

外泌体源性非编码RNA在消化系统恶性肿瘤中的研究进展及展望

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[摘要] 外泌体是纳米级、双层膜的囊泡, 由多种细胞分泌, 广泛存在于多种体液中。外泌体中含有RNA和蛋白质等多种活性物质, 在细胞物质间和信号转导中起重要作用。非编码RNA具有重要的基因表达调控功能, 在多种肿瘤的发生、发展过程中起重要作用。外泌体源性非编码RNA的研究是目前新的研究热点, 现就外泌体及外泌体源性非编码RNA在消化系统恶性肿瘤中的研究进展进行综述。

[关键词] 外泌体; 非编码RNA; 消化系统恶性肿瘤

DOI: 10.19401/j.cnki.1007-3639.2017.04.010

中图分类号: R735 文献标志码: A 文章编号: 1007-3639(2017)04-0297-07

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[Abstract] Exosome is a kind of biological membrane structure at nanometer level. It is secreted by various cells and widely distributed in most body fluids. Biological active substances, including non-coding RNAs and proteins, have been identified in the exosomes. Exosome may be involved in cell-to-cell substance transporting and signaling. Non-coding RNAs have important function of regulating gene expression and also play key roles in the occurrence and development of many cancers. Research on exosome-derived non-coding RNA is a new hotspot at present. In this paper, we will review research progress on exosome and exosome-derived non-coding RNA in digestive system malignancy.

[Key words] Exosome; Non-coding RNAs; Digestive system malignancy

外泌体是细胞经过“内吞-融合-外排”等一系列调控过程而形成的具有双层膜结构的囊泡, 直径约50~150 nm^[1], 源于细胞内吞系统的晚期内体^[2]。它富含蛋白、mRNA和核苷酸等多种成分^[3], 能调节受体细胞的生物学行为^[4], 发挥重要的调控作用。多种细胞可分泌外泌体, 包括T细胞、血小板及肿瘤细胞等^[5-9]。在人类基因组中, 编码蛋白质的序列在基因组中所占的比例不到2%, 其他超过90%的序列为非编码区^[10]。非编码RNA作为一类特殊的RNA分子, 包括微小RNA(microRNA, miRNA)、长链非编码RNA(long non-coding RNA,

lncRNA)和环状RNA(circle RNA, circRNA)在内的多种RNA, 具有调控基因表达、参与表观遗传修饰、细胞增殖及细胞凋亡等多种生命活动的功能^[11-12]。外泌体源性非编码RNA在疾病中的研究是目前较新的研究领域, 现就外泌体及外泌体源性非编码RNA(包括miRNA、lncRNA和circRNA)在消化系统恶性肿瘤中的研究进展进行综述。

1 外泌体与消化系统恶性肿瘤

消化系统恶性肿瘤, 包括胃癌、肝癌、结直肠癌、胰腺癌和食管癌等, 是危害人类健康的主要因素之一, 约占肿瘤引起死亡人数的1/4, 在

我国发病率逐年上升, 具有发病率高、症状隐匿及预后差等特点, 其早期诊断、治疗及预后是目前临床消化系统肿瘤防治的重点^[13]。包括外泌体在内的液体活检技术是目前的研究热点, 旨在寻找潜在非侵入性、创伤小、特异性高的诊断和筛查方法。

血液是唯一与所有器官都有接触的组织, 随着检测及分离技术日趋完善, 外周血中的外泌体逐渐被人们了解。外周血中RNA的来源包括: 细胞自身分泌或死亡破裂后所含的RNA直接释放进入循环, 并可经细胞死亡数量增加、细胞外RNA的含量也增加的研究证实; 膜萌芽期RNA装载于微囊泡中或装载于外泌体中进入外周血^[14]。外泌体中的RNA虽然仅占外周血RNA的一小部分, 但因其表面具有标志性蛋白可进行特异性富集, 具有很好的肿瘤特异性。肿瘤细胞来源的外泌体既可以通过微环境介导肿瘤细胞的增生、血管形成及免疫抑制等肿瘤发生、发展的过程, 又可以通过检测其含有肿瘤细胞分泌的特异性成分(如非编码RNA), 对肿瘤进行诊断及监测, 为消化系统恶性肿瘤的诊治提供较好的依据。

肿瘤细胞分泌的外泌体可以通过外泌体的自分泌信号通路来调节肿瘤的局部增生^[15]。不同细胞类型及细胞特性来源的外泌体的自分泌作用存在差异。例如, 源于胃癌细胞系的外泌体的自分泌信号可通过Akt和细胞外信号调节激酶磷酸化作用的增加来促进肿瘤细胞的增殖^[16]。除此之外, 热休克蛋白(HSP70和HSP90)和survivan蛋白因肿瘤细胞缺氧而增加。以上这些蛋白均可抑制细胞凋亡、促进肿瘤细胞增殖, 进而对促进肿瘤细胞生长的微环境提供强大的刺激作用^[17-18]。一方面, 外泌体可以将自身的细胞因子释放至细胞外, 作用于内皮细胞膜表面受体, 间接促使肿瘤新生血管的形成。富含TGFβ1蛋白的肿瘤源性外泌体将静息状态的成纤维细胞活化成肌成纤维细胞, 从而促进肿瘤血管新生和肿瘤生长, 而单纯的可溶性TGFβ1虽然可以激活成纤维细胞, 但却没有促进肿瘤血管新生和肿瘤生长的作用^[19-20]。另

一方面, 肿瘤细胞来源的外泌体可传递组织因子、miRNA-210等直接调控血管内皮细胞的靶基因或信号通路, 促进肿瘤血管新生, 为肿瘤的侵袭转移创造条件^[21]。人体免疫系统正常功能的发挥可以减少肿瘤的进展, 然而有研究表明, 肿瘤患者存在免疫抑制, 进而进一步导致肿瘤的快速生长、进展和播散^[22], 尤其是从相对应恶性病变部位分离出的外泌体会促进肿瘤细胞的快速生长^[16]。外泌体可通过增加免疫抑制细胞、减少NK细胞和T细胞的增殖和细胞毒性、减少抗原递呈细胞的数量和功能等来抑制免疫, 说明肿瘤细胞源性的外泌体可介导病变部位导致的免疫抑制^[23-26]。如胃癌细胞释放的外泌体可以向抗肿瘤的T细胞传递凋亡信号, 而不需要直接的细胞-细胞接触。这些外泌体能部分地被诱导上调Cbl-b和c-Cbl, 抑制Akt的活性及caspase-3、caspase-8和caspase-9的激活。外泌体与免疫细胞之间的相互作用揭示了肿瘤抑制免疫功能的潜在机制^[27]。

2 外泌体源性非编码RNA与消化系统恶性肿瘤

2.1 外泌体源性miRNA与消化系统恶性肿瘤

外泌体中富含miRNA。成熟miRNA占外泌体所有RNA的40%以上, 由起源细胞分泌, 发挥沉默靶细胞的靶mRNA的作用^[28]。外泌体源性miRNA通过介导细胞通讯来调节基因表达^[29]。

外泌体源性miRNA通过肿瘤内皮细胞、血管生成、细胞通讯和免疫抑制等介导肿瘤发生、发展的过程。Liao等^[30]研究报道, 食管癌细胞外泌体源性的miR-21可以通过调控抑癌基因PDCD4和激活其下游的JNK信号通路, 促进肿瘤细胞的进展、转移。Zhou等^[31]研究发现, 胰腺癌细胞来源的外泌体可通过miR-203下调树突细胞TLR4的表达, 进而引起免疫抑制导致胰腺癌的发生。Que等^[32]研究发现, 胰腺癌外泌体源性miRNA可下调DC/细胞因子诱导的杀伤细胞(cytokine-induced killer cells, CIKs)的抗肿瘤活性, 其水平的降低可增强DC/CIKs的抗肿瘤活性。有研究发现, 有11种miRNA特异

的存在于Hep3B细胞来源的外泌体中,说明肝细胞癌的外泌体可选择性募集一系列特异表达的miRNA^[33]。肝细胞癌的癌细胞外泌体源性miRNA可通过抑制TAK1及与TAK1相关的下游信号通路,增强受体细胞中转化细胞的生长,进而导致肝细胞癌的发展^[34]。

2.1.1 外泌体源性miRNA与消化系统恶性肿瘤的早期诊断

消化系统恶性肿瘤通常在诊断时已是局部晚期或发生转移,错过最佳治疗时机,因此提高消化系统恶性肿瘤早期诊断率仍是亟待解决的问题。不少研究以外泌体源性miRNA作为切入点,探讨其作为早期诊断指标的可能性,并取得较好的研究结果。Machida等^[35]研究发现,和健康对照组相比,胰胆道恶性肿瘤患者唾液外泌体源性的miRNA-1246和miRNA-4644显著升高,且两者联合检测,受试者工作特征(receiver operating characteristic curve, ROC)曲线的曲线下面积达到0.833,说明胰胆道恶性肿瘤患者唾液外泌体源性的miRNA可作为早期诊断的标志物。Madhavan等^[36]研究发现,miRNA-1246、miRNA-4644、miRNA-3976及miRNA-4306在83%的胰腺癌患者血清外泌体中显著升高,而在胰腺良性肿瘤患者及健康对照组中没有明显变化,提示胰腺肿瘤细胞来源的miRNA的升高具有诊断价值。Wang等^[37]研究发现,肝细胞癌血清外泌体源性miRNA-21的表达显著高于慢性乙型肝炎和健康对照者,且其敏感性较高,说明外泌体源性miRNA-21可作为早期诊断肝细胞癌的潜在生物学指标。

2.1.2 外泌体源性miRNA与消化系统恶性肿瘤的转移、侵袭及预后评估

肿瘤细胞来源的外泌体影响肿瘤的侵袭、转移。一方面,外泌体可作为载体将miRNA从原发部位运输到其他部位,促进肿瘤的转移;另一方面,通过转运具有侵袭、转移能力的miRNA,提高肿瘤的复发、转移潜能。Tanaka等^[38]研究发现,食管鳞状细胞癌患者血清的外泌体能诱导食管鳞状细胞癌细胞的增殖。与食管良性肿瘤患者相比,外泌体源性的miR-21在

食管鳞状细胞癌的患者血清中高表达,并且和肿瘤的进展及侵袭相关指标呈正相关。而没有外泌体的血清中未能检测到miR-21,说明和肿瘤相关的miRNA可能特异的存在于外泌体中,并通过外泌体的转运功能发挥作用。Nishida等^[39]研究发现,miR-10b在结直肠癌细胞外泌体中显著高表达,且miR-10b的高表达和淋巴结转移及差的预后相关。miR-122是肝脏特异的抗细胞增殖的miRNA,可通过人类肝细胞癌的癌细胞的外泌体进行转运。miR-122的缺失或下调导致肝细胞癌的进展,并且与预后差及转移密切相关^[40-42]。

2.2 外泌体源性lncRNA与消化系统恶性肿瘤

外泌体中的lncRNA约占外泌体总RNA的3%,其介导肿瘤发生的认识体现在:某些特异具有生物学功能的lncRNA可被选择性载入外泌体中;外泌体可转运具有直接沉默表观遗传作用的lncRNA;肿瘤细胞释放富含lncRNA的外泌体,诱导受体细胞发生肿瘤样表型的改变^[43-44]。

2.2.1 外泌体源性lncRNA与消化系统恶性肿瘤发生、发展的关系

近期研究显示,外泌体可作为功能性lncRNA的转运小泡,对受体细胞的表型产生作用。LncRNA TUC339存在于肝细胞癌的癌细胞外泌体中,并且在外泌体中高表达。抑制这种lncRNA的表达可减少细胞增殖、克隆细胞的生长及细胞黏附,说明细胞利用外泌体及TUC339增加周围细胞的增殖,进而促进肝细胞癌的发展^[45]。外泌体源性lncRNA通过调节肿瘤微环境促进肿瘤的发生、发展。有研究显示,肝细胞癌CD90+Huh7细胞可分泌包含有多种lncRNA(HOTAIR、HULU、linc-ROR和H19)的外泌体,与该细胞分泌的外泌体在试管内共培养,外泌体被内皮细胞迅速内化,促使细胞重组为管状样结构,并上调血管内皮生长因子(vascular endothelial growth factor, VEGF)/VEGF-R1 mRNA的表达水平,导致促血管生成作用,且使细胞黏附分子增加,参与内皮细胞的外渗过程,促进肿瘤的进展^[46]。

2.2.2 外泌体源性lncRNA在消化系统恶性肿瘤临床诊治中的潜在应用价值

类似于miRNA, 外泌体源性lncRNA广泛存在于多种体液中, 样品取材方便, 性质稳定, 可通过常用实验技术如实时荧光定量聚合酶链反应(real-time fluorescent quantitative polymerase chain reaction, RTFQ-PCR)、基因芯片及测序等检测, 具有较好的临床应用前景^[15,47-48]。

LncRNA稳定存在于血浆、血清和其他体液中, 可作为非侵入性的指标成为肿瘤诊断的标志物^[49-50]。与胃上皮不典型增生患者和健康对照组相比, LINC00152在胃癌患者血浆外泌体中高表达, 并且LINC00152的表达水平在等量血浆及等量血浆来源的外泌体中差异无统计学意义, 提示LINC00152在血浆中受外泌体的保护而稳定存在于外泌体中。外泌体源性LINC00152诊断胃癌的灵敏度是48.1%, 特异度是85.2%, ROC曲线的曲线下面积是0.66, 提示其具有较好的诊断优势^[51]。此外, 血清外泌体源性lncRNA-CRNDE-h的升高可以鉴别结直肠癌及结肠良性疾病患者、健康对照者, 其诊断的灵敏度和特异度分别为70.3%和94.4%, ROC曲线的曲线下面积达0.89, 可用于结直肠癌患者的早期诊断^[52]。

外泌体源性lncRNA在一定程度上影响着消化系统肿瘤的转移、侵袭及预后。ROR是一种lncRNA, 在阿霉素处理过的肝细胞癌的癌细胞的外泌体中高表达, 经含有ROR的外泌体处理肝细胞癌的癌细胞后, 发现其化疗抵抗作用增强, 敲除ROR后化疗的灵敏度增加。说明肿瘤细胞可通过外泌体及lncRNA来增加周围细胞的化疗抵抗, 促进肿瘤的局部侵袭能力^[53]。TGF- β 可诱导上皮细胞间质化, 促进癌细胞的侵袭和转移。TGF- β 诱导胰腺癌细胞中的多个lncRNA上调, 其中HULU的变化最为明显。沉默HULU后细胞的存活、侵袭和迁移能力减弱, 经TGF- β 诱导胰腺癌细胞来源外泌体中的HULU水平也增高。经癌细胞及Panc-1胰腺癌细胞来源的外泌体温育后, 细胞中的黏附分子增加, 说明胰腺癌细胞可通过外

泌体源性的lncRNA-HULU来增强细胞的侵袭及迁移能力^[54]。结直肠癌患者血清外泌体源性lncRNA-CRNDE-h的水平与局部淋巴结转移($P=0.019$)和远处转移相关($P=0.003$), 可用于评价结直肠癌患者的转移情况及预后^[52]。

2.3 外泌体源性circRNA与消化系统恶性肿瘤

2.3.1 CircRNA概述

CircRNA是一类新发现的非编码RNA分子, 由一个或几个外显子形成的环状结构^[55]。CircRNA既可以与miRNA结合, 通过影响miRNA下游靶基因来发挥调控作用, 又可以调控选择性剪接、宿主基因转录^[56]。最早于20世纪70年代在病毒中发现, 后来发现在真核细胞中也存在^[57-58]。目前随着高通量测序等技术的快速发展, circRNA目前被证实在真核细胞转录组中大量存在^[59-62]。具有种类多样、存在普遍、序列保守、不被核酸外切酶降解、组织和时序特异性的生物学特点^[63]。关于其生物合成的机制主要有外显子跳读导致成环、反向剪接成环及蛋白促进成环^[64]。

2.3.2 外泌体源性circRNA与消化系统恶性肿瘤

Li等^[65]首次报道, 不仅细胞来源的外泌体, 人血清外泌体中也含有大量完整稳定的circRNA, 并且结直肠癌患者血清外泌体中的circ-KLHDC10与健康人群差异明显, 提示肿瘤来源的exo-circRNA有望成为肿瘤检测的潜在标志物。目前, 外泌体源性circRNA在消化系统恶性肿瘤发生、发展过程中的分子机制、临床应用等认识还很有限, 需要进一步深入的研究。

3 小结与展望

外泌体及外泌体源性非编码RNA在肿瘤发生、发展中发挥重要作用, 可为多种疾病的发生机制提供思路, 也为临床诊断、预后及治疗提供新的标志物。但目前关于外泌体及外泌体源性非编码RNA的研究仍处于初始阶段, 面临缺乏完善的数据库、机制不明确及肿瘤特异性较强的非编码RNA不多等问题。相信随着生物技术的不断发展, 外泌体及外泌体源性非编码RNA在肿瘤中的功能及机制会逐渐被发现, 为肿瘤的诊治提供有效依据。

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- (收稿日期: 2016-12-19 修回日期: 2017-03-06)

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