究中可能需要提高 AMG-386 的使用剂量[72]。

ARQ-197 是 c-Met 和 VEGFR 的双重酪氨酸激酶抑制剂,在动物模型中显示了良好的抗肿瘤效果。在初治非小细胞肺癌中厄洛替尼联合 ARQ-197 与单用厄洛替尼组相比,没有看到生存获益,但是 KRAS 突变患者与非突变患者相比,PFS 与 OS 明显延长[73]。XL-184 在卵巢癌、软组织肉瘤、前列腺癌、甲状腺癌和非小细胞肺癌的Ⅱ期临床试验中表现了鼓舞人心的疗效。目前正在启动在甲状腺癌患者中的Ⅲ期临床试验。

Zibotentan 特异性靶向 ET_AR,在体外实验和动物模型中表现了激动人心的抗肿瘤效果。在晚期前列腺癌的Ⅱ期临床中,与对照组相比,明显延长了患者 PFS 和 OS[74],但是在后续的Ⅲ期临床中[66],这一结果并没有得到证实。在卵巢癌和非小细胞肺癌患者中进行的Ⅱ期临床试验依然没有看到生存获益[67-68]。

3 问题与展望

抗血管治疗无论在基础研究还是临床应用中都取得了一定的成果,但是也随之而来出现了一些问题。首先是缺少公认的可以预测疗效的标志物。有报道[75-77]称,治疗前 VEGF-A 和 VEGFR2 水平、微血管密度及治疗相关的高血压[78]等都可以作为预测指标,但是这些结果仍需要进一步验证。其次,抗血管治疗过程中出现的高血压[79]、出血[80-81]等危及患者生命的不良反应,限制了其在临床的广泛应用。再次是获得性耐药,理论上抗血管药物作用靶点为血管内皮细胞,不应该出现耐药,但是在临床实践中却的确有患者出现原发或继发耐药的情况。有学者从肿瘤血管的异质性[82]、治疗中的血管正常化窗口期[83]等不同的角度进行研究,但问题尚没有得到解决。转化医学的发展使基础研究和临床研究的界限越来越模糊,随着对肿瘤血管生成信号通路基础研究的不断深入,一定能为临床中抗血管药物的合理设计提供理论指导,并转化为临床治疗肿瘤的有效手段。根据治疗过程中出现的新问题,不断进行深入研究与验证,进下达到提高疗效,造福患者的目的。

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·简　讯·

本刊主编曹雪涛院士当选德国国家科学院院士

近日,德国国家科学院院长致函我国医学免疫学国家重点实验室主任曹雪涛教授,祝贺其当选德国科学院院士。

德国科学院起源于 1652 年成立的利奥波第那科学院(Leopoldina),已有 350 多年历史。2008 年 7 月 14 日,德国政府将其更名为德国国家科学院(German National Academy of Sciences)。目前德国国家科学院由 1 400 多位院士组成,先后有 157 位诺贝尔奖获得者为德国国家科学院院士。

自 2005 年中科院院士路甬祥、卢柯当选德国科学院外籍院士至今,我国大陆目前一共有 7 位学者当选德国国家科学院院士,包括 2007 年当选的上海交通大学张杰教授(中科院院士)、2011 年当选的浙江大学来茂德教授、2012 年当选的深圳华大基因研究院杨焕明教授(中科院院士)、中国农业科学院李家洋教授(中科院院士)和今年当选的曹雪涛教授(中国工程院院士)。

曹雪涛教授是著名的免疫学家,在天然免疫与免疫调控的基础研究、疾病免疫治疗的转化与应用研究方面取得了系统性创新性成果,以通讯作者身份在 *Cell*、*Nature Immunol*、*Cancer Cell*、*Immunity*、*PNAS* 等杂志发表 SCI 论文 212 篇,获得国家发明专利 10 项。2005 年 41 岁时当选中国工程院院士,2006 年创建医学免疫学国家重点实验室并担任主任。目前是中国医学科学院院长、中国免疫学会理事长、亚洲大洋洲地区免疫学会联盟主席、全球慢性疾病防控联盟候任主席。

此次曹雪涛院士当选德国科学院院士极大地提升了我国免疫学研究在国际学术界的影响力,也标志着我国免疫学的发展受到了国际学术界的高度关注和认可。

(本刊编辑部)