组织因子在抗体偶联药物开发中的研究进展

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摘要: 组织因子 (tissue factor, TF), 是一种在正常组织中表达的跨膜糖蛋白, 其在胚胎发育、止血和非止血途径中具有多种生理学功能。研究发现TF在多种肿瘤组织中过表达且促进肿瘤进展, Kaplan-Meier (K-M) 生存分析显示TF基因的高表达与肾癌和胰腺癌的不良预后有关。因此, TF作为肿瘤免疫治疗靶点受到广泛关注, 已有多款抗体偶联药物 (antibody-drug conjugates, ADC) 进入临床研究阶段。本文就TF的基因结构、表达、生物学功能以及与肿瘤的相关性进行了系统阐述, 并对新一代TF-ADC药物设计提出方向, 以期为该靶点的药物研发提供理论支持和开发方向。

关键词: 组织因子; 功能; 肿瘤; 靶向药物; 抗体偶联药物

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Research progress of tissue factor in the development of antibody conjugated drugs

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Abstract: Tissue factor (TF), a transmembrane glycoprotein expressed in normal tissues, has a variety of physiological functions in embryonic development, hemostasis and non hemostasis pathways. Studies have found that TF is overexpressed in a variety of tumor tissues and promotes tumor progression. Kaplan Meier (K-M) survival analysis showed that high expression of TF gene was associated with poor prognosis in renal and pancreatic cancer. Therefore, TF has received extensive attention as a target of tumor immunotherapy, and a number of antibody-drug conjugates (ADC) drugs have entered the clinical research stage. In this paper, the gene structure, expression, biological function and the correlation with tumor of TF were systematically elaborated, and the direction of drug design for the new generation of TF-ADC was proposed, in order to provide theoretical support and development direction for the drug research and development of this target.

Key words: tissue factor; function; tumor; targeted drug; antibody-drug conjugate

基于2024年全球癌症统计数据, 癌症的患病人数持续增长, 且仍然是人群中的主要死亡原因之一[1], 因此, 开发有效的抗癌药物是迫切之需。21世纪以来, 美国食品药品监督管理局 (food and drug administration, FDA) 批准的癌症疗法趋势表明靶向治疗药物数量显著增多, 靶向治疗已成为抗肿瘤疗法中一个重要开发方向[2]。随着抗体偶联药物 (antibody-drug conjugates, ADC) 良好的临床治疗效果披露, 以ADC为代表的大分子靶向治疗药物成为近些年的研究热点。ADC药物的独特结构充分发挥了抗体的靶向特异结合优势, 不仅使药物高效精准递送至肿瘤部位, 而且减少对健康组织的损伤, 降低药物的不良反应, 提高药物疗效。因此, 被广泛研究和应用于临床治疗。到目前为止, FDA

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已批准15款ADC药物上市, 治疗靶点包括分化簇33 (cluster of differentiation 33, CD33)、CD30、人表皮生长因子受体-2 (human epidermalgrowth factor receptor-2, HER2)、CD22、组织因子 (tissue factor, TF)、叶酸受体α (folate receptor, FR) 等, 涉及淋巴瘤、白血病、乳腺癌、多发性骨髓瘤等治疗领域。

TF也称为凝血活酶、CD142或凝血因子III, 是由氨基酸残基组成的跨膜单链糖蛋白。最早报道以术语“血栓激酶”和“凝血活酶”作为外源性凝血途径的启动者正式确定[3]。随后被Nemerson和Bach分离, 称为组织因子[4]。TF在正常组织中表达有限, 在肿瘤组织中过表达, 有不少研究发现TF在促进肿瘤细胞生长、转移、侵袭等方面发挥作用[5]。基于TF的表达差异和与肿瘤进展的关系, 尤其是在宫颈癌、卵巢癌、非小细胞肺癌等多种肿瘤中, TF成为开发ADC药物的理想靶点。

1 TF的蛋白类型

TF分子质量约为47 kDa, 其基因定位于人类染色体1p21.3[6], 在人体内以三种形式存在: 全长TF (full-length tissue factor, flTF)、替代性可溶性TF (alternative soluble tissue factor, asTF) 以及通过替代性剪接产生的外显子1A-TF (alternative exon 1A-tissue factor, TF-A)[7] (图1)。flTF由295个氨基酸组成, 包含胞外、跨膜和胞质三个结构域[8]。asTF缺少跨膜结构域, 末端具有独特的肽序列[9]。TF-A是通过第一个内含子的可变剪接产生的TF基因的新转录本, 称为外显子1A[8], 其具体功能目前尚不明确。基于TF的结构特性, 现阶段TF-ADC药物均是结合全长TF, 因此本文重点关注与研究的是全长TF。

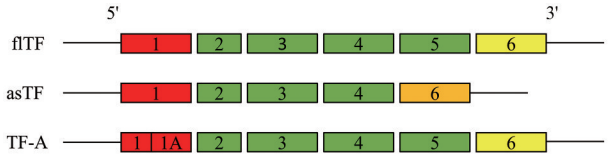

Figure 1 A schematic representation of the mRNA splicing products of tissue factor (TF) gene. *F3* gene encodes six exons that form open reading frames; five introns are removed during mRNA processing. Three distinct mRNA products are produced, each of which contains coding sequences. It results in the production of TF, asTF, by excluding alternative splicing exon 5. TF-A is a newly identified transcript of the TF gene that is produced by an alternative splicing mechanism involving the first intron. This process causes the incorporation of a sequence from the first intron known as exon 1A into the transcript. Red: Leader sequence; Green: Extracellular domain; Yellow: Transmembrane domain and cytoplasmic domain; Orange: C-terminal region unique to asTF. flTF: Full-length tissue factor; asTF: Alternative soluble tissue factor; TF-A: Alternative exon 1A-tissue factor

2 TF的表达分布

在正常情况下, TF由血管外膜组织的成纤维细胞和平滑肌细胞表达。内皮细胞处于静息状态时不表达TF, 当内皮细胞受损或受到凝血酶、内毒素、细胞因子等刺激时, 内皮细胞活化并表达TF[10,11]。

研究表明, 在脓毒症、心肌梗死、动脉硬化和癌症等多种病理状况下, TF在单核细胞、内皮细胞和肿瘤细胞表面的表达增加[12], 特别是在多种肿瘤细胞和肿瘤组织上高表达, 包括宫颈癌、黑色素瘤、结直肠癌、乳腺癌等共计十余种瘤系 (图2)。

3 TF的功能研究进展

3.1 TF的外源凝血功能

TF在正常生理状态下的功能是启动外源性凝血途径 (图3A)。当血管受到损伤时, TF与凝血因子VII (congenital factor VII, FVII) 结合触发外源性凝血途径。凝血因子X (congenital factor X, FX) 与TF-活化因子VII (activated factor VII, FVIIa) 连接, 后者裂解生成活化因子X (activated factor X, FXa), 与其活化的辅因子V (activated factor V, FVa) 相互作用, 将凝血酶原转化为凝血酶。因此纤维蛋白形成, 血小板被激活, 最终导致血凝块形成[13]。若TF与FVII结合受到影响, 将对外源凝血系统产生干扰, 可能会影响血液的凝固能力, 从而导致出血或血栓形成的风险增加。

3.2 TF的内吞功能

一般来说, 正常的内吞作用可分为三个阶段: 芽的形成; 膜的弯曲和囊泡的成熟; 膜的断裂并释放到细胞质中。多种内吞途径有重叠的方面, 因此内吞的一般过程是高度灵活和复杂的。按具体的作用机制可分为网格蛋白介导的内吞作用 (clathrin-mediated endocytosis, CME)、小窝介导的内吞作用、小窝蛋白非依赖性载体蛋白/糖基磷脂酰肌醇锚定蛋白富集内体区室的内吞作用、巨胞饮作用等[14]。TF是通过CME进入细胞的[15]。CME在概念上是一个简单的过程, 包括几个连续和部分重叠的步骤, 其具体作用机制如图3B所示。药物剂量−暴露−效应关系的确定是ADC成功的关键部分, 抗原内吞作用是这种关系的基石, 这对大多数ADC的有效性来说是至关重要的一步。在内吞后, 药物释放到细胞质中, 可以通过分子特异性机制发挥药理效应, 杀死癌细胞。

3.3 TF在肿瘤发生发展中的功能

TF与癌症之间存在密切联系, 一方面癌细胞表达高水平的flTF和asTF; 另一方面TF在促进血管生成、肿瘤细胞生长、转移和侵袭等方面发挥重要作用 (图4A～C)。通过对TF的机制研究, 可以开发新的疗法, 并可能改善癌症患者的预后。

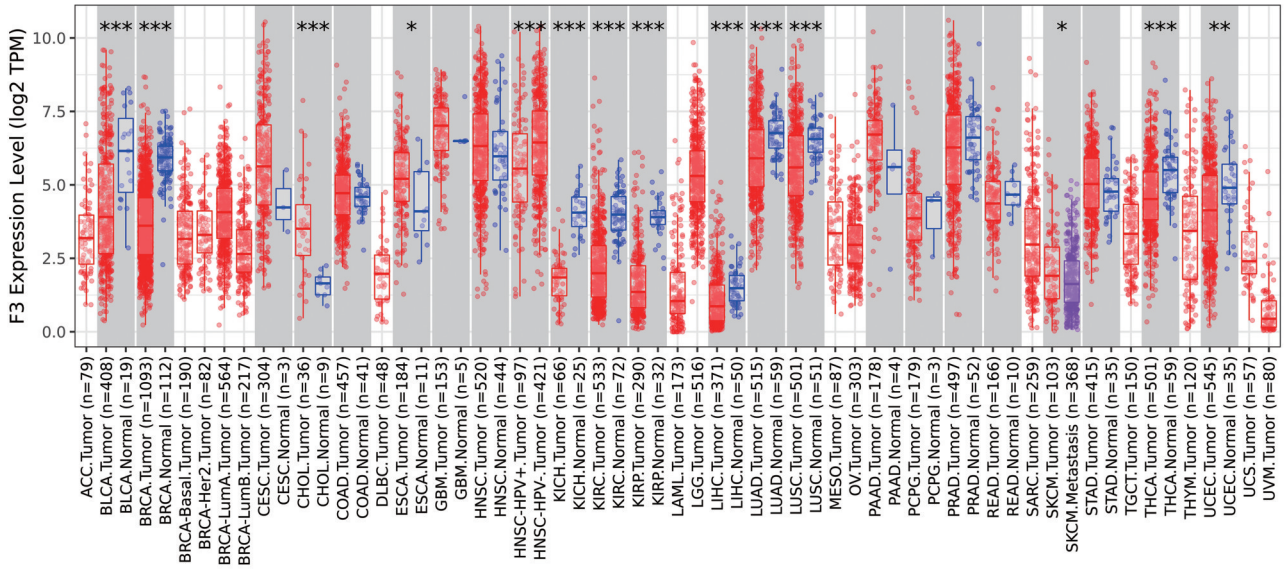

Figure 2　Differences in the expression levels of *F3* gene in normal tissues and tumor tissues (data source: http://timer.cistrome.org). *F3* gene encodes tissue factor. ACC: Adrenocortical carcinoma; BLCA: Bladder urothelial carcinoma; BRCA: Breast invasive carcinoma; CESC: Cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL: Cholangiocarcinoma; COAD: Colon adenocarcinoma; DLBC: Lymphoid neoplasm diffuse large B-cell lymphoma; ESCA: Esophageal carcinoma; GBM: Glioblastoma multiforme; HNSC: Head and neck squamous cell carcinoma; KICH: Kidney chromophobe; KIRC: Kidney renal clear cell carcinoma; KIRP: Kidney renal papillary cell carcinoma; LAML: Acute myeloid leukemia; LGG: Brain lower grade glioma; LIHC: Liver hepatocellular carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; MESO: Mesothelioma; OV: Ovarian serous cystadenocarcinoma; PAAD: Pancreatic adenocarcinoma; PCPG: Pheochromocytoma and paraganglioma; PRAD: Prostate adenocarcinoma; READ: Rectum adenocarcinoma; SARC: Sarcoma; SKCM: Skin cutaneous melanoma; STAD: Stomach adenocarcinoma; TGCT: Testicular germ cell tumors; THCA: Thyroid carcinoma; THYM: Thymoma; UCEC: Uterine corpus endometrial carcinoma; UCS: Uterine carcinosarcoma; UVM: Uveal melanoma; TPM: Transcripts per million. $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$

3.3.1　TF促进肿瘤血管生成　到目前为止肿瘤形成的具体原因尚不明确, 但已有研究证明肿瘤的发生发展与血管生成密切相关[16]。血管生成的关键因素是血管内皮生长因子 (vascular endothelial growth factor, VEGF), 它可以被TF刺激, 促进血管新生[17,18]。TF依赖整合素信号转导参与血管生成, TF与蛋白酶激活受体2 (protease activated receptors 2, PAR2) 信号转导也导致产生VEGF和促血管生成分子 (图4A) [19]。除此之外, asTF与整合素结合可调节内皮细胞的黏附和定位, 增强内皮的毛细血管的形成和动脉的生芽作用[7]。

3.3.2　TF促进肿瘤细胞生长　TF-FVIIa复合物通过激活PAR2, 可导致激活蛋白-1 (activating protein-1, AP-1)/蛋白激酶Cα (protein kinases C α, PKCα) 磷酸化, 促进细胞外调节蛋白激酶1/2 (extracellular regulated protein kinases 1/2, ERK1/2) 和核因子κB (nuclear factor kappa-B, NF-κB) 磷酸化, 激活磷脂酰肌醇3激酶 (phosphatidylin-ositol-3-kinase, PI3K) 和丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK) 信号通路, 从而促进肿瘤细胞生长 (图4B) [20,21]。相反, asTF介导PAR2非依赖性信号转导, 与整合素β1结合直接激活PI3K与MAPK途径[22]。有研究表明, TF还可以在肿瘤微环境中调节免疫反应, 逃避宿主免疫细胞攻击, 促进肿瘤生长, 如白细胞介素-8 (interleukin-8, IL-8)、趋化因子等[19]。其中促血管生成IL-8诱导是MAPK、ERK和PI3K依赖性的, 并且在TF细胞质结构域缺失后, PI3K调节亚基的TF免疫共沉淀被消除, 这表明该结构域与PI3K向TF信号复合物的募集有关。

3.3.3　TF促进肿瘤转移　TF与FVIIa、FXa通过结合PAR共同刺激肿瘤细胞迁移[20]。TF-FVIIa-FXa复合物激活凝血酶, 激活血小板并产生纤维蛋白。激活的血小板和纤维蛋白抑制自然杀伤细胞功能, 吸引单核/巨噬细胞, 帮助转移和肿瘤存活。此外, TF-FVIIa通过激活蛋白激酶B (protein kinase B, PKB/AKT), Rab蛋白活化, 使肌动蛋白聚合和微泡释放, 促进肿瘤细胞侵袭和转移[23]。还可以增加尿激酶型纤溶酶原激活物受体 (urokinase-type plasminogen activator receptor, uPAR) 的表达, 从而增加肿瘤细胞侵袭 (图4C) [7]。

3.3.4　TF对肿瘤预后的影响　据基因表达谱交互式分

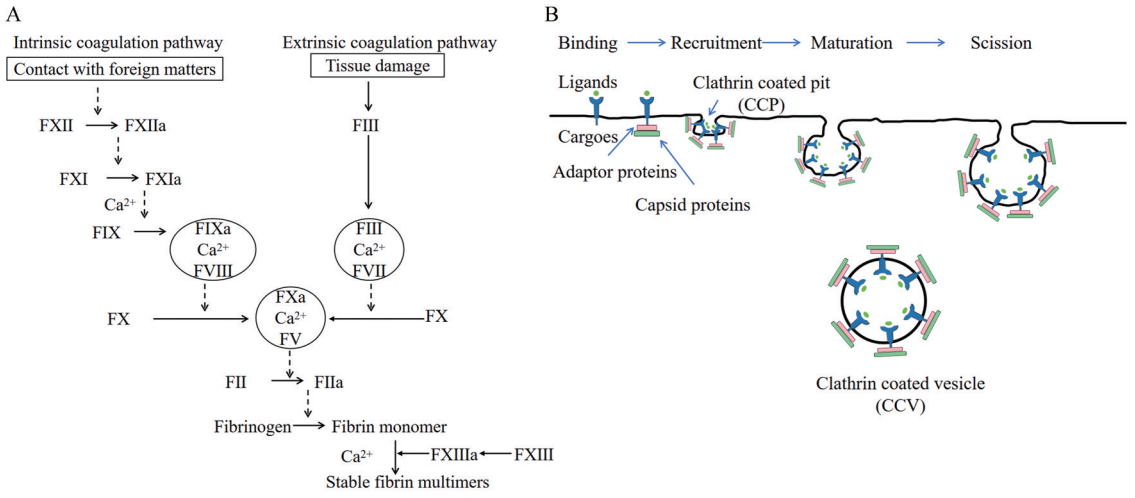

Figure 3 Role of TF in coagulation pathway (A). When blood vessels are damaged, TF binds to factor VII, activates X and reactivates prothrombin, eventually leading to coagulation. TF completes endocytic function through clathrin mediated endocytosis (B). Clathrin mediated endocytosis (CME) can be initiated structurally by some receptors on the plasma membrane, or it requires ligand and/or antibody binding. CME begins when endocytic capsid proteins in the cytoplasm begin to aggregate on the inner leaflet of the plasma membrane. Capsid proteins continue to assemble and grow by recruiting from the cytoplasm and interacting with additional protein adaptors. Key adaptor proteins bend the membrane, thereby concentrating internalized receptors / ligands into a "clathrin coated pit" (CCP). As the CCP invagination increases, the CCP neck narrows and separates from the plasma membrane through a fracture process. Actin polymerization helps pull CCP inward into the cytoplasm until the break is complete, and CCP is released and becomes a clathrin coated vesicle (CCV). Finally, the CCV shell is disassembled, and CCV fuses with endosomes to transport to specific subcellular locations, or can be recycled back to the cell surface. FII-FXIII: Congenital factor II-XIII; FIIa-FXIIIa: Activated factor II-XIII

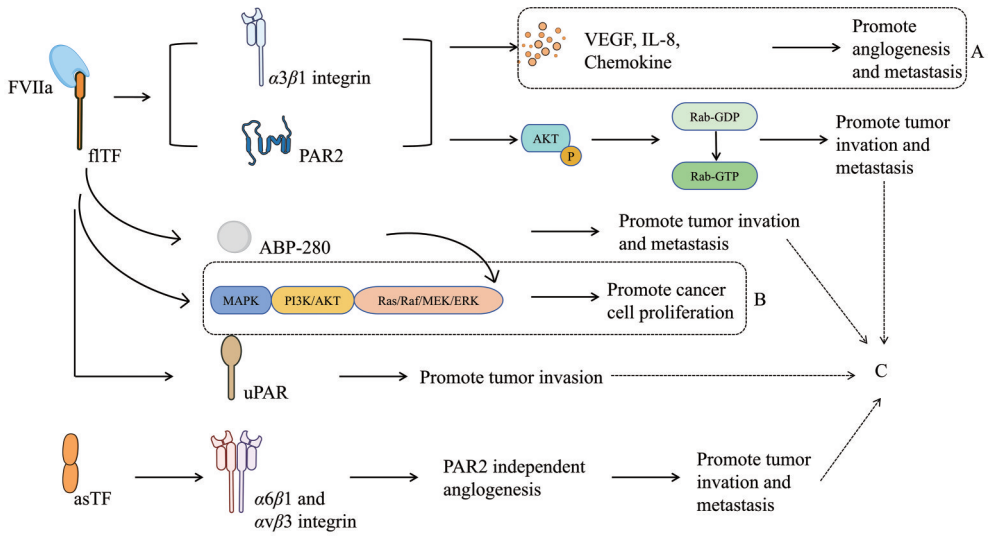

Figure 4 TF promotes anglogenesis and metastasis (A), TF promotes cancer cell proliferation (B), and TF promotes tumor invation and metastasis (C). flTF-VIIa plays a role in carcinogenesis in several ways: 1) phosphorylation and activation of AKT following PAR2 activation, which results in the conversion of inactive Rab-GDP to active Rab-GTP, actin polymerization, ultimately resulting in tumor cell invasion and metastasis, and activate VEGF, IL-8, chemokines, *etc*., and increase tumor angiogenesis and metastasis; 2) increasing cancer cell growth following activation of the P42-P44 MAPK, PI3K/AKT, and RAS/RAF/MEK/ERK signaling pathways; 3) *via* binding to ABP-280 can activate the aforementioned signaling pathways; 4) increasing UPAR expression and consequently tumor cell invasion. Instead, binding to integrins $\alpha6\beta1$ and $\alpha V\beta3$, asTF leads to PAR2-independent signaling and consequently increases tumor cell metastasis. PAR2: Protease activated receptors 2; AKT: Protein kinase B; Rab: Targeting GTPase; VEGF: Vascular endothelial growth factor; IL-8: Interleukin-8; ABP-280: Actin binding proteins-280; MAPK: Mitogen-activated protein kinase; PI3K: Phosphoinositide 3-kinase; Ras/Raf/MEK/ERK: A well-established MAPK pathway; uPAR: Urokinase-type plasminogen activator receptor

析 (gene expression profiling interactive analysis, GEPIA) 数据库检索, *F3*基因的表达与肾上腺皮质癌 (adrenocortical carcinoma, ACC)、食管癌 (esophageal carcinoma, ESCA)、肾嫌色细胞癌 (kidney chromophobe, KICH)、肾乳头状细胞癌 (kidney renal papillary cell carcinoma, KIRP)、胰腺癌 (pancreatic adenocarcinoma, PAAD)、胃癌 (stomach adenocarcinoma, STAD) 和葡萄膜黑色素瘤 (uveal melanoma, UVM) 的预后呈负相关 (图 5)。有三阴性乳腺癌的研究报道, 确定了 TF 在肿瘤进展和治疗耐药中的机制, 证明肿瘤细胞中的 TF 表达阻断 T 细胞募集趋化因子 CXCL9/10/11 的合成和分泌[24]。TF 过表达促进非小细胞肺癌对 KRAS-G12C 突变抑制的耐药性[25]。靶向 asTF 的首创新药 (first-in-class) 人源化抗体也发现增强了胰腺导管腺癌临床前模型中化疗的抗转移疗效[26]。在宫颈癌的治疗上, TF-ADC 药物 tisotumab vedotin 的获批上市显示了 TF 靶点在癌症治疗中的潜力[27]。且该药已被证明具有的良好内吞特性[28], 这使得 TF-ADC 药物能够被有效地内化并释放毒素, 从而增强 ADC 药物的疗效, 为 TF 靶点开发成 ADC 药物提供了更多可能性。

4　TF-ADC

4.1　ADC 基本原理概述

ADC 药物的发展已然成为抗肿瘤疗法的一种必然趋势。它是一种结合抗体特异性和小分子药物细胞

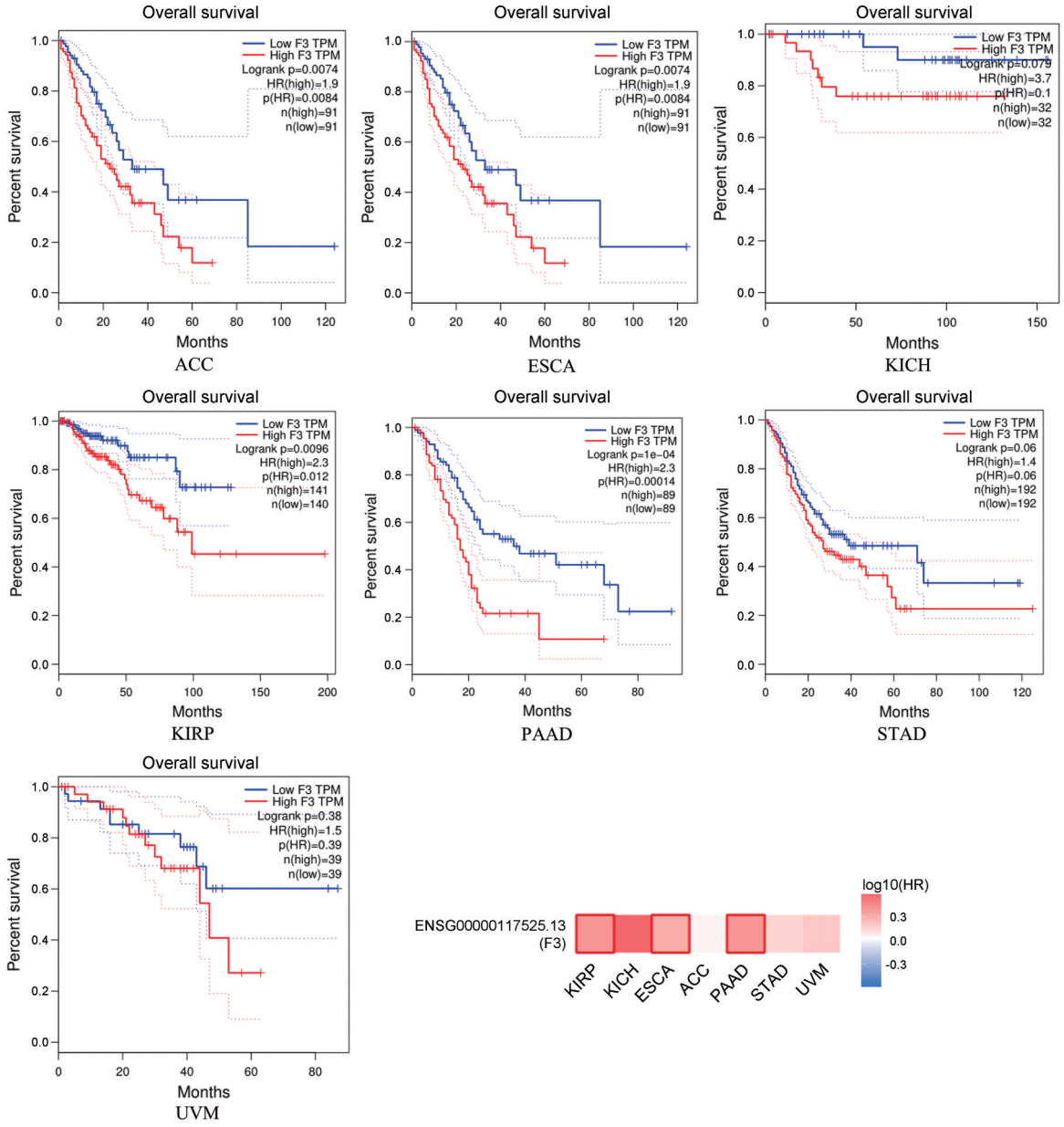

Figure 5　Correlation between *F3* expression levels and tumor prognosis. *F3* expression was negatively correlated with ACC, ESCA, KICH, KIRP, PAAD, STAD and UVM survival. HR: Hazards ratio (data source:http://gepia.cancer-pku.cn)

毒性的靶向治疗药物, 由抗体、细胞毒性药物和连接子三部分组成。其设计原理是利用抗体对特定抗原的精准识别, 将细胞毒性药物递送到目标细胞, 从而实现对肿瘤细胞的特异性杀伤。抗体部分特异性识别并结合肿瘤细胞表面的抗原, 如HER2等, 形成ADC-抗原复合物, 随后被肿瘤细胞内化。之后进入溶酶体, 连接子断裂释放细胞毒素发挥杀伤作用。其中, 连接子又可分为可切割的连接子和不可切割的连接子。细胞毒素也可根据其性质分为DNA靶向剂、微管蛋白抑制剂以及拓扑异构酶抑制剂。释放的细胞毒素不仅作用于被ADC直接靶向的肿瘤细胞, 还能扩散到邻近的肿瘤细胞, 发挥旁观者效应, 进一步增强抗肿瘤效果[29]。

4.2 TF-ADC药物研发进展

从TF发现开始, 基于TF靶点的药物研究涉及多个方向, 包括蛋白、抗体和ADC。截至目前仅有一款针对TF靶点ADC上市药物tisotumab vedotin。在ClinicalTrials. gov上查询TF靶点药物开发情况均聚焦在肿瘤领域, 主要处于临床I/II期, 详见表1。

4.2.1 Tisotumab vedotin 作为首个且唯一上市的TF-ADC药物, 它是由靶向TF的单克隆抗体tisotumab与细胞毒素单甲基奥瑞他汀E (monomethyl auristatin E, MMAE) 通过可剪切多肽连接子连接而成。2014年, Breij等[30]报道了TF-011-MMAE的分子设计, 以及该分子的亲和力、对凝血功能的干扰、内化特性、细胞毒性以及在小鼠体内药效。截至目前, 已披露的临床数据如表2、3所示。

Tisotumab vedotin单药治疗复发/转移宫颈癌已完全获批上市。通过对比研究发现, innovaTV 301[31]研究结果与早期研究innovaTV 201/204[32,33]相近, 整体ORR (overall response rate, ORR) 只有20%～30%左右。综合tisotumab vedotin过往的临床研究显示, tisotumab vedotin安全性较差: 一方面是毒素导致的眼部毒性, 已被FDA列入黑框警告; 同时因抗体带来的出血风险发生概率也较高, 达到62%, 40%患者用药受影响或停

Table 1 Antibody-drug conjugates (ADCs) developed for the TF (as of November 2024). MMAE: Monomethyl auristatin E

Drug name/Category	Toxin	Highest status	Indication	Developer
Tisotumab vedotin	MMAE	Approved	Cervical cancer	Genmab and Seagen
XB002	Modified MMAE	Clinical phase I	Pancreatic cancer and cervical cancer	Iconic Therapeutics
MRG004A	MMAE	Clinical phase II	Pancreatic cancer	Lepu Biopharma
XNW-28012	YL0014	Clinical phase I	Pancreatic cancer and cervical cancer	Evopoint Biosciences
ADCE-T02	Topoisomerase I inhibitors	Clinical phase I	Undisclosed	Adcendo and Multitude

Table 2 Clinical data of tisotumab vedotin monotherapy. r/m CC: Recurrent or metastatic cervical cancer; ORR: Overall response rate; CRR: Complete response rate; DCR: Disease control rate; PFS: Progression-free survival; OS: Overall survival; NR: No response

Study	InnovaTV201	InnovaTV204		InnovaTV301	
Mode of administration	Tisotumab vedotin	Tisotumab vedotin	Tisotumab vedotin	Tisotumab vedotin	Chemotherapy
Clinical phase	I/II	II	I/II	III	III
Indication	r/m CC	r/m CC	r/m CC	r/m CC	r/m CC
ORR	22%	24%	29.4%	17.8%	5.2%
CRR	2%	7%	70.6%	2.4%	0%
DCR	NR	72%	0%	75.9%	58.2%
PFS/month	4	4.2	3.1	4.2	2.9
OS/month	NR	12.1	11.4	11.5	9.5
Adverse events of grade 3 or worse	Peripheral neuropathy, hemorrhage, ocular adverse reactions	Peripheral neuropathy, hemorrhage, ocular adverse reactions, hemoglobin decreased	Peripheral neuropathy, hemorrhage, ocular adverse reactions, hemoglobin decreased	Peripheral neuropathy, hemorrhage, ocular adverse reactions, hemoglobin decreased	Peripheral neuropathy, hemorrhage, ocular adverse reactions, hemoglobin decreased

Table 3 Clinical data of tisotumab vedotin in combination therapy (InnovaTV205)

Mode of administration	Tisotumab vedotin+carboplatin	Tisotumab vedotin+pembrolizumab	
Clinical phase	I/II	I/II	I/II
Indication	1L r/m CC	1L r/m CC	2L/3L r/m CC
ORR	54.5%	40.6%	35.3%
CRR	15.2%	15.6%	11.8%
DCR	90%	81.3%	73.5%
PFS/month	6.9	5.3	5.6
OS/month	NR	NR	15.3
Adverse events of grade 3 or worse	Hemorrhage, diarrhea, nausea and thrombocytopenia	Hemorrhage, diarrhea, nausea and thrombocytopenia	Hemorrhage, diarrhea, nausea and thrombocytopenia

药。如果患者出现以上安全问题后, 均要接受干预治疗后才可继续使用药物, 也会出现因不安全等级较高问题而直接停止用药。

除单药研究之外, tisotumab vedotin正在开展与贝伐珠单抗、卡铂或帕博利珠单抗联合治疗宫颈癌的临床II期研究innovaTV 205[34], 初步显示ORR在35%～55%左右。联合用药方案显著优于tisotumab vedotin单药组, 但也同样出现贫血、腹泻、恶心和血小板减少等三级及以上不良反应, 推测可能原因是TF-ADC在结构设计上尚有不足之处。且在单药使用上已显示出各种不良反应, 导致在联合治疗的小分子选择上存在限制。因此, 后续可继续优化TF-ADC的分子设计, 以期提高疗效, 延长患者生存期。

4.2.2　其他临床在研TF-ADC　目前, 除一款上市药物外, 还有其他几款TF-ADC正处于临床开发阶段。第一款是XB002。它是由Zymeworks与Exelixis合作开发, 选择改构的MMAE作为细胞毒性有效载荷, 使用可剪切的多肽连接子与单克隆抗体连接而成, 以期提高TF-ADC的安全性和疗效。2021年, 根据Exelixis Inc.报道的XB002临床前结果, FDA宣布接受该药物的研究性新药申请, 以评估其在难治性实体瘤患者中的安全性和初步疗效。2024年发表了在头颈部鳞状细胞癌扩大队列的研究设计[35], 并在最新的ASCO2024会议上公布了其在转移性去势抵抗性前列腺癌上的研究计划[36]。第二款是MRG004A。它也是由MMAE通过多肽连接子与单抗连接而成, 目前正在美国与中国进行I/II期临床研究NCT04843709。第三款是XNW28012, 关于这款ADC药物的描述并不多。有报道称XNW-28012小分子部分使用宜联生物TMALIN平台, 有效载荷为YL0014。2023年7～8月先后获得药品审评中心 (center for drug evaluation, CDE) 和FDA批准临床试验, 主要用于治疗实体瘤。据其官方展示的非临床研究显示其在TF高表达的多种实体瘤模型中展现出了良好抗肿瘤活性, 且安全性特征良好, 整体安全性可控, 目前处于临床I期。最后一款是最新公布的ADCE-T02。ADCE-T02是一种高度差异化的抗TF-ADC, 也是首个基于拓扑异构酶I抑制剂有效载荷的ADC, 已在澳大利亚、美国和欧洲进入临床开发阶段。据官方报道, 其独特的抗体设计最大限度地减少了对凝血途径的影响, 而T1000-exatecan linker-payload技术平台已被证明可以放大旁观者效应, 提高连接子稳定性, 并有可能克服潜在的耐药机制。其抗体的设计有望改善出血风险, 毒素杀伤能力弱于tisotumab vedotin的MMAE毒素。这些差异化特征有望通过减少毒性驱动的治疗终止、中断或剂量减少, 转化为卓越的治疗窗口、更好的安全性、更高的反应率和更长的反应持续时间。

4.3　新一代TF-ADC研发现状

上市药物tisotumab vedotin已显示出初步的抗肿瘤疗效, 为癌症患者提供更多的治疗选择和生存获益。然而, 根据tisotumab vedotin所表现的安全性、有效性问题, 以及靶向治疗可能面临的耐药性问题, 在新一代TF-ADC设计时应充分考虑这些因素。

4.3.1　改善安全性　如前所述, tisotumab vedotin所面临的安全性问题是提高疗效的关键。因此, Zymeworks与Exelixis公司充分考虑tisotumab vedotin出现的各种临床不良反应, 筛选亲和力强、内化性能高且不影响正常凝血功能的单克隆抗体, 提高TF-ADC靶向特异性、内化效率的同时降低出血风险。在2022年一项关于XB002的晚期实体瘤患者 (JEWEL-101) 中的第一阶段剂量递增的研究显示, XB002在多个剂量水平下耐受性良好, 治疗相关的不良反应可控, 包括眼毒性, 无出血事件和神经病变, 未观察到剂量限制性毒性[37]。除此之外, 在未来ADC设计上, 可通过靶向多个靶表位或蛋白质, 双抗原或双特异性ADC增强选择性, 提高细胞内化率[38]。通过对药物的稳定性、纳米尺寸、荷电性、偶联方式、肿瘤微环境响应型连接子的选择以及亲水疏水平衡的调节等多方面综合考虑, 采用多学科技术交叉融合构建的纳米偶联药物技术平台, 提高药物递送的效率和对肿瘤的渗透性。在有效载荷部分, 选择具有不同效力和作用机制的细胞毒性分子, 再加上不同的抗体药物比 (drug-to-antibody ratio, DAR) 和连接技术, 可以开发出活性更强的药物[38]。据报道, 相同有效载荷的较低的DAR值可能与提高疗效或允许更高的剂量有关[39]。

4.3.2　提升有效性　由于tisotumab vedotin在临床中出现的安全性问题, 限制给药剂量的同时也限制了疗效的提升范围。在提升有效性方向, MRG004A取得了一定进展。MRG004A使用GlycoConnect定点偶联技术及HydraSpace极性间隔技术将MMAE共价连接至TF靶向单抗的可结晶段 (fragment crystallizable, Fc) 区域, 相较于传统偶联技术, 药物的均一性和稳定性均有望得到提升。并且借鉴tisotumab vedotin, 严格控制入组条件以平衡疗效与不良反应, 在ASCO2024会议上公布了中期临床数据[40], 结果显示MRG004A在胰腺癌患者中观察到显著抗肿瘤活性, ORR为33.3%, 疾病控制率 (disease control rate, DCR) 为83.3%, 并且高TF表达的胰腺癌患者的ORR为80%, DCR为100%。此外, MRG004A对三阴性乳腺癌及宫颈癌患者亦有疗效。在4名接受过多线治疗的三阴性乳腺癌患者中, ORR和DCR分别为25%和50%。在2名接受过四线治疗的宫

颈癌患者中, 1名患者达到部分缓解, 1名患者病情稳定。7.9%的患者曾出现严重不良事件。这些结果表明MRG004A在经历了多线治疗的情况下对多种肿瘤类型仍显示出可控的毒性以及显著的抗肿瘤活性。

4.3.3 解决耐药性 肿瘤细胞可能通过多种机制对ADC产生耐药性, 包括对有效载荷的耐药性、抗原表达水平的下调和细胞内运输途径的改变等[39]。而对于tisotumab vedotin, ATP结合盒转运蛋白(如P-糖蛋白)在对有效载荷MMAE的外排作用中发挥积极作用[41]。因此, 对于耐药性问题, 可能的解决方案是: ① 为防止细胞外排, 可将TF-ADC的细胞毒性有效载荷转变为外排底物较差的毒素, 如喜树碱类衍生物DXd、Eribulin等。由Adcendo和Multitude联合宣布开发的ADCE-T02, 是首个基于拓扑异构酶I抑制剂有效载荷的TF-ADC, 通过选择不同的有效载荷, 可能克服潜在的耐药机制。② 由于药物外排转运蛋白比亲水性化合物更有效地外排疏水化合物, 因此可以使用基于马来酰亚胺基的亲水接头设计TF-ADC, 如PEG4Mal在耐药模型的临床前研究中显示出有前景的活性[42]。③ 采用间歇给药的方式, 或者根据患者的个体差异和肿瘤的特性, 进行个性化剂量调整, 可以减少药物的耐药性。④ 开发双靶点或双表位ADC以克服耐药性[43]。⑤ 联合使用免疫治疗药物或化疗药物, 可以增强TF-ADC药物的疗效, 克服肿瘤细胞的免疫逃逸[44]。

5 展望

TF在多种肿瘤组织中过表达, 可介导血管生成、肿瘤细胞生长、侵袭和迁移, 且作为生物标志物可预测肿瘤患者预后。因此, TF可以作为抗肿瘤治疗的靶点, 对新型抗肿瘤药物的开发具有相当的研究价值和发展前景。作为在多种肿瘤中过度表达的跨膜蛋白, TF特别适合基于抗体的药物开发: 比如单克隆抗体、双特异性抗体、ADC、病毒样颗粒以及与传统化疗、免疫治疗、放射免疫治疗、光免疫治疗和靶向TF的纳米颗粒相结合的抗体药物等, 尤其TF靶向ADC的出现使得TF成为晚期转移性恶性肿瘤的可行且极具前景的治疗靶点, 因此, 在后续TF-ADC的设计中, 也值得在临床前和临床研究中进一步研究和探索。

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