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评 述
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外泌体介导的肿瘤免疫学及合成生物技术在肿瘤治疗中的应用

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摘要 外泌体是一类具有代表性的细胞外囊泡, 通过多泡体与质膜融合释放到细胞外. 随着研究的深入, 除了直接的细胞间接触和信号分子释放, 外泌体被证实是一种新的细胞间通讯方式. 这些囊泡具有复杂的生物学内容物, 包括mRNA、微小RNA(microRNA, miRNA)、蛋白质、脂质、糖类及其他生理活性物质, 可在局部和全身发挥作用. 事实上, 肿瘤来源外泌体(tumor-derived exosomes, TEXs)携带亲代细胞的抗原和效应分子, 在肿瘤微环境的免疫应答调控中发挥关键作用. TEXs可通过转运内容物重编程应答细胞的生物学功能, 调控其表型特征, 进而以促进肿瘤免疫或抗肿瘤免疫的方式调节宿主免疫应答. 本文综述了TEXs对自然杀伤细胞和T淋巴细胞的免疫调控能力, 并阐述了其在肿瘤来源外泌体背景下的生物学功能, 为利用合成生物技术制备工程化外泌体治疗肿瘤提供理论基础.

关键词 肿瘤来源外泌体, 肿瘤免疫学, 自然杀伤细胞, T淋巴细胞

外泌体是一类纳米级囊泡, 大小为30~150 nm, 悬浮密度为1.13~1.19 g/mL, 并具有双层磷脂膜结构, 其腔内囊泡由内体(现称为多泡体)的限制膜进一步内陷形成, 随后通过多泡体与质膜融合分泌到细胞外[1~3] (图1). 20世纪80年代中期, Johnstone等人[4,5]首次在成熟的哺乳动物绵羊网织红细胞(未成熟红细胞)中发现外泌体, 1987年Johnstone等人[6]将其命名为“exosomes”. 此后研究表明, 几乎所有哺乳动物细胞均可通过ATP依赖的过程分泌外泌体, 包括健康细胞(如B淋巴细胞[7]、T淋巴细胞[8]、自然杀伤细胞[9]、树突状细胞[10]、肥大细胞[11]、上皮细胞[12]、血小板[13])和肿瘤细胞[14]. 外泌体稳定性高, 广泛存在于各种体液中, 如循环血液[15]、尿液[2]、胸腔积液[16]、唾液[17]、脑脊液[18]、鼻腔分泌物[19]等. 研究表明, 常规羊膜穿刺术收集的羊水也可能含有大量胎儿来源的外泌体[20]. 外泌体最初被认为是细胞的“垃圾场”, 是细胞处理废

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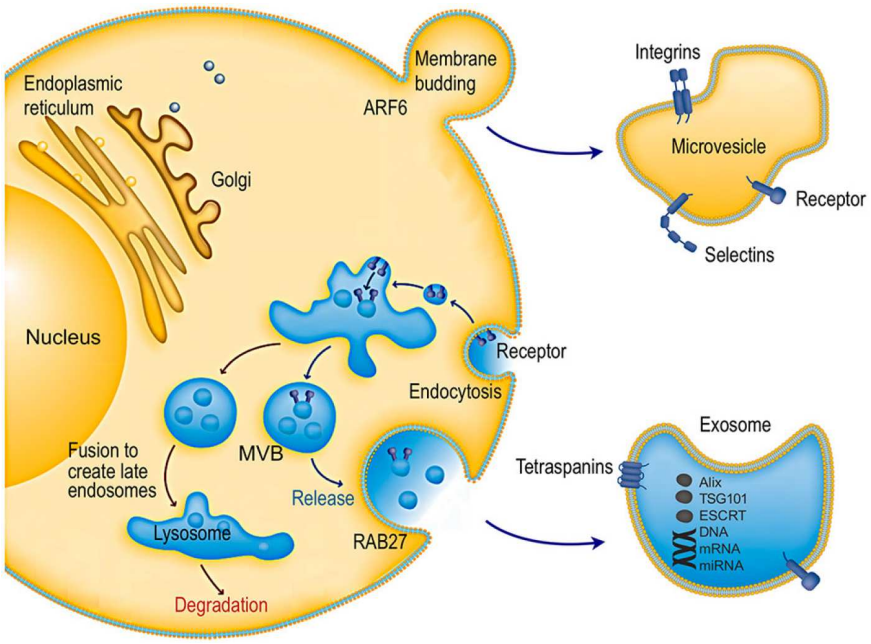

图 1 外泌体的生物发生和分泌的细胞内途径(图片引用自文献[3], 已获American Chemical Society版权许可)
Figure 1 The intracellular pathways of exosome biogenesis and secretion (reproduced from ref. [3] with copyright permission from American Chemical Society)

弃成分的一种机制[6], 但现在被重新视为丰富且稳定的循环生物标志物来源. 外泌体作为重要的旁分泌/内分泌介质, 含有大量生物分子, 包括但不限于蛋白质[21,22]、脂质[23,24]、mRNA/微小RNA[25,26]、DNA[27,28]及其他能与靶细胞相互作用的可溶性因子.

外泌体能够介导局部和远处受体细胞之间的细胞间通讯, 并通过转运内容物表观遗传调控应答细胞的生物学功能和表型特征, 如调节免疫应答[29]、细胞代谢[30]、肿瘤转移[31]、细胞迁移[32]及赋予药物耐药性[33]等, 最终改变宿主环境.

肿瘤细胞在肿瘤微环境中释放大量外泌体, 这些肿瘤来源外泌体(tumor-derived exosomes, TEXs)密切反映亲代癌细胞的生理和病理特征. TEXs携带特定或相关的肿瘤相关抗原(tumor-associated antigen, TAA)[34,35], 包括但不限于MAGE3/6[36]、Melan-A/MART-1[14]、HER2/Neu[37]、癌胚抗原(carcinoembryonic antigen, CEA)[38]、间皮素[39]、上皮细胞黏附分子(epithelial cell adhesion molecule, EpCAM)[40]、gp100[35]等, 以及主要组织相容性复合体(major histocompatibility complex, MHC)分子、伴侣热休克蛋白(heat shock protein, HSP)、共刺激分子(CD86及CD37, CD53, CD63, CD81, CD82等四跨膜蛋白)等重要免疫分子[41](图2). 在肿瘤生长早期, 宿主免疫系统的抗肿瘤应答在肿瘤微环境中占主导地位, 携带多种抗原的TEXs可增强肿瘤抗原识别、刺激T淋巴细胞($CD8^+$细胞毒性T淋巴细胞)活化, 从而诱导有效的抗原特异性抗肿瘤免疫应答[42~46]. 同时, 体内外研究表明, TEXs比细胞裂解物和凋亡小体更能激发免疫应答[47], 使其成为无与伦比的无细胞癌症疫苗肿瘤抗原来源, 用于刺激抗肿瘤免疫应答[34,38,48]. 然而, 在晚期癌症患者中, 有效的免疫刺激效应尚未被充分观察到, 这是因为肿瘤微环境调控新因子的表达[49,50], 可能促使TEX分子向引起免疫抑制的方向分选, 如白细胞介素10(interleukin 10, IL-10)[51]、转化生长因子-β(transforming growth factor β, TGF-β)[52]、前列腺素E2[53]、潜伏膜蛋白1[54,55]、自然杀伤细胞2族成员D(natural killer group 2 member D, NKG2D)配体[56]及人类白细胞抗原(human leukocyte antigen-G, HLA-G)[57]等. 这些因子通过不同水平和途径同时抑制多个靶标的免疫功能, 帮助肿瘤逃避宿主免疫监视, 破坏免疫细胞的抗肿瘤能力, 增强肿瘤对免疫系统的免疫抑制作用, 促进肿瘤免疫逃逸. 本文主要总结TEXs对自然杀伤细胞和T淋巴细胞的作用.

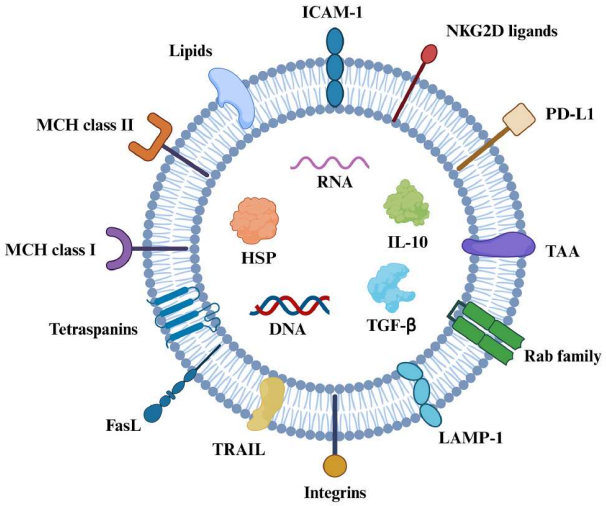

图 2 TEX的内容物成分示意图
Figure 2 Schematic diagram of the components of TEX contents

1 肿瘤来源的外泌体对免疫细胞的调控作用

1.1 肿瘤来源外泌体调控自然杀伤细胞活性

自然杀伤(natural killer, NK)细胞是一类淋巴细胞, 在固有免疫和适应性免疫中均发挥重要作用. 然而, 癌症患者中NK细胞的频率、活性及NK细胞相关受体的表达水平常受到抑制[58]. 值得注意的是, 一项研究表明, 胰腺导管腺癌荷瘤小鼠的唾液外泌体与外周NK细胞相互作用, 导致NK细胞活化水平降低(表现为表面受体NKG2D和CD69下调), 进而使其对胰腺肿瘤细胞的细胞毒性减弱. 抑制胰腺导管腺癌细胞的外泌体生物合成可消除唾液外泌体对NK细胞的影响, 并逆转外周NK细胞受损的细胞毒性潜能[59]. 这提示TEXs可能与NK细胞功能异常相关. 事实上, 用含有circUHRF1、膜相关转化生长因子β1(transforming growth factor β1, TGF-β1)或NKG2D配体MICA*008等成分的TEXs处理NK细胞, 已被证实可通过各自的作用机制影响NK细胞功能[60~62]. 例如, Clayton等人[58]发现, 人胸膜间皮瘤或前列腺癌细胞系来源的外泌体可快速且持续地下调NKG2D的表达, 这至少部分依赖于外泌体膜相关的TGF-β1. TGF-β1通过激活受体细胞内的SMAD2/3信号通路, 进而抑制NKG2D的转录表达, 最终导致NK细胞功能受损.

众所周知, NKG2D是主要在免疫系统细胞毒性臂上表达的活化受体, 其在癌症中的异常缺失是免疫逃逸的关键机制[63]. 然而, 外源性IL-15处理可通过干扰SMAD信号通路, 逆转NK细胞表面NKG2D表达的下调, 从而对抗TEXs相关TGF-β1的抑制作用[62]. 有趣的是, 研究发现, 用TEXs处理后, NK细胞的NKG2D表达下调, 而其他标志物(如CD69)未发生变化, 这表明该应答具有选择性和非活化性[58], 与之前的现象存在矛盾[59], 这可能是因为不同肿瘤细胞来源的外泌体含有广谱及特异性效应分子, 从而对NK细胞产生不同影响. 此外, 白细胞介素2(interleukin 2, IL-2)在淋巴细胞的功能平衡中起关键作用[64,65], 而TEXs可通过改变IL-2应答来减弱同基因NK细胞的保护作用. TEXs可抑制IL-2刺激的NK细胞生长信号[66], 还可通过选择性降低穿孔素的表达(由IL-2通过激活Jak3/Stat5信号调控)增强对NK细胞溶细胞活性的抑制[52,66].

此外, 已有报道称TEXs在特定情况下可刺激有效的NK细胞介导的抗肿瘤免疫应答. Multhoff团队[67]首次证实, TEXs中Hsp70/Bag-4阳性膜囊泡可通过颗粒酶B介导的凋亡刺激NK细胞活性、迁移能力及对靶肿瘤的Hsp70反应性溶细胞活性. 多项对富含HSPs的TEXs的研究也报道, 膜结合HSP70可作为自然杀伤细胞介导的溶细胞攻击的识别位点[68~71]. 而且, 当HSP70家族成员与决定其功能的其他共伴侣蛋白协同作用时, 其效力会增强[71~73]. 然而, 需要注意的是, 上述效应并非在所有类型癌症来源的外泌体中均一致存在. 具体而言, TEXs对NK细胞介导的抗肿瘤免疫的刺激作用与TEXs中包裹的一类称为损伤相关分子模式(damage-associated molecular patterns, DAMPs)的特定分子相关. DAMPs包括HSPs、S100蛋白、核酸(双链DNA、线粒体DNA、核糖核蛋白)、核染色质结合蛋白(高迁移率族蛋白盒1(high mobility group box-1, HMGB1)、组蛋白)及钙网蛋白[74~76]. 这些分子由死亡、受损或受感染的细胞释放, 作为佐剂通过激活先天免疫细胞引发强效抗肿瘤免疫应答[77,78]. 先前的研究表明, 经辐射或DNA损伤剂处理的肿瘤细胞来源的含DAMP外泌体, 可通过刺激树突状细胞(dendritic cells, DCs)的干扰素基因刺激因子(stimulator of interferon gene, STING)通路依赖和/或Ⅰ型干扰素依赖途径延缓肿瘤生长[79~81]. 此外, 它们可引发不依赖$CD8^+$ T细胞, 但依赖产生干扰素γ的肿瘤浸润NK细胞的宿主先天和适应性抗肿瘤免疫[82]. 激活的肿瘤浸润NK细

胞能够通过分泌cDC1趋化剂C-C基序趋化因子配体(C-C motif chemokine ligand, CCL)5和X-C基序趋化因子配体1刺激常规I型树突状细胞(conventional type 1 dendritic cell, cDC1)的募集, 从而促进抗肿瘤免疫应答[83]. 总之, 来自受损或死亡肿瘤细胞的含有DAMPs的外泌体可引发炎症并增强抗肿瘤免疫反应.

1.2 肿瘤来源外泌体及其对T细胞的免疫调控功能

T细胞(又称T淋巴细胞)是免疫系统的关键组成部分, 负责赋予机体对抗原的免疫应答特异性. T细胞的功能受到多种因素的严格调控, 包括营养缺乏[84]、缺氧[85]、高浓度免疫相关代谢物[86]、细胞因子[87]及趋化因子[88]等, 这些因素可直接或间接影响T细胞功能. 然而, 近年来的研究揭示, TEXs可能通过诱导活化T细胞凋亡及调节辅助性T细胞分化等方式调控T细胞功能, 这些效应可能由TEXs中含有的特定内容物(如调节性微小RNA、细胞因子及其他免疫调节剂)介导. 因此, TEXs可能代表了肿瘤微环境中调控T细胞应答的一种新机制, 值得进一步研究.

1.2.1 肿瘤来源外泌体调控T细胞增殖

TEXs对T细胞增殖的影响尚不明确, 尤其是与亲代肿瘤细胞相比时——外泌体来源于三种黑色素瘤相关细胞系. 尽管各细胞系来源的外泌体在形态上相似, 但它们对原代$CD8^+$ T细胞的功能影响存在差异: B16F0外泌体以剂量依赖方式抑制T细胞增殖, Cloudman S91来源的外泌体促进细胞增殖, 而Melan-A外泌体的影响可忽略不计[89]. 归根结底, TEXs对T细胞增殖的调控取决于外泌体膜相关成分或可溶性成分. 多种免疫相关分子已被证实在T细胞增殖调控中发挥作用[90]. 此外, 缺氧可增强癌细胞的外泌体分泌, 并通过外泌体TGF-β1抑制T细胞增殖, 从而促进肿瘤生长发育[91]. 研究表明, 缺氧诱导因子HIF-1α可直接上调肿瘤细胞中TGF-β1的表达并促进其分选进入外泌体[92]. 外泌体TGF-β1的效力比可溶性TGF-β1更强, 这可能是体内缺氧微环境中实体瘤快速生长的机制之一[52]. 与TGF-β1类似, IL-10和前列腺素E2等其他成分在特定情况下也可作为关键免疫调节因子阻碍T细胞增殖[93,94]. 除上述TEXs对T细胞的直接作用外, 间接机制也逐渐被发现, 包括肿瘤外泌体抑制能诱导$CD4^+$ T细胞增殖的DCs, 这部分依赖于程序性死亡配体1(programmed death-ligand 1, PD-L1)[95].

另一方面, 就TEXs对受体T细胞抗肿瘤效力的影响而言, 其对T细胞增殖的作用已得到明确证实. TEXs倾向于抑制抗肿瘤免疫, 促进肿瘤进展, 大量有说服力的研究支持这一观点[36,96,97]. 例如, 骨髓瘤来源的外泌体抑制反应性$CD4^+$ T细胞增殖, 但促进$CD8^+$ T细胞和调节性T细胞(regulatory T cell, Treg)增殖. 尽管$CD8^+$ T细胞数量增加, 但其功能下降[98]. 此外, 携带半乳糖凝集素9的Epstein-Barr病毒(Epstein-Barr virus, EBV)感染的鼻咽癌细胞来源外泌体可诱导EBV特异性CD^+ T细胞凋亡[99], 但参与$CD4^+CD25^+$Treg细胞的生成[100].

1.2.2 肿瘤来源外泌体介导辅助性T细胞分化

效应性辅助性T(T helper cell, Th)细胞是免疫功能的关键介质, 在抗原呈递细胞或肿瘤细胞的调控下由$CD4^+$ T细胞分化而来, 根据细胞因子分泌和免疫调节功能可分为Th1, Th2, Th17和Tfh亚群. 近年来研究表明, 肿瘤细胞介导辅助性T细胞分化的一个重要途径是通过肿瘤来源外泌体的复杂内容物, 本文重点关注Th17和Th1. 文献中记载的TEX介导的Th17分化调控机制包括微小RNA/5′-AMP激活蛋白激酶(AMPK)/mTOR通路[101]、外泌体长链非编码RNA CRNDE-h/RORγt/IL-17轴[102]、HSP70/IL-6/TGF-β1通路[103]及外泌体微小RNA/MAPK1通路[104]等. 例如, 热应激肿瘤细胞来源的外泌体含有丰富的HSP70, 可通过IL-6将免疫抑制性调节性T细胞转化为Th17细胞[103]. 此外, 人鼻咽癌细胞来源的外泌体微小RNA可通过干扰分子信号(包括通过MAPK通路调控STAT蛋白的磷酸化水平)阻碍Th17细胞分化[104]. 同样, RORγT作为Th17细胞的关键转录因子, 在与不同TEXs共培养时表达水平不同, 进而导致Th17分化结果的矛盾[96,102]. 肿瘤细胞类型、状态等的差异最终反映在TEXs的内容物中, 此外, 受体细胞的类型也会导致这些结果差异. 这种矛盾现象也体现在Th1分化中, 例如, 肿瘤外泌体(无论是来自Lewis肺癌还是4T1细胞)均可显著抑制$CD4^+$ T细胞向$CD4^+$IFN-γ^+Th1细胞分化[95]. 相反, 在异基因小鼠模型中, HSP70富集的TEXs可诱导强烈的Th1型免疫应答并减少调节性T细胞数量, 表现为IgG2a和IFN-γ的产生显著增加, 从而在自体和异基因小鼠模型中体内清除癌细胞[105].

1.2.3 肿瘤来源外泌体调控CD8$^+$ T细胞功能

CD8$^+$ T细胞在先天性抗肿瘤免疫应答中起关键作用. 然而, 肿瘤细胞可通过多种机制影响CD8$^+$ T细胞功能. 其中, T细胞的代谢稳态对其功能至关重要, 而TEXs可打破这种平衡. 例如, 外泌体circTRPS1可通过circTRPS1/miR141-3p/GLS1/谷氨酰胺代谢轴清除活性氧(reactive oxygen species, ROS), 从而促进恶性表型并诱导CD8$^+$ T细胞耗竭[106]. T细胞耗竭(T cell exhaustion)是指在慢性抗原刺激(如肿瘤微环境)下, CD8$^+$ T细胞逐渐丧失效应功能(如IFN-γ, TNF-α分泌能力), 高表达抑制性受体(如PD-1, TIM-3, LAG-3等), 并伴随表观遗传重编程的一种功能失调状态. ROS水平对T细胞活化、后续扩增及生物学功能维持至关重要[107,108]. 此外, ROS清除还可通过抑制mTOR/Myc将CD4$^+$ T细胞阻滞在细胞周期G0/G1期[109], 抗氧化剂也有类似作用[110].

TEXs还含有CD39和CD73, 分别介导ATP(或ADP)和5′-AMP的水解, 通过增加腺苷生成在微环境中负调控CD8$^+$ T细胞功能[111]. 另一方面, TEXs通过影响CD8$^+$ T细胞的关键蛋白来调节其生理活性, 进而影响其功能. 例如, 富含TGF-β1的TEXs可通过下调表面受体NKG2D来阻止CD8$^+$ T细胞活化, 这也部分依赖于外泌体MIC[58]. 同样, 这可显著抑制CD8$^+$ T细胞的细胞毒性功能[56].

成功的信号转导对细胞生理活性至关重要. 黑色素瘤来源的外泌体hsa-miR-3187-3p通过直接靶向PTPRC 3′非翻译区(untranslated region, UTR)并以剂量依赖方式降低CD45表达, 从而减少T细胞受体(T-cell receptor, TCR)信号[112]. CD45与Src激酶的相互作用对T细胞的抗原受体信号转导至关重要[113]. 此外, 外泌体circUSP7/miR-934/SHP2轴通路可导致细胞毒性T淋巴细胞耗竭[114], 进而导致CD8$^+$ T细胞功能受损和免疫应答异常. circUSP7还可诱导对抗PD1免疫治疗的耐药性[114]. 当PD1与其生理配体(PD-L1或PD-L2)结合时, 通过招募SHP2(使TCR介导的信号转导的主要整合子Zap70去磷酸化并失活)来抑制T细胞的活化和功能[115~118].

CD8$^+$ T细胞免疫抑制表型的转变也是影响其功能的机制之一. 多种头颈部癌来源的外泌体半乳糖凝集素1及RNA的协同作用, 通过减少免疫共受体CD27/CD28的表达, 促成新的功能异常相关表型转换[119]. 此外, TEXs可通过“中间细胞”(包括但不限于调节性B细胞(Breg)、Treg或巨噬细胞)间接对CD8$^+$ T细胞发挥免疫调控作用. 例如, TEXs诱导具有M2表型特征的免疫抑制性PD-L1$^+$或PD1$^+$肿瘤相关巨噬细胞群体, 进而通过不同作用机制损害细胞毒性CD8$^+$ T细胞应答, 包括降低CD8$^+$ T细胞比例, 减少细胞毒性细胞因子产生及促进T细胞凋亡[120~122]. 细胞生理的调控最终通过广义上的蛋白质实现, 本文仅讨论部分案例.

1.2.4 肿瘤来源外泌体驱动调节性T细胞的分化和扩增

在肿瘤微环境中, 积聚的Treg常通过产生免疫抑制性细胞因子[123], 诱导应答T细胞凋亡[124], 以及通过免疫抑制受体细胞毒性T淋巴细胞相关抗原4(cytotoxic T lymphocyte-associated antigen-4, CTLA-4)抑制抗原呈递细胞成熟等方式, 阻碍抗肿瘤T细胞的活化、存活和扩增[125]. 因此, 研究TEXs对Treg细胞的调控机制, 有助于开发新的治疗策略以减轻Treg对肿瘤T细胞的抑制, 增强免疫系统对肿瘤细胞的免疫监视.

肿瘤微环境中Treg的异常积聚是免疫抑制的明确标志[126]. 一方面, 肿瘤可驱动Treg在微环境中的募集[127], 先前研究表明趋化因子促进这一过程[128~130]. Delhem团队[131]证实, 鼻咽癌来源的富含CCL20的外泌体不仅优先在肿瘤内募集Treg, 还具有独特的免疫调节能力, 以剂量依赖方式诱导具有更强抑制功能的Treg扩增[131]. 另一方面, TEXs可诱导其他表型的T细胞向Treg转化. 如前所述, 鼻咽癌外泌体能够促进Treg在肿瘤内的募集. 此外, TEXs可募集CD4$^+$CD25$^-$ T淋巴细胞, 并以CCL20[131], TGF-β1/IL-10[132], PD-L1[95]或相关分子依赖[52]的方式诱导Treg表型相关细胞标志物的过表达, 使其转化为CD4$^+$CD25$^+$FOXP3的Treg. 从胸腺细胞悬液或人初乳及成熟母乳中分离的外泌体也能使CD4$^+$CD25$^+$FOXP3高表达的Treg的转化得到促进[133,134].

另一项研究表明, 结直肠癌细胞来源的外泌体可通过激活TGF-β/Smad信号、抑制SAPK信号, 上调Treg相关基因, 从而将受体细胞(Jurkat细胞、外周血单个核细胞及CD4$^+$ T细胞)的表型改变为具有显著促肿瘤活性的Treg样细胞[135]. 除趋化因子和细胞因子外, 外泌体微小RNA还可通过MAPK通路改变STAT蛋

白的磷酸化或调控磷酸酶和张力蛋白同源物介导的信号级联反应, 促进初始CD4$^+$ T细胞向Treg分化[136].

与先前报道一致, 鼻咽癌细胞已被证实可诱导Treg分化[137]. 此外, 研究观察到TEXs可促进Treg增殖并上调免疫抑制基因(如TGF-β1、IL-10、CTLA-4、磷酸化STAT3、磷酸化SMAD2/3及腺苷)的表达, 从而增强其抑制活性[29,132,136]. 除上述αβ T细胞外, 占所有T淋巴细胞0.5%~5%的γδ T细胞在先天和适应性免疫监视[138]及强效抗癌活性中均发挥关键作用[139]. 然而, γδ T细胞也可被极化为特定表型, 促进肿瘤逃避宿主免疫系统[140]. Huang团队[141]发现, 乳腺癌来源的外泌体SNHG16/miR-16-5p/SMAD5调控轴可增强TGF-β1/SMAD5通路激活, 导致γδ1 T细胞中CD73表达上调. 肿瘤浸润的CD73$^+$γδ1 T细胞是乳腺癌中主要的Treg群体, 主要通过腺苷介导的通路发挥免疫抑制功能.

1.2.5 肿瘤来源外泌体诱导T细胞凋亡

肿瘤细胞操控T细胞的最佳策略包括诱导T细胞耗竭或凋亡, 特别是针对抗肿瘤效应T细胞, 这可以最大程度地抑制肿瘤免疫系统, 从而最大程度地促进肿瘤进展. 这种状态可与HIV病毒相比, HIV通过CCR5和CXCR4共受体识别并攻击大多数免疫细胞, 导致其死亡, 尤其是CD4$^+$ T淋巴细胞[142]. 正如预期的那样, 肿瘤细胞通过导致抗肿瘤效应细胞的过早死亡来促成抗肿瘤活性的缺失[36,143]. 先前的研究进一步表明, CD8$^+$ T细胞比CD4$^+$ T细胞对凋亡更敏感, 且CD8$^+$ T细胞的效应亚群和肿瘤特异性亚群优先成为凋亡的靶标[144,145]. 大量证据支持癌症患者循环T细胞的凋亡是一种普遍现象, 并不局限于特定肿瘤类型[146~148].

越来越多的证据表明, TEXs参与肿瘤细胞诱导的T细胞耗竭或凋亡. TEX介导的T淋巴细胞凋亡机制包括Fas-FasL(CD95-CD95L)相互作用通路[149,150]、半乳糖凝集素9-Tim-3相互作用通路[99]、miR-135b-5p/特异性蛋白1(SP1)轴通路[151]、APO2L/TRAIL[152,153]、p38 MAPK介导的内质网应激[154]、外泌体Cbl家族泛素连接酶/PI3K/Akt信号[155]、pGSN/FLIP/胱天蛋白酶-8(3)轴[156]、微小RNA(miR-690)/线粒体凋亡通路[157]等, 无论TEXs来自新鲜肿瘤细胞系还是癌症患者的血清[158,159].

综上所述, 根据上述机制可将凋亡机制分为两类: 由死亡受体诱导的外源性通路和与线粒体相关的内源性通路(由多种非受体介导的刺激触发)[160]. 这两种通路并非完全独立, 外源性通路的激活也会导致线粒体的变化. 例如, TEXs膜相关形式的FasL与Fas的相互作用可抑制T细胞活化信号成分TcR/CD3-ζ, JAK3及p-STAT5的表达[36,161,162], 并伴随胱天蛋白酶激活、膜间凋亡蛋白(细胞色素c、SMAC和AIF)释放、线粒体膜电位丧失[145,163]及促凋亡与抗凋亡比率(Bcl-2/Bax)的逆转[96,164].

据我们所知, Bax与Bcl-2的比率决定细胞的存活状态[165]. 值得注意的是, 膜相关形式的FasL触发Fas介导凋亡的效率高于其可溶性形式[166]. 有证据表明, 膜FasL向可溶性形式的转化会下调其促凋亡活性[167]. 此外, 研究发现, 外泌体Cbl家族泛素连接酶通过与p85调节亚基相互作用诱导PI3K泛素化和降解, 进而以时间和剂量依赖的方式降低下游Akt活性, 并激活死亡受体(胱天蛋白酶3和8)和线粒体(胱天蛋白酶3和9)通路[155].

除直接作用外, 通过转运细胞间接诱导T细胞凋亡也是TEXs发挥作用的机制之一[120]. 将T细胞与富含miR-23a-3p的TEXs共培养可刺激巨噬细胞, 降低CD8$^+$ T细胞比例, 同时增加T细胞凋亡[121]. 此外, 同一类型外泌体中已发现携带多种凋亡相关分子[161,168]. 用ZB4抗Fas单克隆抗体阻断可显著降低(但不能完全抑制)来自活动性口腔鳞状细胞癌患者血清的外泌体的促凋亡活性, 已知这些外泌体含有FasL[163].

2 合成生物学在利用外泌体治疗肿瘤中的应用

合成生物学与纳米医学工程的交叉创新为肿瘤治疗和疾病调控开辟了全新路径. 外泌体及类似纳米囊泡系统作为细胞间信息传递和药物载体近几年正受到广泛关注: 其来源不仅限于肿瘤细胞, 也包括微生物或植物. 武汉大学张先正团队[169~171]提出的合成材料强化微生物(Material-Assisted MicroOrganisms, MAMO)概念, 通过将微生物与纳米材料结合, 构建了如口服菌群鸡尾酒、靶向性纳米药物等系统, 实现了对肿瘤微环境和肠道菌群的精准调控; 西南大学肖波团队[172]从天然植物中提取外泌体样纳米囊泡, 如茶树花外泌体样纳米囊泡(nanovehicles from tea flowers, TFENs)用以抑制乳腺癌生长转移并调节肠道菌群, 展示了天

然囊泡系统在疾病治疗中的独特价值. 通过构建含同步裂解电路(engineered synchronized lysis circuit, eSLC)的大肠杆菌, 实现肿瘤内群体裂解并释放治疗性载荷[173], 或利用可编程封装系统动态调控细菌的免疫逃逸与可控清除, 这些设计思路为用合成生物学制备工程化外泌体提供了重要工具. 工程化细菌可被编程为可控的“微型工厂”, 外泌体作为天然存在的纳米级囊泡, 同样具备基因工程化改造的巨大潜力. 通过合成生物学手段可赋予外泌体靶向递送、信号激活等功能, 成为连接天然生物活性与人工精准个性化设计调控的理想桥梁.

合成生物学在纳米医学中的应用近期已展现出突破性进展. 本实验室近期也构建了一种口服纳米疫苗系统*E. coli* (AH1-CDA-Co1)@iPDA[174](图3): 该系统以基因工程改造的大肠杆菌1917为底盘, 通过iPDA涂层抵御胃肠道酸性环境并延长肠道滞留时间, 在超声刺激下定向分泌含AH1肿瘤抗原、STING激动剂CDA及M细胞靶向肽Co1的外泌体样囊泡(outer membrane vesicles, OMVs). 这些OMVs可高效穿越肠道上皮屏障, 激活cGAS-STING与TLR4天然免疫通路, 诱导长

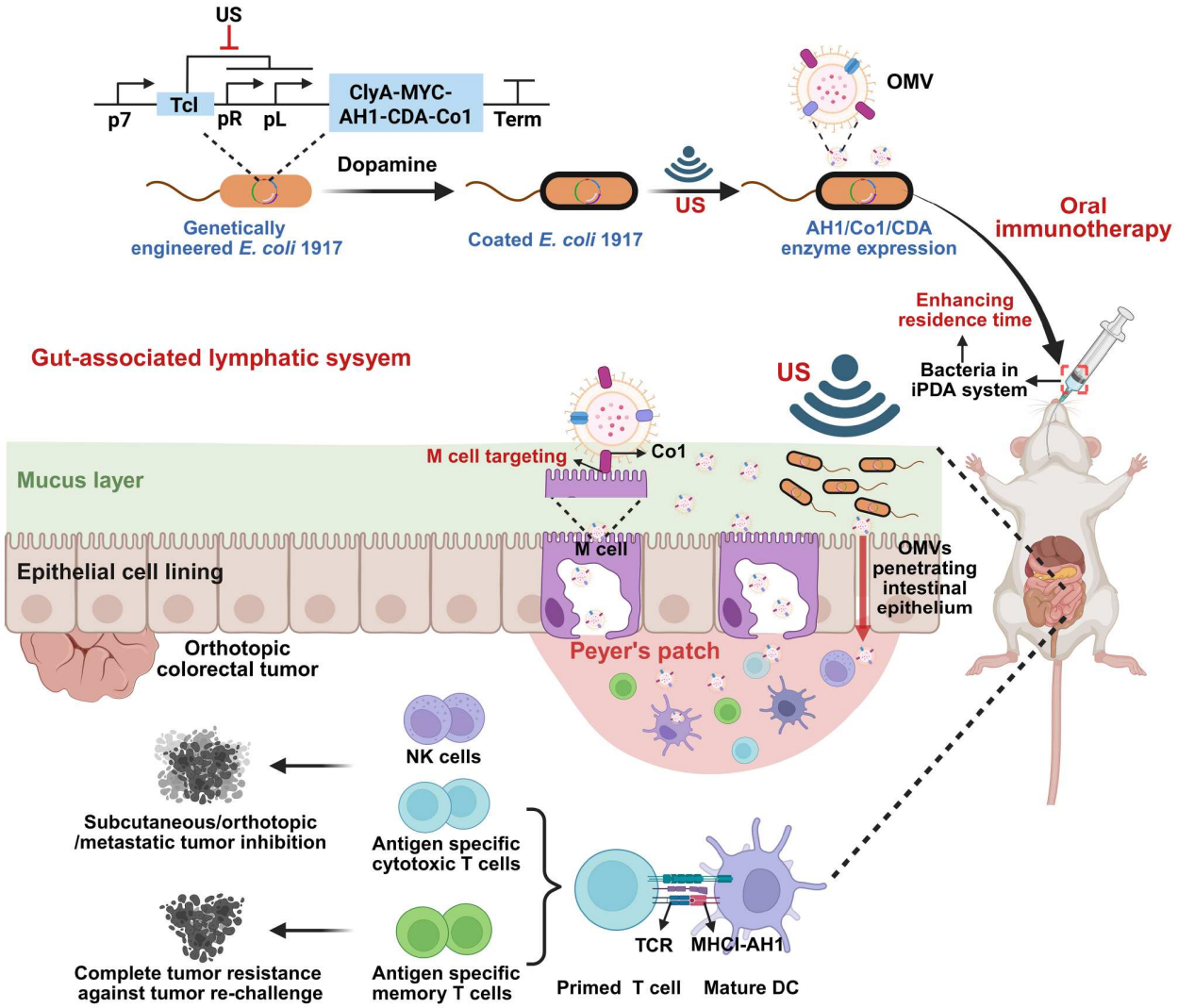

图 3 大肠杆菌(AH1-CDA-Co1)@iPDA作为原位超声响应型口服结肠癌疫苗的制备及作用机制(图片引用自文献[174], 已获John Wiley and Sons版权许可)

Figure 3 Preparation and the action mechanism of *E. coli* (AH1-CDA-Co1)@iPDA as an *in situ* ultrasound-responsive oral vaccine for colon cancer (reproduced from ref. [174] with copyright permission from John Wiley and Sons)

期抗原特异性免疫应答，在皮下、原位及术后淋巴转移结直肠癌模型中均实现显著肿瘤抑制，延长存活且无复发，充分证明了外泌体样囊泡在合成生物学驱动的肿瘤免疫治疗中的核心价值. 这类研究不仅拓展了外泌体的应用场景, 更揭示了其作为合成生物学“天然载体”的独特优势: 既能保留生物相容性与靶向性，又可通过基因编辑和外部刺激实现精准调控. 这为深入理解外泌体在肿瘤免疫微环境中的作用机制提供了全新视角，也为后续探讨其免疫学调控功能奠定了重要基础.

除细菌OMV系统外，合成生物学在工程化囊泡领域呈现出多元化的技术路线，极大拓展了外泌体在肿瘤治疗中的应用前景. (ⅰ) 细菌外泌体: 因易于基因工程改造和大规模生产，它们是理想的疫苗载体和药物递送平台[173]. (ⅱ) 植物源外泌体样囊泡: 例如，从茶树花中提取的外泌体样纳米囊泡可通过调节ROS-MAPK通路抑制乳腺癌转移并重塑肠道菌群，展示了天然植物囊泡的治疗潜力[172]. (ⅲ) 哺乳动物干细胞工程化外泌体: 间充质干细胞来源的外泌体具有天然的低免疫原性和良好的组织相容性. 通过CRISPR激活(CRISPR activation, CRISPRa)系统对其工程化，使其过表达CD47抗体, 可显著增强外泌体的肿瘤靶向性并避免被单核巨噬系统清除[175]. 近期研究进一步证实，肿瘤细胞衍生囊泡可通过合成生物学技术负载IL-12 mRNA: 通过基因工程改造肿瘤细胞, 使其分泌的囊泡表面修饰靶向肽(如CD44配体)，同时内载IL-12 mRNA，静脉注射后可精准富集于肿瘤部位，通过释放IL-12 mRNA激活NK细胞和$CD8^+$ T细胞增殖，下调肿瘤微环境中Treg和M2型巨噬细胞比例，实现免疫微环境重塑与肿瘤抑制协同作用[176]. 该研究首次实现肿瘤细胞囊泡对功能性mRNA 的高效包载与靶向递送，为工程化外泌体的免疫治疗应用提供了全新技术范式. (ⅳ) 人工合成纳米模拟体: 利用合成生物学理念设计的脂质纳米粒(lipid nanoparticle, LNP)可高效模拟外泌体的结构和功能. 例如，负载STING激动剂cGAMP的LNP能有效激活抗肿瘤免疫应答，同时具备批间稳定性高、免疫原性低的优势[177]. 这些系统共同构成了工程化囊泡技术的工具箱，为下一代肿瘤免疫治疗提供了丰富选择.

3 结论

TEXs因其独特的从亲代肿瘤细胞转运生物活性成分的能力，日益被认为是协调免疫信息系统的关键组成部分. 携带免疫调节内容物的TEXs传递分子信号，通过正向和负向方式重编程自然杀伤细胞和T淋巴细胞的生物学功能、调控其表型特征，进而调节免疫应答. 然而，TEXs的抗肿瘤免疫特性可能不明确，其结果存在差异，且涉及多种作用机制. 这种变异性可归因于癌细胞类型的差异(进而导致外泌体表型的差异)以及迄今为止所研究的免疫环境的不同. 本文深入探索了外泌体在肿瘤免疫中的作用机制，为开发利用合成生物技术制备工程化外泌体治疗肿瘤提供理论基础和设计思路.

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Exosome-mediated tumor immunology and the application of synthetic biology in cancer treatment

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Exosomes are a representative class of extracellular vesicles released into the extracellular space through the fusion of multivesicular bodies with the plasma membrane. As research advances, exosomes have been identified as a novel mode of intercellular communication, distinct from direct cell-to-cell contact and the release of signaling molecules. These vesicles carry a complex array of biological contents, including mRNA, microRNA (miRNA), proteins, lipids, carbohydrates, and other physiologically active substances, which can act both locally and systemically. Indeed, tumor-derived exosomes (TEXs) carry antigens and effector molecules from their parental cells, playing a pivotal role in regulating immune responses within the tumor microenvironment. TEXs can reprogram the biological functions of recipient cells and modulate their phenotypic characteristics by transferring their cargo, thereby regulating host immune responses in ways that can either promote tumor immunity or anti-tumor immunity. This review summarizes the immunomodulatory capabilities of TEXs in natural killer cells and T lymphocytes, elucidates their biological functions within the context of tumor-derived exosomes, and lays the theoretical groundwork for utilizing synthetic biotechnology to engineer exosomes for cancer therapy.

tumor-derived exosomes, tumor immunology, natural killer cells, T lymphocytes

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