

外泌体在肿瘤负向免疫调控中的作用

Progress in tumor immunosuppressive function of exosomes

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[摘要] 外泌体(exosome)是一类直径30~100 nm的囊泡样小体,其含有蛋白质、mRNA、微小RNA(miRNA)、DNA片段等,是细胞间物质和信息转导的重要媒介。外泌体参与肿瘤的发生、发展、侵袭和转移等各个过程,其在肿瘤免疫中发挥双向调控功能。本文重点阐述外泌体在肿瘤负向免疫调控中的作用,如肿瘤来源外泌体(tumor-derived exosome, TEX)能够阻碍DC的分化和成熟,促进巨噬细胞极化,减弱B细胞功能及诱导调节性B细胞(regulatory B cell, Breg)产生,促骨髓前体细胞分化为髓系抑制性细胞(myeloid-derived suppressor cell, MDSC),减弱NK及T淋巴细胞的杀伤功能,诱导调节性T细胞(regulatory T cell, Treg)等;又如免疫细胞来源外泌体(immunocyte-derived exosome, IEX),主要为Treg、CD8⁺ T细胞来源的外泌体,同样具有免疫抑制功能。

[关键词] 外泌体; 肿瘤; 免疫调控

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外泌体(exosome)最早于1983年在绵羊的网织红细胞中被发现,其一度被认为是细胞排泄产物的一种方式^[1]。随着研究的深入,发现多种细胞可分泌外泌体,包括肿瘤细胞、成纤维细胞、免疫细胞、间质细胞等,其可在细胞间传递mRNA、微小RNA(miRNA)、DNA片段、蛋白质、脂质等^[2-4]。外泌体具有脂质双分子膜,使其包含的内容物在远距离传递中仍可保持稳定,其可通过融合或相互作用参与调节特异性的细胞与细胞间的交流。这种由外泌体调节的细胞间信号转导参与多种生理及病理过程,尤其是在肿瘤的发生、发展、侵袭和转移过程中^[5-6]。外泌体在肿瘤免疫中发挥双向调控功能:一方面,外泌体可作为肿瘤抗原,引发机体的抗肿瘤免疫反应;另一方面,外泌体可负向调控多种免疫细胞功能。越来越多的研究^[7-8]表明,肿瘤来源外泌体(tumor-derived exosomes, TEX)内含miRNA、细胞因子等可抑制宿主免疫应答,引起免疫耐受。同时,免疫细胞本身也可分泌外泌体,通过作用于其他免疫细胞起到负向免疫调控作用。然而,外泌体在肿瘤细胞与免疫细胞间物质交换和信号转导中具体的作用机制仍未充分明了。笔者在本文中重点讨论TEX及免疫细胞来源外泌体(immunocyte-derived exosome, IEX)在肿瘤负向免疫调控中的作用,深化对外泌体在肿瘤免疫中功能的认识,以期对肿瘤诊断及治疗提供理论基础及药物靶点。

1 TEX的免疫抑制作用

外泌体的研究为肿瘤的生物行为方面的研究提供了新的视角,TEX包含多种肿瘤组分及免疫抑制分子,不仅可作为肿瘤诊断的生物标志物,更在肿瘤的免疫逃逸过程中发挥了重要作用^[9-12]。TEX直接或间接的影响了免疫细胞的发展、成熟和抗肿瘤活性,通过给免疫细胞传递DNA、mRNA、miRNA等组分起到重编程相应免疫细胞的作用^[13]。

1.1 抑制DC的分化和成熟

DC属于专职APC,在免疫应答的起始和调解中发挥重要作用^[14],不成熟的DC低表达共刺激分子,常会引起抗原特异性T细胞无能^[15]。有研究^[16-17]表明,小鼠乳腺癌细胞产生的外泌体可在体内靶向CD11b⁺骨髓前体细胞,体外实验发现,在TEX刺激骨髓前体细胞12 h后,其IL-6及磷酸化的STAT-3水平升高,从而阻碍骨髓前体细胞分化为DC,在人乳腺癌细胞来源的外泌体也同样发现了该现象。人TEX可使CD14⁺单核细胞分化为CD14⁺HLA-DR^{-low}细胞,从而抑制T细胞增殖和溶细胞作用^[18]。在迟发型过敏的小鼠模型中,包含卵清蛋白的TEX通过TGF-β1通路抑制DC成熟而无法诱发延迟型过敏反应^[19]。调节因

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子X相关蛋白(regulatory factor x-associated protein, RFXAP)是一种重要调控MHC-II类分子的转录因子,来源于胰腺癌细胞的外泌体内含miR-212-3p,可抑制DC中RFXAP,从而减少MHC-II类分子表达,引起DC免疫耐受^[20]。同时,TEX可通过影响DC表面表达的模式识别受体(pattern recognition receptors, PPR)减弱DC的免疫应答,胰腺癌细胞来源的外泌体内含miRNA-203,可下调DC上Toll样受体4(Toll-like receptor 4, TLR4)的表达,并抑制TNF- α 、IL-12等细胞因子的产生,抑制DC参与的抗肿瘤应答,同时,miR146a可通过激活smad4信号通路抑制DC的成熟,而耗尽其外泌体中的miR,可增强DC/CIK的抗肿瘤活性^[21-24]。

1.2 促进巨噬细胞的极化

巨噬细胞可分为M1型与M2型。M1型巨噬细胞有促炎作用,可产生IL-12、IL-23等细胞因子,有抗肿瘤作用;M2型巨噬细胞与免疫抑制相关,在肿瘤的进展和转移中发挥作用^[25]。肿瘤相关巨噬细胞在被TEX刺激后,巨噬细胞中TIMP1、IFN- γ 、IL-16表达下调,IL-8、CCL2、MIP2和IL-1Ra表达上调,引起巨噬细胞功能的极化,与肿瘤侵袭和转移密切相关^[26]。TEX可引起巨噬细胞中Wnt5a的表达,Wnt5a可从巨噬细胞转移至肿瘤细胞,通过激活 β -联蛋白依赖的Wnt信号通路促进肿瘤转移^[27]。来源于非小细胞肺癌的外泌体内含miR21和miR29a,可在肿瘤微环境中募集巨噬细胞,并与其表面TLR8结合,激活NF- κ B信号通路,使IL-6、TNF- α 分泌增多,这种炎症环境有助于肿瘤的生长和扩散^[28]。

1.3 减弱B细胞功能及诱导Breg产生

关于TEX对B细胞的作用并没有一个明确的认识,存在于肿瘤患者血浆内循环的TEX因其表面有肿瘤抗原,可与机体分泌的抗体结合,从而减弱了B细胞抗体依赖细胞介导的细胞毒作用^[29]。来源于B细胞淋巴瘤的外泌体内含CD20,从而可消耗利妥昔单抗等治疗性的CD20的单克隆抗体,同时可消耗补体,减弱了补体依赖的细胞毒作用^[30-31]。支原体作为常见的机会致病菌,可引起多种人类疾病,支原体同样可诱发宿主的免疫应答,被支原体感染的肿瘤细胞释放的外泌体可特异性地引起脾B淋巴细胞的活化,该种B淋巴细胞可产生多种细胞因子,包括促炎的IFN- γ 和抗炎的IL-10,从而产生抑制T细胞增殖的效应,蛋白组学分析这一现象可能与外泌体中含支原体的蛋白组分有关^[32]。

1.4 促骨髓前体细胞分化为MDSC并在靶器官中募集

骨髓来源的抑制细胞(myeloid-derived suppressor cells, MDSC)是一类未成熟的骨髓细胞,其在免

疫应答中具有双重作用:负向调控抗原的加工和提呈,产生大量免疫抑制因子。小鼠体内实验证明TEX可引导骨髓前体细胞分化为MDSC,使其在小鼠肿瘤组织、淋巴器官和血液中积聚^[33]。当C57BL/6小鼠被TEX预处理过后,可发现大量MDSC在肺中募集,这类MDSC可通过MyD88途径抑制T细胞活化及IL-6和TNF- α 的产生^[34]。同时,TEX表面的热激蛋白72(heat shock protein, Hsp72)也可通过TLR2/MyD88途径引起STAT-3通路的激活和IL-6的产生,增强了MDSC的抑制功能^[35]。TEX内含RNA,主要为核内小RNA(small nuclear RNA, snRNA),可激活肺泡上皮的TLR3,引起趋化因子分泌从而募集中性粒细胞,促进肺组织中转移前微环境的形成^[36]。

1.5 减弱NK细胞的细胞毒作用

正常情况下,NK细胞可通过释放穿孔素、颗粒酶,表达死亡配体Fas-L,抗体依赖细胞介导的细胞毒作用及分泌多种细胞因子来杀伤肿瘤细胞,而在肿瘤微环境的作用下,NK细胞的细胞毒作用大大削减。来源于低氧环境下的TEX可高表达miR210和miR23a,前者影响抗原特异性的免疫应答,后者直接调控CD107a的表达,起到免疫抑制作用^[37-38]。NK细胞表面有多种激活型受体,如NKG2D、NKP30、NKP46和NKG2C等,它们与相应配体结合后可促进NK细胞发挥细胞毒作用。TEX能够下调这类受体,尤其是NKG2D。I类主要组织相容复合物有同源物MICA和MICB,可作为NKG2D的配体^[39]。有临床研究^[40]表明,人急性髓系淋巴瘤(acute myeloid leukemia, AML)患者血清中的外泌体包含MICA/MICB、mTGF- β 1、CD34、CD33和CD117,可减弱NK细胞的细胞毒性($P<0.01$)及下调NK细胞表面NKG2D的表达($P<0.01$),而用TGF- β 1的中和抗体阻断其作用后可改变这一现象。Clayton等^[41]发现,CD3⁺外周血淋巴细胞在与TEX作用后NKG2D的表达下调,使效应CD8⁺T细胞的细胞毒性减弱。这一作用依赖于TEX内表达NKG2D的配体,这一现象同样适用于NK细胞,含有MICA的外泌体培养NK细胞可削弱NK细胞的细胞毒性^[42]。另一方面,TEX的内容物可减少NKG2D配体的表达。乳腺癌干细胞样细胞(breast cancer stem like cells, BCSC)具有易转移和对化疗耐受的特性,其外泌体内含miR-20a,可下调I类MICA/MICB,它们是NKG2D的配体,这样可减少NK细胞的激活^[43]。在卵巢癌细胞中也发现了该现象,miR-20a可直接结合在MICA/BmRNA的3'UTR区,使MICA/B的表达下调^[44]。

1.6 减弱T细胞的应答和诱导Treg产生

有效的CD4⁺T细胞和CD8⁺T细胞的应答对抗肿

瘤免疫至关重要,TEX可影响这类T细胞的增殖、激活和凋亡。在鼻咽癌患者血清及细胞系中均检测出其分泌的外泌体高表达多种miRNA:has-miR-24-3p、has-miR-891a、has-miR-106a-5p、has-miR-20a-5p、has-miR-1908,这些miRNA可减少ERK、STAT1、STAT3表达从而下调MARK1,抑制了T细胞的增殖及分化为Th1和Th17细胞并促进Treg产生^[45]。在小鼠皮下注射人成胶质细胞瘤细胞株GL26,其产生的外泌体可减少CD8⁺T细胞的百分比及抑制其活化,包括减少IFN- γ 和颗粒酶B的产生^[46]黑色素瘤细胞系B16F0分泌的外泌体可上调PTPN11,其是免疫检查点重要的磷酸酶,从而可抑制T细胞增殖^[47]。CD3- ζ 链作为T细胞受体(TCR)复合体的重要组成部分,在TCR-MHC-肽相互作用和T细胞激活后的信号通路中发挥重要作用,TEX内含TNF- α ,通过活性氧途径影响TCR-CD3复合体,抑制CD4⁺T细胞和CD8⁺T细胞的激活^[48]。同时,TEX可调节T细胞的凋亡,如表达FasL或PD1-L,但并不是所有的TEX均包含PD1-L^[49]。腺苷对效应T淋巴细胞(effector T cells, Teffs)有抑制作用,可通过腺苷A_{2A}受体(A_{2A}R)上调cAMP水平抑制Teffs功能。外核苷酸酶对ATP依赖的腺苷的产生至关重要,TEX作为运载体,可运载外核苷酸酶至靶细胞,增加腺苷产生^[50]。TEX内含磷酸酶和张力蛋白同源物(phosphatase and tensin homology, PTEN),可调节接收细胞中的磷酸化,共培养激活的CD8⁺T细胞和TEX可引起T细胞内时间依赖的AKT去磷酸化和BCL-2、BCL-XL、MCL-1等抗凋亡蛋白表达的持续下调,同时促凋亡蛋白Bax表达上调^[51]。

TEX与CD4⁺CD25⁻T细胞共培养可使其转化为Treg,这些Treg高表达TGF- β 1、IL-10和CTLA4,从而抑制免疫应答^[52]。TEX内含miRNA-214,可下调T细胞中PTEN表达促进Treg的增殖^[53]。结直肠癌细胞来源的外泌体可通过激活TGF- β /smad通路和抑制SAPK通路来改变T细胞表型为Treg样细胞,这类细胞具有显著的在体内和体外促进肿瘤生长的活性^[54]。

2 IEX的免疫抑制作用

2.1 Treg产生的外泌体

CD8⁺CD25⁺Treg分泌的外泌体具有免疫调节功能,给C57BL/6的小鼠静脉输注卵清蛋白刺激的DC和Treg来源的外泌体,发现其减弱了CD8⁺T细胞的应答,同时,其对表达卵清蛋白的BL6-10OVA小鼠黑色素瘤细胞的应答减弱,应答的有效性从2.52%下降至1.08%和1.81%($P<0.05$)^[55]。同时,Treg来源外泌体内含未成熟和成熟的miRNA,如miR-466家族、miR-195和miR-16,这些miRNA可抑制Prgs2,从而

限制Th1细胞的相关应答。同时,Treg来源外泌体可将Let-7d运载至Th1细胞,抑制Th1细胞的增殖和IFN- γ 的分泌。体内和体外实验证实CD8⁺Treg来源外泌体抑制了DC激活的CD8⁺T细胞的应答,因此Treg来源外泌体可能是肿瘤免疫治疗的新靶点^[56]。已知腺苷是一种抗炎介质,其与活化的Teffs上表达的腺苷受体A_{2A}R结合后,可激活细胞内cAMP通路,抑制细胞因子产生,从而限制T细胞应答。Treg来源的外泌体内含CD73,其作为一种胞外酶,在体外与5'AMP共培养后可产生腺苷,因此可推测Treg来源外泌体作用于原位肿瘤微环境后产生腺苷也是其发挥负向免疫调控的机制。有研究^[57]表明,CD4⁺CD25⁺Foxp3⁺Treg细胞来源外泌体内含CD25和CTLA-4,可调节免疫应答。Nolte-'t Hoen等^[58]发现,来源于大鼠失能T细胞的外泌体在体外与DC及B细胞共培养后可抑制APC诱导的Teffs应答。这些外泌体中高表达CD25,与APC结合后,能结合游离IL-2,从而耗竭相关细胞因子和促Teffs凋亡。当然,这类外泌体在肿瘤负向免疫调控中的作用还未完全证实。

2.2 CD8⁺T细胞产生的外泌体

CD8⁺T细胞具有抗肿瘤作用已达成共识,而近几年的研究表明,其来源的外泌体在肿瘤免疫中可发挥负向调控作用。已知Fas属于TNF受体超家族的一类穿膜蛋白,与其配体FasL结合后可在敏感细胞中传递凋亡信号,Fas参与调节的凋亡在多种生物过程中发挥作用^[59]。几乎所有的肿瘤细胞均表达Fas,Fas/FasL的途径在肿瘤细胞的生长、存活中发挥重要作用^[60]。虽然Fas可引起肿瘤细胞凋亡^[61],但在适当水平FasL的作用下,可促进Fas耐受的肿瘤细胞增殖^[62],还可促进肿瘤细胞的迁移和侵袭能力^[63]。将来源于OT-I小鼠的初始CD8⁺T细胞与卵清蛋白致敏的DC共培养,其分泌的外泌体含FasL,可抑制DC刺激的CD8⁺CTL的应答^[64]。同时,因活化的T细胞来源的外泌体含FasL,可引起T细胞自身凋亡,体外实验证明,纯化的外泌体增加了细胞FLICE抑制蛋白的表达,从而激活了ERK和NF- κ B通路,增加了小鼠黑色素瘤细胞系B16中MMP9的表达;体内肿瘤侵袭实验也表明活化的CD8⁺T细胞的外泌体可促进B16黑色素瘤细胞迁移至肺,而阻断FasL可明显减少肺中的转移灶,在小鼠肺癌细胞系3LL中同样重复了该现象,这也为肿瘤转移提供了新的治疗靶标^[65]。

3 结 语

外泌体概念的提出及关于其在肿瘤免疫中发挥作用的研究深化了人们对于肿瘤生长、侵袭、转移一系列过程的理解,也给肿瘤免疫治疗提供了新靶点,

有广阔的临床应用前景。然而,外泌体在肿瘤免疫中也发挥着双重作用,其在肿瘤细胞和免疫细胞间相互作用的许多具体机制仍不清楚,也限制了其临床应用。近年来,关于外泌体在肿瘤免疫中的作用一直是研究的热点,许多关键性分子不断被发现,然而,关于外泌体所包含的可引起负向免疫调控的内容物的研究仍局限在几种分子,如具有免疫抑制功能的白介素、miRNA等,缺少具有肿瘤特异的物质发现。因为外泌体在肿瘤免疫的调控中发挥双重作用,且其不仅作用于免疫细胞,还可直接影响肿瘤细胞的生物学调控,整个调控机制复杂而精密,增加了其在临床肿瘤治疗中应用的复杂性。最后,除了直接参与肿瘤的免疫调控,外泌体还可通过影响肿瘤微环境间接影响肿瘤的免疫应答,如是否在营造肿瘤生长的慢性炎症环境中发挥了一定的作用,这也可以为研究炎症与肿瘤之间的相互关系提供新的思路,加深对外泌体功能的研究可为日后其在肿瘤临床治疗中应用起到极大推动作用。

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