王红霞, 主任医师, 教授, 上海交通大学医学院附属第一人民医院肿瘤中心主任, 博导。上海市优秀学术带头人、中国肿瘤青年科学家奖、上海浦江人才、上海医树奖（一等奖）、上海市三八红旗手等。主要从事肿瘤复发转移的基础与转化研究。主持国家级、省部级等课题20多项, 在*Nat Cell Biol*、*Cell Res*、*Cancer Discov*、*Nat Commun*、*Sci Adv*、*Biomaterials*、*J Hematol Oncol*、*PNAS*等发表SCI文章30多篇, 申请国家专利11项, 国际PCT专利1项, 发起并主持多项多中心临床试验。

四次跨膜蛋白超家族成员与肿瘤的研究进展

俞思薇　王红霞*

(上海交通大学医学院附属第一人民医院肿瘤中心, 上海 201600)

摘要　Tetraspanins又称四次跨膜蛋白超家族(transmembrane 4 superfamily, TM4SF), 包含33个家族成员, 通过形成二聚体或异二聚体, 或与其他蛋白质分子如整合素、黏附分子、主要组织相容性复合体II类抗原(major histocompatibility complex class II, MHC II)、T细胞受体等相互作用, 调控细胞黏附、增殖、组织分化、免疫反应等生物学过程。越来越多研究表明, 一些TM4SF分子也与肿瘤发生发展密切相关, 参与迁移、上皮–间质转化、血栓形成、肿瘤干细胞及外泌体信号转导等多阶段过程。对能够促进或抑制肿瘤发生发展的TM4SF功能和调控机制的深入了解, 将为未来有针对性的靶向干预提供新的策略。

关键词　四次跨膜蛋白超家族; 肿瘤; 转移

Research Progress on TM4SF Members and Tumors

YU Siwei, WANG Hongxia*

(*Department of Oncology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 201600, China*)

Abstract　Tetraspanins, also known as the TM4SF (transmembrane 4 superfamily), contain 33 family members. They regulate a series of biological processes, such as cell adhesion, proliferation, differentiation and immune response, by forming dimers or heterodimers, or interacting with other protein molecules, including integrin, adhesion molecules, MHC class II antigens and T cell receptors. Increasing studies have shown that some TM4SF members are closely related to tumorigenesis and development, playing critical roles in cancer cell migration, epithelial mesenchymal transformation, thrombosis, stemness and tumor-derived exosomes. An in-depth understanding of the functions and underlying mechanisms of TM4SF in tumor progression will shed light on development of tar-

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*通讯作者。Tel: 13524491606, E-mail: whx365@126.com

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*Corresponding author. Tel: +86-13524491606, E-mail: whx365@126.com

geted interventions in the future.

Keywords TM4SF; tumor; metastasis

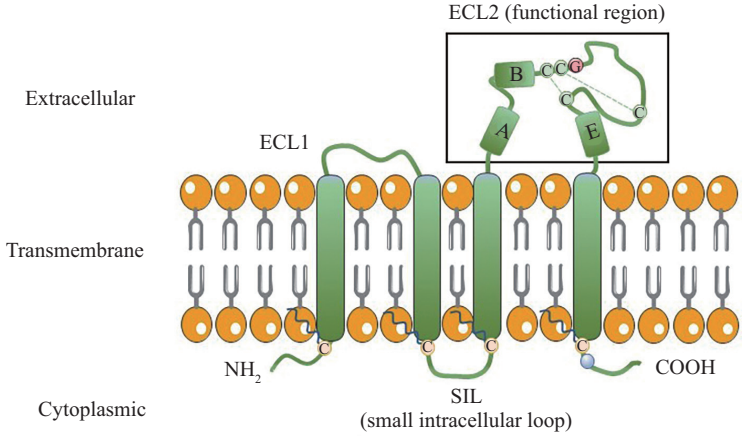
四次跨膜蛋白超家族(transmembrane 4 superfamily, TM4SF)成员定位于真核细胞生物胞膜上, 哺乳动物包含33种亚型, 在进化中具有高度保守性[1]。TM4SF蛋白直到1990年才见陆续报道[2], 包括分化相关蛋白9(CD9)、CD37、CD53、CD81、CD82、CD151和TSPAN8(tetraspanin-8)等。随着对其认识的不断深入, 发现该家族分子广泛参与到肿瘤转移、受精、膜动力学、感染、突触形成、血小板聚集、免疫反应等多种生物学过程[3]。除细胞膜外, TM4SF也大量存在于具有内吞作用的细胞器和外泌体中, 是外泌体的主要组成部分, 在不同细胞之间信号转导和受体细胞选择中起重要作用[4]。

1 TM4SF的分子结构与tetraspanin-web

顾名思义, TM4SF具有四次跨膜结构, 但并不是所有的四次跨膜分子都是TM4SF。该家族成员在结构上由短的氨基和羧基末端、4个跨膜区(transmembrane, TM)和2个细胞外环(extracellular loop, ECL)组成。TM区的极性残基可稳定其三级结构[5], ECL2包括基本恒定区和可变区, 其中恒定区与二聚反应有关, 可变区主要参与其他蛋白分子的互作。基于酪氨酸基序(Yxxφ), 一些TM4SF被分选输送到特定胞内间隔, 或通过与其他蛋白伴侣结合而被内化[6](图1)。

TM4SF没有已知的天然配体, 主要通过自身形成二聚体、或与其他家族成员及跨膜/胞质蛋白相互作用形成复合物而发挥生物学功能, 这就导致TM4SF在细胞表面组织了一个分子间相互作用的网络, 被称为"TM4SF网络"[7]。与TM4SF相互作用的蛋白质可分为四大类: 整合素和其他黏附分子、具免疫球蛋白结构域的蛋白质、外切酶(包括外切肽酶和金属蛋白酶)和细胞内信号分子, 如异三聚体G蛋白、磷酸肌醇4激酶(phosphatidylinositol 4-kinase, PI4K)和活化蛋白激酶C(protein kinase C, PKC)等[8-10]。

ECL2域中具有高度保守的半胱氨酸是其基本特征, 半胱氨酸棕榈酰化被认为是启动TM4SF网络形成所必需的, 保护TM4SF免于被溶酶体降解及促进胆固醇和神经节苷脂结合。某些特定整合素棕榈酰化也有助于TM4SF复合物的形成[11-12]。TM4SF与



ECL2为TM4SF的功能区域, 其基本恒定区由A、B、E螺旋构成, B和E螺旋之间常包含一保守CCG序列以及高度保守半胱氨酸残基(绿色点), 并可形成分子内二硫键(绿色线); 黄色点表示TM4SF的棕榈酰化位点, 可保护TM4SF免受溶酶体降解, 并可促进与胆固醇和神经节苷脂的结合; 蓝色点表示酪氨酸分选基序(Yxxφ), 基于该序列TM4SF被递送至特定胞内间隔。

ECL2 is the functional region of TM4SF. Its constant region is composed of A, B and E helices. A conserved CCG motif and highly conserved cysteine residues (green dots) form two intramolecular disulphide bonds (green lines) between B and E helices. The yellow dots indicate the palmitoylation site of TM4SF, which can protect TM4SF from lysosomal degradation and promote the binding with cholesterol and gangliosides; The blue dot presents a tyrosine-based sorting motif (Yxxφ), leading to the delivery of TM4SF to specific intracellular compartments.

图1 TM4SF的四次跨膜结构

Fig.1 The four-transmembrane structure of TM4SF

胆固醇、神经节苷脂结合后形成TM4SF复合物, 被称为富含tetraspanin膜微结构域(tetraspanin-enriched membrane microdomains, TEMs), 它提供了一个蛋白间相互修饰调控的信号转导平台[3,7]。尽管TEMs与脂筏具有一些共同特征, 但它们是由独立的结构组成的: TEMs在4 ℃时可被Triton X-100破坏, 而经典脂筏的特征分子(如糖基磷脂酰肌醇锚定蛋白和小窝蛋白)与TEMs功能未见报道[13]。

2 TM4SF和肿瘤发生发展

肿瘤转移包含着癌细胞从原发灶逃逸、渗透进入血管、循环播散、远端定植的级联反应过程。现有证据表明, TM4SF通过整合素信号调控肿瘤细胞扩散、迁移和黏附力改变[7,14]。TM4SF还可与肽酶、去整合蛋白和金属蛋白水解酶(a disintegrin and metalloprotease, ADAMs)(尤其ADAM10)[15]、基质金属蛋白酶(matrix metalloproteinases, MMPs)[16]和尿激酶纤溶酶原激活物表面受体(urokinase-type plasminogen activator receptor, uPAR)[17]等结合来调节细胞侵袭性。尽管TM4SF成员在结构上具有高度的保守型、TEMs中结合的跨膜和信号转导分子组装没有根本性差异, 但它们在肿瘤发生发展中的调控作用又不尽相同, 分别表现为促进或抑制肿瘤的发生发展(表1)。

2.1 TSPAN8

TSPAN8最初被认为是肿瘤相关性抗原。最近, 研究发现TSPAN8在多种人类肿瘤中高表达, 且与肝转移密切相关[29,51-52]。TSPAN8在肿瘤发生发展中表达上调的机制尚不清楚。我们前期研究发现, 乳腺癌进展中EGF/EGFR信号通路(epidermal growth factor (EGF)/EGFR signaling)被激活, 通过SOX9上调*TSPAN8*转录[53]。

与原发肿瘤相比, 转移瘤中TSPAN8表达进一步增加, 这一现象支持其在肿瘤进展中的重要作用。TSPAN8与α6β4结合, 伴随α6β4-CD151和TSPAN8复合物的内化, 细胞向迁移表型转化, 导致细胞运动性增加和肝转移的形成[54]。此外, TSPAN8诱导ADAM12显著表达, 参与癌细胞迁移、侵袭和转移调控[28]。TSPAN8还可与非整合素伴侣如EWI-F、EPCAM、CD13、PKC和PI4KII等相互结合[55]。TSPAN8高表达可激活PI3K-AKT、增强癌细胞抗凋亡能力[56], EpCAM-claudin 7复合物也在其中发挥作用[56]。

值得注意的是, 我们发现乳腺癌干细胞中TSPAN8表达上调, 且与治疗抵抗和不良预后相关, 上调TSPAN8表达可导致肿瘤细胞耐药及干性增强[27]。机制上, TSPAN8通过与PTCH1相互作用, 招募ATXN3去泛素化酶抑制蛋白酶体介导的SHH/PTCH1复合物降解, 激活Hedgehog信号通路增强乳腺癌细胞干性。这与FU等[57]的报道一致, $Lgr5^{+}TSPAN8^{hi}$亚群代表一个深度静止的乳腺干细胞群体, 其转录组与claudin-low肿瘤转录组高度相似。WANG等[58]也报道TSPAN8是胰腺癌起始细胞的生物标志物。

以往研究认为, 细胞膜上TSPAN8通过自身形成二聚体、或与其他蛋白分子在质膜上形成多聚体复合物发挥功能。偶然的, 我们发现TSPAN8也存在于细胞质和细胞核内, TSPAN8核定位可在多个肿瘤细胞系和肿瘤组织中被检测到[59]。在这一过程中, TSPAN8的棕榈酰化修饰以及其与胆固醇结合形成TSPAN8-胆固醇复合物对于其全长形式结构保护和跨膜提取非常重要。机制上, EGF-EGFR信号通路通过激活下游激酶AKT, 诱导胞质中非膜形式TSPAN8特定位点的磷酸化, 磷酸化后的TSPAN8与14-3-3θ和importin β1相互结合转位入核, 调控染色质重塑和下游促侵袭转移相关基因的转录, 如*MYC*、*BCL2*、*MMP9*等。这条EGFR-AKT-TSPAN8轴在多种人类癌症中被发现过度激活, 并与侵袭性表型和不良预后相关[60]。

2.2 CD81

CD81属于四肽蛋白家族, 完整的CD81蛋白晶体结构已被解析[61]。CD81分子的四个跨膜结构域内存在紧密的胆固醇结合位点, 且胆固醇的结合参与了CD81细胞外环(extracellular loop, ECL)的构象变化。CD81通过上皮−间质转化调控乳腺癌、结直肠癌的发生发展, 抑制CD81表达可导致癌细胞迁移能力减弱和肺转移减少[46]。此外, 研究报道人类黑色素瘤、骨肉瘤和结肠癌细胞中CD81的表达增高也可促进肿瘤的进展和转移[45-46,62]。

2.3 CD151

CD151过表达见于多种肿瘤类型, 如乳腺癌、胰腺癌、结直肠癌和非小细胞肺癌等, 与预后不良相关。然而在前列腺癌中, CD151高表达与组织学分级良好相关[63]。*CD151*敲除肿瘤细胞中MMP2、MMP7和MMP9表达降低。CD151通过与proMMP7

表1 TM4SF成员在肿瘤发生发展中的作用

Table 1 The role of TM4SF in tumorigenesis

四次跨膜蛋白超家族 Tetraspanins	肿瘤类型 Cancer type	作用 Function	参考文献 References
Tumor promoter			
TSPAN1 (NET-1)	Pancreatic cancer, gastric cancer	Promotes cell proliferation through mutations in the LIR motifs or as miR-573 target gene	[18-19]
TSPAN2	Lung cancer	Promotes cell migration and invasion by p53-TSPAN2 axis	[20]
TSPAN3	Leukemia	Inhibits cell proliferation and migration partly through the reduced TSPAN3 expression via miR-570-3p up-regulation induced by exosome-mediated circ_0004136 knockdown	[21-22]
TSPAN4	Esophageal squamous cell carcinoma, gastric cancer	Enhances cancer cells resistance	[23-24]
TSPAN5	Hepatocellular carcinoma	Promotes cell proliferation and migration by activating Notch signaling or being transcriptional activated by MRTF-A	[25-26]
TSPAN8	Breast cancer, esophageal carcinoma, colon carcinoma	Promotes cell proliferation, migration and stemness by (1) interacting with E-cadherin; (2) upregulating ADAM12 expression or (3) activating Hh signaling pathway	[27-29]
TSPAN9	Gastric cancer	Enhances cancer cells resistance to 5-fluorouracil	[30]
TSPAN15	Hepatocellular carcinoma	Promotes cell proliferation by activating EGFR/MAPK/ERK axis	[31]
TSPAN17	Glioblastoma multiforme	Suppresses cell proliferation and migration via miR-378-3p mediated TSPAN17 down-regulation	[32]
TSPAN20	Bladder cancer	Promotes cell proliferation, migration by activation of Wnt/β-catenin pathway	[33]
TSPAN21	Bladder cancer	Suppresses cell proliferation by downregulating TSPAN21 expression	[34]
TSPAN24 (CD151)	Skin squamous cell carcinoma	Promotes cell proliferation possibly depend on activation of STAT3	[35]
TSPAN31	Hepatocellular carcinoma	Promotes cell invasion and motility by activating the Akt/GSK-3β/β-catenin pathway	[36]
Tumor suppressor			
TSPAN6	Colorectal cancer	Promotes cell proliferation via the deletion of TSPAN6 which results in the increased level of TGF-α transmembrane form associated with extracellular vesicles and then activates EGF-dependent signaling pathways	[37]
TSPAN7	Bladder cancer	Suppresses cell proliferation and migration through upregulating PTEN expression and downregulating p-PI3K, p-AKT expression	[38]
TSPAN12	Non-small cell lung cancer	promotes cell proliferation via miR-196b-5p mediated down-expression of TSPAN12	[39]
TSPAN23	Lung cancer	Suppressor of cell migration, invasion	[40]
TSPAN27 (CD82)	Lung cancer	Suppressor of cell migration	[41]
TSPAN30 (CD63)	Colon carcinoma	Suppresses cell migration and invasion by associating with LN-5 and α3β1/CD63 complex	[42]
Inconsistent roles in different cancers			
TSPAN13 (NET-6)	Osteosarcoma,	Promoter of cell proliferation, migration	[43]
	breast cancer	Suppresses cell migration and invasion by downregulating MMPs	[44]
TSPAN28 (CD81)	Colorectal cancer, melanoma,	Promotes cell proliferation and migration by interacting with SHP-2 or upregulating MT1-MMP	[45-46]
	hepatocellular carcinoma	Suppresses cell migration through interacting with PI4KIIβ and promoting vesicles formation	[47]
TSPAN29 (CD9)	Pancreatic cancer,	Promotes tumor invasion by regulating glutamine metabolism	[48]
	ovarian carcinoma, fibrosarcoma	Suppresses cell migration and invasion by affecting several β1 integrin subsets or forming EWI-2/EWI-F/β1 complex and inactivating Akt, p38 and EGFR signaling pathways	[49-50]

结合, 促进MMP7激活和细胞外基质(extracellular matrix, ECM)水解, 抗CD151抗体可抑制MMP表达[64]。CD151在整合素运输过程中起关键作用, 通过与α3β1、α6β4和MMPs结合来调节细胞迁移。CD151对稳态的整合素α3和α6表达虽然没有影响, 但可以调控α3β1和α6β4在肿瘤−基质细胞中的定位[65], *CD151*突变或敲除可显著减弱α3β1、α5β1和α6β1内吞和在胞内囊泡积聚[66], 细胞运动能力受损、黏附增强[67]。

2.4 CD82

CD82上ECL2中含有六个半胱氨酸[68], 具有内化基序[6], 位于内体−溶酶体和外泌体中[6]。晚期癌症中CD82表达下调[69], 与多种肿瘤如前列腺癌、胃癌、黑色素瘤、结肠癌、卵巢癌等不良预后和转移密切相关[70]。体内外研究显示, CD82表达抑制癌细胞迁移和侵袭能力[41,71]。机制上, CD82与整合素α6和EGFR结合, 调控层黏连蛋白黏附和迁移[72]。CD82还可通过与EWI-2结合, 抑制层黏连蛋白和纤维连接蛋白活性[73], 促进uPAR和α5β1相结合[74], 干扰肝细胞生长因子受体(hepatocyte growth factor receptor, HGFR)信号转导进而激活Rac和CDC42[75]等系列机制抑制细胞的侵袭。

CD82对EGFR的活性调控受神经节苷脂GD1a影响, GD1a对富含CD82微结构域的空间组织很重要, 干扰CD82招募负调节EGFR的分子如酪氨酸磷酸酶[76]。与GD1a-CD82-EGFR复合物类似, CD82、整合素α3和HGFR间串扰也由神经节苷脂调节。神经节苷脂GM2-GM3-CD82复合物干扰HGFR激活, 伴随着MAPK通路上游GRB2和HRA以及PI3K上游GAB1活性下降, 从而影响细胞运动和增殖[77]。此外, GM3-CD82复合物可使PKCα易位和磷酸化EGFR上苏氨酸654位点, 调控EGFR内化[78]。CD82可与血管内皮细胞Duffy抗原/趋化因子受体(Duffy antigen receptor for chemokines, DARC)相互作用, 降低TBX2表达和上调p21诱导细胞衰老[79]。

尽管越来越多证据表明, CD82抑制肿瘤迁移, 但目前尚无证据表明CD82突变或杂合子缺失在肿瘤中存在。CD82 CpG岛高甲基化见于多发性骨髓瘤患者中[80]。MARREIROS等[81]报道野生型p53缺失与*CD82* mRNA水平下调相关。*CD82*启动子上有核因子NF-κB p50亚单位结合位点, IL-1β促进HTATIP-Fe65-Pontin复合物(也称RUVBL1)募集, 后者作为NF-κB p50共激活因子, 增强*CD82*转录。转移性肿瘤细胞中, HTATIP下调, RUVBL2取代RUVBL1并抑制NF-κB活性[82]。CD82下调的另一种模式可能是exon 7表达缺失导致对其的选择性剪接[83]。

2.5 CD9

早期观点认为, CD9抑制肿瘤转移, 其功能与抑制整合素介导的运动有关。卵巢癌中, CD9表达水平与整合素β1、α2、α3、α5和α6相关, CD9表达下调导致基质黏附减弱和弥漫性生长[50]。神经节苷脂在促进CD9-整合素复合物形成中发挥重要作用[84]。高GM3表达促进GM3-CD9-整合素α3复合物形成, 抑制SRC与Rac功能[85]。反之, GM3-CD9-整合素复合物缺乏, 细胞运动性和软琼脂集落形成增加[84]。

研究表明, CD9对细胞迁移能力的影响与EGF-EGFR信号通路有关。CD9交联可促进EGFR内化, 降低EGFR自身磷酸化水平, 减弱由EGFR磷酸化启动的信号激活。CD9抑制转化生长因子(transforming growth factor α, TGFα)裂解[86], 可溶性TGFα激活EGFR同时诱导受体下调, 抑制自分泌生长刺激和细胞迁移[87]。微阵列分析表明, CD9可调控Wnt家族相关分子如Wnt1、Wnt2b、Wnt5a, Wnt1诱导信号通路蛋白1(Wnt1-inducible signaling pathway protein 1, WISP1)、WISP3、MYC、血管内皮生长因子A(vascular endothelial growth factor, VEGFA)和MMP26表达, 这种调控与侵袭性生长和肿瘤进展相关。此外, CD9可与血小板聚集诱导因子podoplanin结合抑制肿瘤转移。在SCID小鼠中, CD9与podoplanin共表达抑制肺转移发生, 并伴有血小板聚集受损[88]。血小板通过CLEC2与podoplanin结合, 诱导血小板脱颗粒[89]。由于CLEC2不识别CD9相关性podoplanin, 因此血小板聚集功能受损。血小板聚集可促进微血管栓塞和转移形成, 并保护肿瘤细胞免受免疫攻击。

然而, 关于CD9与肿瘤的关系目前报道不一致[90]。WANG等[48]报道CD9是胰腺癌起始细胞的标志物。$CD9^{high}$细胞增加了类器官及克隆形成能力。$CD9^{high}$胰腺癌细胞形成的肿瘤很好再现了异质性状态, 而$CD9^{low}$细胞仅产生导管样上皮后代。在机制上, CD9促进谷氨酰胺转运体ASCT2(alanine-serine-cysteine transporter 2)的质膜定位, 增强胰腺癌细胞对谷氨酰胺的摄取。此外, 有研究报道肿瘤浸润边

缘表达高水平CD9。CD9过度表达的黑色素瘤细胞MMP2表达增加, 促进了跨内皮迁移。

2.6 CD63

CD63表达通常与肿瘤转移抑制相关, 但也有相反性报道。CD63抑制转移形成可能依赖于整合素内吞、MMP14溶酶体降解和金属蛋白酶组织抑制剂1(tissue inhibitor of metalloproteinases 1, TIMP1)募集[91]。CD81通过与α-肌动蛋白4作用重塑肌动蛋白细胞骨架来抑制肝癌细胞的运动[47]。在黑色素瘤中, G蛋白偶联受体GPR56与Gαq、CD81形成复合物, GPR56结合组织谷氨酰胺转胺酶2(transglutaminase 2, TGM2), TGM2是细胞外基质中的主要交联酶。GPR56-Gαq-CD81复合物与TGM2的结合促进细胞黏附, 从而干扰肿瘤细胞迁移[92]。对于CD63在肿瘤进展中的潜在作用需要进一步深入研究。

3 TM4SF与肿瘤免疫

TM4SF参与免疫反应得到越来越多的证实, *TM4SF*(CD37、CD53、CD81、CD82、Tssc6、CD151)敲除的小鼠在体液和/或细胞免疫应答中存在缺陷[93], 并体现在T细胞过度增殖[94]、抗体产生受损[95]和抗原呈递受限等方面[96]。其中, CD53、CD81、CD82和CD37已被证明与MHC II类复合物相关[97]。

T细胞激活依赖于免疫突触形成期间抗原递呈细胞表面MHC-肽复合物的抗原识别。最近研究发现, CD9和CD151在T细胞免疫突触上支持整合素介导的信号转导[98]。T细胞中的CD81通过与细胞间黏附分子-1(intercellular cell adhesion molecule-1, ICAM-1)和CD3相互作用参与免疫突触的调控[99]。有趣的是, 研究表明浸润性乳腺癌患者免疫细胞上的CD9与更长的无病生存期相关, 而肿瘤细胞上的CD9表达则显示相反的效果[100]。

为产生足够的免疫反应, 免疫细胞需要从外周组织迁移到引流淋巴结和肿瘤部位。TM4SF与多种整合素相互作用, 从而影响细胞迁移能力[101]。在免疫系统中, CD151缺失会降低T细胞运动性[102]。*CD37*$^{-/-}$小鼠与野生型小鼠相比, 表现出肿瘤排斥反应缺陷, 表明CD37直接参与抗肿瘤免疫[103]。另一项研究证实*CD37*$^{-/-}$树突状细胞(dendritic cells, DCs)和中性粒细胞[104]的运动性降低, 而*CD82*$^{-/-}$ DCs的运动性增加[105], 提示CD82与CD37具有反向制衡的免疫调控功能。

4 TM4SF与外泌体

TM4SF在各种类型的内吞细胞器和外泌体(exosome)膜上大量存在[106]。越来越多研究揭示了肿瘤源性外泌体蛋白在肿瘤进展、免疫调节和转移中的预后和功能重要性[107]。外泌体是由细胞分泌产生的直径50~200 nm的一类细胞外囊泡(extracellular vesicle, EVs), 其携带丰富生物活性分子(蛋白质、RNA等)[108], 故被认为是一种有效的细胞间通讯模式, 在免疫反应、传染性物质细胞间传播和肿瘤进展中起重要作用。研究人员在外泌体中发现CD63、CD9、TSPAN8和TSPAN6等TM4SF蛋白表达, 表明它们在细胞间信号转移中发挥作用[109]。研究发现, 蛋白质、mRNA和microRNA的相对丰度在外泌体和供体细胞之间存在差异[4], 这种差异可能体现在多泡体(multivesicular bodies, MVBs)阶段通过对蛋白质的单泛素化、富含胆固醇膜微域中定位或更高阶寡聚来实现对所包裹cargos的选择性[4,110]。CD9、CD63和CD81是文献中报道的最常见的外泌体相关标记物, 在许多研究中被用于外泌体捕获[111]。这些TM4SF中的每一种都已被证明在外泌体生物发生或cargos分拣中发挥积极作用, 表明它们在外泌体分泌途径中起着重要作用[91]。但最近的研究表明, 它们实际上在外泌体中异质表达[112], 这种表达差异表明存在明显功能差异的外泌体亚群[113]。

TM4SF及其相关蛋白在外泌体中显著富集, 然而它们对外泌体功能的影响尚未确定。LIU等[114]报道, 血清细胞外小泡上TSPAN8表达升高与非小细胞肺癌的远处转移有关。TSPAN8促转移的另一个机制在于参与血管生成。小鼠肿瘤中过表达D6.1A导致弥散性血管内凝血(disseminated intravascular coagulation, DIC)[115], DIC是一种血栓前状态, 常发生在癌症患者中。虽然DIC发生是多种因素共同作用的结果, 但肿瘤引发的血管生成和肿瘤血管的渗漏被认为是重要的原因[116]。D6.1A是一种强血管生成诱导剂, D6.1A通过肿瘤细胞来源性外泌体的传递促进全身血管生成开关[117], 肿瘤细胞内表达的整合素在其中也起调控作用。

5 展望

虽然越来越多研究揭示了TM4SF家族成员在

肿瘤细胞发生发展中的重要性, 但介于该家族成员生物学功能的复杂性, 其具体分子机制及调控多样性仍有待进一步深入探索。此外, 前期数据提供了部分TM4SF蛋白在促进或抑制肿瘤发生发展中的不一致结论, 其原因可能在于TEMs的组成以及相互作用的蛋白质伴侣不同。这些互作蛋白分子与TM4SF网络的形成决定了最终信号转导的走向与调控节点, 多聚体复合物中的互作蛋白修饰后或被降解、或通过细胞转运重新返回膜上、或以外泌体的形式将信息从肿瘤细胞传递到邻近受体细胞, 从而产生不同的生物学效应与调控结局。

TM4SF内化后在胞内囊泡的行程轨迹以及通过外泌体/胞外囊泡在细胞间进行信号传递是抑制或促进肿瘤转移的重要调控方式之一。TM4SF在外泌体/胞外囊泡膜上大量富集, 不但本身可以与受体细胞表面受体蛋白相互作用参与信号传递过程, 同时也决定了从本体细胞膜上脱落外分泌的外泌体/胞外囊泡以及胞内MVBs包裹输送信号分子(蛋白、microRNA等)的分选和选择过程。

一些*TM4SF*基因敲除小鼠仅在病理条件下表现出血管生成缺陷表型, 强调了TM4SF功能的动态性质, 在生理与病理状态下可能具有完全不同的调控模式。尽管现有研究仅露出冰山一角, 但越来越多数据揭开了TM4SF在肿瘤发生发展中的神秘面纱。随着我们对TM4SF功能更全面的了解, 将为未来有针对性的靶向干预提供新的诊疗策略。

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