DOI: 10.13376/j.cbls/2019125
文章编号：1004-0374(2019)10-1019-06

外泌体在非小细胞肺癌转移中的作用及其机制

吴小凤[1,2]，唐旭东[1,2]*
(1 广东医科大学生物化学与分子生物学研究所，湛江 524023；
2 广东医科大学抗肿瘤活性物质研发协同创新中心，湛江 524023)

摘　要：非小细胞肺癌 (non-small cell lung cancer, NSCLC) 常伴有不同器官转移。外泌体由活细胞分泌，可作为细胞与细胞之间信号传递的介质，参与机体病理生理过程，如肿瘤的上皮 - 间质转化、免疫抑制和逃逸、血管生成、炎症反应等，共同促进肿瘤转移。近年来大量研究表明，外泌体与 NSCLC 转移密切相关，尤其是外泌体在 NSCLC 迁移和侵袭潜力、免疫系统调节、转移前生态位形成方面具有重要作用。因此，对近年来外泌体在这几方面的作用及其机制的研究进展做一综述，有助于进一步了解外泌体在 NSCLC 发展中的作用。

关键词：外泌体；非小细胞肺癌；上皮 - 间质转化；免疫抑制；转移前生态位
中图分类号：R392；R734.2　　**文献标志码：**A

Role of exosomes in metastasis of non-small cell lung cancer and the underlying mechanisms

WU Xiao-Feng[1,2], TANG Xu-Dong[1,2]*
(1 Institute of Biochemistry and Molecular Biology, Guangdong Medical University, Zhanjiang 524023, China;
2 Collaborative Innovation Center for Antitumor Active Substance Research and Development,
Guangdong Medical University, Zhanjiang 524023, China)

Abstract: Non-small cell lung cancer (NSCLC) is often diagnosed with different organ metastasis. Exosomes, secreted by living cells, are served as mediators in cell-to-cell communication and involved in pathophysiological processes including epithelial-mesenchymal transition, immunosuppression and immunologic escape, angiogenesis and inflammation, contributing to tumor progression. In recent years, accumulating evidence has implicated that exosomes are closely related to NSCLC metastasis, especially migration and invasion abilities, immunoregulation, and pre-metastatic niche formation. Here, we summarized the recent findings regarding the role of exosomes in these processes and the underlying mechanisms, contributing to the further understanding of the role of exosomes in the development of NSCLC.

Key words: exosomes; non-small cell lung cancer; epithelial-mesenchymal transition; immunosuppression; pre-metastatic niche

肺癌是最常见癌症 (发病率 11.6%) 和首要的肿瘤死因 (死亡率 18.4%) [1]，80% 以上的患者病理诊断是非小细胞肺癌 (non-small cell lung cancer, NSCLC) [2]。约 47.3% 肺癌患者诊断时已伴有不同器官转移 [3]，

收稿日期：2019-06-03；**修回日期：**2019-07-16
基金项目：国家自然科学基金项目(81372511)；2017年广东省科技发展专项资金(基础与应用基础研究方向)项目(2017A030313539)；广东省“扬帆计划”培养高层次人才项目(201635011)；2018年度湛江市科技发展专项资金竞争性分配项目(2018A01041)；广东医科大学重点培育项目(GDMUZ201804)
***通信作者：**E-mail: tangxudong2599@126.com

且不同器官转移患者的预后不同[4]。

外泌体是细胞分泌的细胞外囊泡，具有脂质双层膜，直径30~150 nm，内容物包括DNA、RNA、蛋白质和脂质等[5-7]，广泛分布于尿液、血浆、灌洗液、浆膜腔积液、脑脊液等体液中[8-9]。外泌体具有两面性，一方面是维持正常生理反应所必需的；另一方面，在病理状态下，尤其是肿瘤环境，可促进癌变、增殖、迁移、侵袭、免疫抑制、血管生成及重塑微环境等[10]。多项研究表明，外泌体内容物的差异表达与NSCLC转移密切相关且在多环节、多步骤中发挥重要作用[11-12]。肿瘤转移是一个极其繁杂的过程，有关肿瘤转移机制研究的理论，包括经典的“种子与土壤”学说、肿瘤休眠、肿瘤细胞遗传异质性等，其内容可以概括为种子因素(癌细胞脱落)、土壤因素(转移前生态位形成)、外部环境(免疫抑制)3部分[13]。癌细胞的脱落实质是肿瘤细胞的迁移和侵袭性增强的表现。与健康人相比，NSCLC患者循环体液中的外泌体更为丰富[14]，且在上述的肿瘤转移3大环节中的作用显著[15]，因此，下面主要对外泌体在NSCLC迁移和侵袭性、免疫逃逸、转移前生态位形成等过程中的作用展开阐述。

1 外泌体增强NSCLC细胞迁移潜力

肿瘤细胞上皮-间质转化(epithelial-mesenchymal transition, EMT)是细胞自身侵袭性增强及肿瘤发生远处转移的关键因素[16]。EMT是上皮细胞内环境改变并获取间充质干细胞表型的过程，表现为上皮特征(如E-钙黏蛋白等)丢失、细胞骨架重建、间充质表型(如波形蛋白等)获得[17]，这种表型间的转换有利于肿瘤细胞摆脱细胞间的连接而更具有侵袭性。此外，转型后的细胞分泌的外泌体富含miR-23a。miR-23a已被证实通过靶向*CDH1*激活Wnt/β-catenin信号转导途径，以正反馈形式加强转化生长因子β1 (transforming growth factor-β1, TGF-β1)诱导EMT的作用并促进肿瘤转移[18]。

研究表明，肺癌患者体内循环外泌体可诱导肺癌细胞EMT[19]，且EMT已被确定为NSCLC的潜在治疗靶点[20]。NSCLC环境中存在上皮细胞和间充质细胞，间充质细胞的*ZEB1*-RNA可通过外泌体转移至上皮细胞内[21]，*ZEB1*直接抑制上皮型剪接调节蛋白1 (epithelial splicing regulatory protein 1, ESRP1)的转录及细胞上皮分化，同时增加间充质剪接体的表达，促进细胞从上皮状态转化成间充质状态。*ZEB1*是肿瘤细胞EMT中TGF-β和*MYC*信号转导重要因子[22]。此外，间充质细胞的外泌体可通过激活Smad2/3、Akt/GSK-3β、MAPK和NF-κB途径促进NSCLC A549细胞中的EMT，上述途径激活与外泌体中的TGF-β1有关[23]，而TGF-β1是EMT过程中最重要的调控生长因子。肿瘤微环境基质细胞外泌体中的miR-193a-3p、miR-210-3p和miR-5100可通过激活STAT3信号途径诱导EMT，从而促进NSCLC细胞的侵袭[24]。

除EMT外，外泌体还可以通过其他方式改变癌细胞的恶性行为。吉西他滨耐药肺癌细胞来源的外泌体通过向受体细胞递送高水平miR-222-3p，后者直接靶向作用SOCS3的启动子来增强亲本细胞的恶性程度[25]。LMO7是肺肿瘤的抑制因子，外泌体可通过miR-96-LMO7轴抑制LMO7的表达，有助于肺癌细胞的增殖和转移[26]。

外泌体还可通过促进炎症反应[27]、血管渗透性[28]、基质(蛋白)降解[29]等调控肿瘤微环境，增强肿瘤细胞的迁移能力[30]。外泌体源性热休克蛋白70和γ-谷氨酰转肽酶-1分别激活TLR2/NF-κB信号通路及半胱氨酰白三烯受体介导肿瘤微环境发生炎症反应[31-32]，NF-κB的活化可加快细胞周期进程和促进血管生成，维持肿瘤细胞增殖。炎症因子、趋化因子分泌水平升高及血管网丰富均可促进肿瘤侵袭、转移。外泌体源性lnc-MMP2-2可通过促进基质金属蛋白酶2 (matrix metalloproteinase 2, MMP2)表达，增加血管内皮的通透性，有利于肺癌细胞向脉管系统的迁移和侵袭[33]。此外，外泌体源性miR-223靶向结合*EPB41L3* mRNA转录产物的3′-UTR并抑制*EPB41L3*表达，从而降低细胞-细胞和细胞-基质之间的黏附能力[34]。肺癌来源的外泌体还可诱导间充质干细胞处于激活状态，并抑制其向脂肪和成骨方向分化[35]，而有利于向成纤维细胞分化。成纤维细胞分泌的可溶性细胞间黏附分子1在体内和体外均可正向调节NSCLC细胞的增殖和EMT，促进肿瘤转移[36]。

2 外泌体介导NSCLC细胞免疫逃逸

免疫防御是维持内环境稳态的基本保障，体液免疫和细胞免疫共同组成“排除异己”的复杂免疫系统，肿瘤发生转移需逃避免疫监督和清除。研究表明[37]，恶性肿瘤来源的外泌体在肿瘤免疫调节中起双重作用，包括免疫刺激和免疫抑制，但在肿瘤微环境中以免疫抑制为主。肿瘤来源的外泌体携带

多种免疫抑制信号，不仅可以与免疫细胞直接作用抑制相关免疫应答，还可诱导组织细胞分泌免疫抑制因子，协同免疫抑制[38]。如肝癌细胞分泌富高迁移率族蛋白 1 (high mobility group box 1, HMGB1) 的外泌体，通过 HMGB1-TLR2/4-MAPK 途径促进表达 T 细胞免疫球蛋白和黏蛋白分子 -1 的调节性 B 细胞 (T cell Ig and mucin domain, regulatory B cells, TIM-1$^+$ Breg) 增殖，TIM-1$^+$ Breg 细胞分泌的白介素 -10 (interleukin-10, IL-10) 作用 CD8$^+$ T 细胞而产生免疫抑制[39]。动物实验模型研究显示，黑色素瘤细胞的外泌体通过激活 FAS/FASL 途径诱导 T 细胞凋亡，从而抑制抗肿瘤免疫效果[40]。同样，肺癌细胞释放含 TGF-β 或 IL-10 的外泌体促进调节性 T 细胞 (regulatory T cells, Treg) 细胞增殖并出现免疫抑制[41]。

NSCLC 患者体内已鉴定出 13 种不同的免疫细胞类型，其中 T 细胞最常见，其占所有肿瘤浸润性 CD45$^+$ 白细胞的 46.5%[42]。因此，诱导 T 细胞免疫应答失效是肿瘤免疫抑制的重要方式。已发现，NSCLC 外泌体中升高的 Tim-3 可引起 T 细胞功能衰竭和骨髓衍生抑制细胞的扩增，提示外泌体 Tim-3 有肿瘤免疫抑制效应[43]。另外，肺癌来源的外泌体通过间接方式使 T 细胞失活，Lewis 肺癌细胞外泌体降低树突状细胞的成熟分化能力并下调其表面趋化因子受体 7 (chemokine receptor 7, CCR7) 的表达，从而使树突状细胞向 T 细胞抗原提呈能力降低及 T 细胞活化受限，最终导致抗肿瘤免疫受抑[44]。PD-L1/PD-1 是常见的免疫抑制途径且在临床上用于 NSCLC 免疫治疗。外泌体上 PD-L1 扩散至全身，与 T 细胞表面 PD-1 结合并相互作用可促进机体免疫抑制[45]。此外，T 细胞还可以反过来增强肿瘤细胞恶性，Cai 等[46] 研究表明，肿瘤活化后的 T 细胞可分泌 FasL$^+$ 外泌体，通过激活 Fas /FasL 依赖的 ERK 和 NF-κB 途径促进肿瘤细胞中基质金属蛋白酶 9 (matrix metalloproteinase 9, MMP9) 升高，导致肺癌细胞侵袭性增强从而逃避免疫监视。

自然杀伤细胞 (nature killer cell, NK 细胞) 是抗肿瘤的重要免疫细胞。缺氧是实体瘤的共同特征，缺氧诱导的肿瘤细胞衍生的外泌体将 TGF-β1 转移至 NK 细胞，降低 NK 细胞表面活化受体 NKG2D 的表达，从而抑制 NK 细胞毒性；同时，外泌体的 miR-23a 作为免疫抑制分子靶向 NK 细胞 CD107a 的表达，共同抑制 NK 细胞的免疫功能[47]。Zhu 等[48] 提出假设，肺癌外泌体分拣蛋白 (sortilin)、神经生长因子前体 (pro-nerve growth factor, proNGF) 与 NK 细胞上的 p75NTR 结合，可能通过 p75NTR-proNGF-sortilin 引发 NK 细胞死亡。该设想还需进一步研究证实。

与其他肺疾病相比，肺癌患者体循环中外泌体富含表皮生长因子受体 (epidermal growth factor receptor, EGFR)，该类型的 EGFR 容易诱导树突状细胞出现免疫耐受，树突状细胞抗原提呈功能丢失，抗肿瘤免疫失效[49]。早已发现肿瘤环境中外泌体可诱导炎症反应，而树突状细胞在炎症反应中可募集和激活调节性 T 细胞，从而间接地发挥免疫抑制作用。

3　外泌体与NSCLC转移前生态位的形成

转移前生态位是指机体内的细胞因子、外泌体、炎症细胞等预先作用于特定靶器官，使其形成适合于失巢肿瘤细胞定植的微环境[50]。外泌体通过诱导定向转移 (亲器官性)、炎症反应[51]、血管生成及通透性增加[28,52]、基质重塑[53] 对转移前生态位进行调节。

3.1　外泌体在定向转移中的作用

肿瘤细胞向靶器官转移并非随机性，外泌体表面表达的整联蛋白是肿瘤细胞向靶器官定向转移的决定因素，整联蛋白可以通过重塑细胞或器官的基质形态来影响黏附作用，如携有整合素 αvβ5 的外泌体易与库普弗细胞特异性地结合，定向引导肿瘤向肝脏转移，而携有整合素 α6β4 和 α6β1 的外泌体更倾向于肺部成纤维细胞和上皮细胞，肿瘤易向肺转移[54]。

与上述靶器官定向转移不同，影响 NSCLC 骨转移的限速步骤是破骨细胞的生成，Xu 等[55] 研究表明，肺腺癌外泌体中的 miRNA-21 可通过靶向抑制 *PDCD4* 促进该过程。此外，NSCLC 源性外泌体中的双调蛋白 (amphiregulin, AREG) 也可影响成熟破骨细胞形成，AREG 诱导 EGFR 途径的激活，引起 NF-κB 受体活化因子配体 (receptor activator of nuclear factor kappa B ligand, RANKL) 表达增加，其可调节 MMP9 和酒石酸抗性酸性磷酸酶表达并诱导成熟破骨细胞形成；同时，RANKL 能够诱导蛋白水解酶的表达，引起骨转移的恶性循环[56]。

3.2　外泌体在炎症反应中的作用

轻度炎症反应是 NSCLC 转移的有利条件[57]。肺癌细胞衍生的外泌体可通过其表面热休克蛋白 70 激活 TLR2/NF-κB 信号，将幼稚间充质干细胞转化成一种新的促炎性间充质干细胞，分泌 IL-6、IL-8

和人单核细胞趋化蛋白 -1 以维持低度炎症的微环境 [31]。此外，外泌体中的 RNA 可激活肺上皮细胞表面的 TLR3，诱导中性粒细胞募集并促进转移前生态位的形成 [58]。炎症反应贯穿肿瘤发生发展全过程，持续的慢性炎症反应可诱导免疫耐受，外泌体介导微环境向免疫抑制状态发展来启动转移前生态位的形成 [59]。

3.3 外泌体在血管生成中的作用

血管生成是肿瘤转移的关键步骤，也是肿瘤生长所必需的条件。血管形成受多种因素调节，包括刺激血管生成的血管内皮生长因子 -A、血管内皮生长因子 -D、上皮 - 中性粒细胞激活肽 -78、胎盘生长因子、IL-8、血管生成素、碱性成纤维细胞生长因子和瘦蛋白等，这些均与肺腺癌外泌体显著相关 [60]。已证实肿瘤来源外泌体中的 miR-25-3p、miR-126 可诱导血管渗漏及脉管网形成 [61-62]。众所周知，缺氧可刺激血管生成，肿瘤微环境缺氧通过缺氧诱导因子 -1α 介导的转录调节上调肿瘤细胞 miR-494 并通过外泌体递送至内皮细胞 (endothelial cell, EC) 中，在 EC 中下调 PTEN 并激活 Akt/eNOS 途径促进血管生成，从而加剧肿瘤发展 [63]。肺腺癌影响肿瘤内皮细胞 (tumor-derived endothelial cell, TEC) 蛋白表达，TEC 内钙黏蛋白 -2 高水平表达与肿瘤胸膜转移显著相关 [64]。

3.4 其他因素

除上述因素之外，肿瘤微环境中基质重塑及黏附力增强有助于脱落肿瘤细胞在转移器官种植。*mutp53* 突变可影响肿瘤细胞外泌体唾液黏蛋白含量，促进成纤维细胞中 α5β1 整联蛋白的 RCP/DGKα 依赖性运输，从而改变细胞沉积的细胞外基质形态和黏附性质，有助于肿瘤细胞的转移 [65]。

4 总结和展望

外泌体作为细胞间重要的信息载体参与机体各项生命活动，在 NSCLC 中，外泌体通过激活不同的信号途径介导 EMT、免疫抑制、转移前生态位形成 (包括血管生成、炎症反应、基质重塑) 等病理过程，共同促进肿瘤的发生发展。外泌体富集于机体循环体液中，液体活检技术的不断发展加快了外泌体的临床应用进程，外泌体内容物有望成为下一代新兴生物标志物。

虽然目前对外泌体的研究已取得突破性进展，但仍然存在以下争议及问题。(1) 有报道显示，外泌体在 NSCLC 中也可表现出抑制肿瘤转移的潜力 [66]，因此外泌体可能具有双重作用，那么这两种相反的效应是否同时存在同一个体中？若是，孰主孰次需进一步研究；若否，则需要阐明这两种不同的作用机制是如何选择性发生的。(2) 外泌体在肿瘤转移过程中涉及多步骤、多环节，最关键、最核心的环节有待进一步确定。(3) 外泌体内含物的差异表达是否可以在肿瘤转移前进行监测、跟踪及临床干预需进一步研究。

[参 考 文 献]

[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2018, 68: 394-424

[2] Otsmane A, Kacimi G, Adane S, et al. Clinico-epidemiological profile and redox imbalance of lung cancer patients in Algeria. J Med Life, 2018, 11: 210-7

[3] Tamura T, Kurishima K, Nakazawa K, et al. Specific organ metastases and survival in metastatic non-small-cell lung cancer. Mol Clin Oncol, 2015, 3: 217-21

[4] Yang J, Zhang Y, Sun X, et al. The prognostic value of multiorgan metastases in patients with non-small cell lung cancer and its variants: a SEER-based study. J Cancer Res Clin Oncol, 2018, 144: 1835-42

[5] Carretero-Gonzalez A, Otero I, Carril-Ajuria L, et al. Exosomes: definition, role in tumor development and clinical implications. Cancer Microenviron, 2018, 11: 13-21

[6] Chen L, Feng Z, Yue H, et al. Exosomes derived from HIV-1-infected cells promote growth and progression of cancer via HIV TAR RNA. Nat Commun, 2018, 9: 4585

[7] Chuo ST, Chien JC, Lai CP. Imaging extracellular vesicles: current and emerging methods. J Biomed Sci, 2018, 25: 91

[8] Liu F, Vermesh O, Mani V, et al. The exosome total isolation chip. ACS Nano, 2017, 11: 10712-23

[9] Fitts CA, Ji N, Li Y, et al. Exploiting exosomes in cancer liquid biopsies and drug delivery. Adv Healthc Mater, 2019, 8: e1801268

[10] Isola AL, Chen S. Exosomes: the messengers of health and disease. Curr Neuropharmacol, 2017, 15: 157-65

[11] Zhang R, Xia Y, Wang Z, et al. Serum long non coding RNA MALAT-1 protected by exosomes is up-regulated and promotes cell proliferation and migration in non-small cell lung cancer. Biochem Biophys Res Commun, 2017, 490: 406-14

[12] Wang N, Song X, Liu L, et al. Circulating exosomes contain protein biomarkers of metastatic non-small-cell lung cancer. Cancer Sci, 2018, 109: 1701-9

[13] Liu Q, Zhang H, Jiang X, et al. Factors involved in cancer metastasis: a better understanding to “seed and soil” hypothesis. Mol Cancer, 2017, 16: 176

[14] Jin X, Chen Y, Chen H, et al. Evaluation of tumor-derived exosomal miRNA as potential diagnostic biomarkers for early-stage non-small cell lung cancer using next-generation

sequencing. Clin Cancer Res, 2017, 23: 5311-9
[15] Frydrychowicz M, Kolecka-Bednarczyk A, Madejczyk M, et al. Exosomes — structure, biogenesis and biological role in non-small-cell lung cancer. Scand J Immunol, 2015, 81: 2-10
[16] Thiery JP, Acloque H, Huang RY, et al. Epithelial-mesenchymal transitions in development and disease. Cell, 2009, 139: 871-90
[17] Kim J, Kim TY, Lee MS, et al. Exosome cargo reflects TGF-β1-mediated epithelial-to-mesenchymal transition (EMT) status in A549 human lung adenocarcinoma cells. Biochem Biophys Res Commun, 2016, 478: 643-8
[18] Ma F, Li W, Liu C, et al. MiR-23a promotes TGF-β1-induced EMT and tumor metastasis in breast cancer cells by directly targeting CDH1 and activating Wnt/β-catenin signaling. Oncotarget, 2017, 8: 69538-50
[19] Rahman MA, Barger JF, Lovat F, et al. Lung cancer exosomes as drivers of epithelial mesenchymal transition. Oncotarget, 2016, 7: 54852-66
[20] Li Q, Ran P, Zhang X, et al. Downregulation of *N*-acetylglucosaminyltransferase GCNT3 by miR-302b-3p decreases non-small cell lung cancer (NSCLC) cell proliferation, migration and invasion. Cell Physiol Biochem, 2018, 50: 987-1004
[21] Lobb RJ, van Amerongen R, Wiegmans A, et al. Exosomes derived from mesenchymal non-small cell lung cancer cells promote chemoresistance. Int J Cancer, 2017, 141: 614-20
[22] Larsen JE, Nathan V, Osborne JK, et al. ZEB1 drives epithelial-to-mesenchymal transition in lung cancer. J Clin Invest, 2016, 126: 3219-35
[23] Zhao X, Wu X, Qian M, et al. Knockdown of TGF-β1 expression in human umbilical cord mesenchymal stem cells reverts their exosome-mediated EMT promoting effect on lung cancer cells. Cancer Lett, 2018, 428: 34-44
[24] Zhang X, Sai B, Wang F, et al. Hypoxic BMSC-derived exosomal miRNAs promote metastasis of lung cancer cells via STAT3-induced EMT. Mol Cancer, 2019, 1: 40
[25] Wei F, Ma C, Zhou T, et al. Exosomes derived from gemcitabine-resistant cells transfer malignant phenotypic traits via delivery of miRNA-222-3p. Mol Cancer, 2017, 16: 132
[26] Wu H, Zhou J, Mei S, et al. Circulating exosomal microRNA-96 promotes cell proliferation, migration and drug resistance by targeting LMO7. J Cell Mol Med, 2017, 21: 1228-36
[27] Chow A, Zhou W, Liu L, et al. Macrophage immunomodulation by breast cancer-derived exosomes requires Toll-like receptor 2-mediated activation of NF-κB. Sci Rep, 2014, 4: 5750
[28] Fang JH, Zhang ZJ, Shang LR, et al. Hepatoma cell-secreted exosomal microRNA-103 increases vascular permeability and promotes metastasis by targeting junction proteins. Hepatology, 2018, 68: 1459-75
[29] Didiasova M, Zakrzewicz D, Magdolen V, et al. STIM1/ORAI1-mediated Ca^{2+} influx regulates enolase-1 exteriorization. J Biol Chem, 2015, 290: 11983-99
[30] Tang YT, Huang YY, Li JH, et al. Alterations in exosomal miRNA profile upon epithelial-mesenchymal transition in human lung cancer cell lines. BMC Genomics, 2018, 19: 802
[31] Li X, Wang S, Zhu R, et al. Lung tumor exosomes induce a pro-inflammatory phenotype in mesenchymal stem cells via NFκB-TLR signaling pathway. J Hematol Oncol, 2016, 9: 42
[32] Lukic A, Wahlund CJE, Gomez C, et al. Exosomes and cells from lung cancer pleural exudates transform LTC4 to LTD4, promoting cell migration and survival via CysLT1. Cancer Lett, 2019, 444: 1-8
[33] Wu DM, Deng SH, Liu T, et al. TGF-β-mediated exosomal lnc-MMP2-2 regulates migration and invasion of lung cancer cells to the vasculature by promoting MMP2 expression. Cancer Med, 2018, 7: 5118-29
[34] Liang H, Yan X, Pan Y, et al. MicroRNA-223 delivered by platelet-derived microvesicles promotes lung cancer cell invasion via targeting tumor suppressor EPB41L3. Mol Cancer, 2015, 14: 58
[35] Wang S, Li X, Zhu R, et al. Lung cancer exosomes initiate global long non-coding RNA changes in mesenchymal stem cells. Int J Oncol, 2016, 48: 681-9
[36] Kim E, Kim W, Lee S, et al. TRAF4 promotes lung cancer aggressiveness by modulating tumor microenvironment in normal fibroblasts. Sci Rep, 2017, 7: 8923
[37] Whiteside TL. The effect of tumor-derived exosomes on immune regulation and cancer immunotherapy. Future Oncol, 2017, 13: 2583-92
[38] Whiteside TL. Exosomes carrying immunoinhibitory proteins and their role in cancer. Clin Exp Immunol, 2017, 189: 259-67
[39] Ye L, Zhang Q, Cheng Y, et al. Tumor-derived exosomal HMGB1 fosters hepatocellular carcinoma immune evasion by promoting $TIM\text{-}1^{+}$ regulatory B cell expansion. J Immunother Cancer, 2018, 6: 145
[40] Zhou J, Yang Y, Wang W, et al. Melanoma-released exosomes directly activate the mitochondrial apoptotic pathway of $CD4^{+}$ T cells through their microRNA cargo. Exp Cell Res, 2018, 371: 364-71
[41] Wang Y, Yi J, Chen X, et al. The regulation of cancer cell migration by lung cancer cell-derived exosomes through TGF-β and IL-10. Oncol Lett, 2016, 11: 1527-30
[42] Stankovic B, Bjorhovde HAK, Skarshaug R, et al. Immune cell composition in human non-small cell lung cancer. Front Immunol, 2018, 9: 3101
[43] Gao J, Qiu X, Li X, et al. Expression profiles and clinical value of plasma exosomal Tim-3 and Galectin-9 in non-small cell lung cancer. Biochem Biophys Res Commun, 2018, 498: 409-15
[44] Ning Y, Shen K, Wu Q, et al. Tumor exosomes block dendritic cells maturation to decrease the T cell immune response. Immunol Lett, 2018, 199: 36-43
[45] Chen G, Huang AC, Zhang W, et al. Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response. Nature, 2018, 560: 382-6
[46] Cai Z, Yang F, Yu L, et al. Activated T cell exosomes

promote tumor invasion via Fas signaling pathway. J Immunol, 2012, 188: 5954-61

[47] Berchem G, Noman MZ, Bosseler M, et al. Hypoxic tumor-derived microvesicles negatively regulate NK cell function by a mechanism involving TGF-β and miR23a transfer. Oncoimmunology, 2016, 5: e1062968

[48] Zhu MC, Xiong P, Li GL, et al. Could lung cancer exosomes induce apoptosis of natural killer cells through the p75NTR-proNGF-sortilin axis? Med Hypotheses, 2017, 108: 151-3

[49] Huang SH, Li Y, Zhang J, et al. Epidermal growth factor receptor-containing exosomes induce tumor-specific regulatory T cells. Cancer Invest, 2013, 31: 330-5

[50] Aguado BA, Bushnell GG, Rao SS, et al. Engineering the pre-metastatic niche. Nat Biomed Eng, 2017, 1: 0077

[51] Fang T, Lv H, Lv G, et al. Tumor-derived exosomal miR-1247-3p induces cancer-associated fibroblast activation to foster lung metastasis of liver cancer. Nat Commun, 2018, 9: 191

[52] Maji S, Chaudhary P, Akopova I, et al. Exosomal annexin II promotes angiogenesis and breast cancer metastasis. Mol Cancer Res, 2017, 15: 93-105

[53] Fong MY, Zhou W, Liu L, et al. Breast-cancer-secreted miR-122 reprograms glucose metabolism in premetastatic niche to promote metastasis. Nat Cell Biol, 2015, 17: 183-94

[54] Hoshino A, Costa-Silva B, Shen TL, et al. Tumour exosome integrins determine organotropic metastasis. Nature, 2015, 527: 329-35

[55] Xu Z, Liu X, Wang H, et al. Lung adenocarcinoma cell-derived exosomal miR-21 facilitates osteoclastogenesis. Gene, 2018, 666: 116-22

[56] Taverna S, Pucci M, Giallombardo M, et al. Amphiregulin contained in NSCLC-exosomes induces osteoclast differentiation through the activation of EGFR pathway. Sci Rep, 2017, 7: 3170

[57] Zhang R, Dong Y, Sun M, et al. Tumor-associated inflammatory microenvironment in non-small cell lung cancer: correlation with FGFR1 and TLR4 expression via PI3K/Akt pathway. J Cancer, 2019, 10: 1004-12

[58] Liu Y, Gu Y, Han Y, et al. Tumor exosomal RNAs promote lung pre-metastatic niche formation by activating alveolar epithelial TLR3 to recruit neutrophils. Cancer Cell, 2016, 30: 243-56

[59] Wen SW, Sceneay J, Lima LG, et al. The biodistribution and immune suppressive effects of breast cancer-derived exosomes. Cancer Res, 2016, 76: 6816-27

[60] Qiu JJ, Lin XJ, Tang XY, et al. Exosomal metastasis-associated lung adenocarcinoma transcript 1 promotes angiogenesis and predicts poor prognosis in epithelial ovarian cancer. Int J Biol Sci, 2018, 14: 1960-73

[61] Zeng Z, Li Y, Pan Y, et al. Cancer-derived exosomal miR-25-3p promotes pre-metastatic niche formation by inducing vascular permeability and angiogenesis. Nat Commun, 2018, 9: 5395

[62] Grimolizzi F, Monaco F, Leoni F, et al. Exosomal miR-126 as a circulating biomarker in non-small-cell lung cancer regulating cancer progression. Sci Rep, 2017, 7: 15277

[63] Mao G, Liu Y, Fang X, et al. Tumor-derived microRNA-494 promotes angiogenesis in non-small cell lung cancer. Angiogenesis, 2015, 18: 373-82

[64] Zhuo H, Zhao Y, Cheng X, et al. Tumor endothelial cell-derived cadherin-2 promotes angiogenesis and has prognostic significance for lung adenocarcinoma. Mol Cancer, 2019, 18: 34

[65] Novo D, Heath N, Mitchell L, et al. Mutant p53s generate pro-invasive niches by influencing exosome podocalyxin levels. Nat Commun, 2018, 9: 5069

[66] Huang WT, Chong IW, Chen HL, et al. Pigment epithelium-derived factor inhibits lung cancer migration and invasion by upregulating exosomal thrombospondin 1. Cancer Lett, 2019, 442: 287-98