

微环境在卵巢癌发生发展中的作用

王雅蕾,王靖怡 综述,齐丽莎 审校

(天津医科大学肿瘤医院病理科,国家肿瘤临床医学研究中心,天津市“肿瘤防治”重点实验室,天津市恶性肿瘤临床医学研究中心,天津 300060)

摘要 肿瘤微环境由基质细胞、免疫细胞、周围血管、淋巴管及细胞外基质(ECM)中的可溶性因子、胞外囊泡等组成,它与肿瘤细胞的共同进化促进了肿瘤进展。由于微环境成分相对稳定,靶向微环境的治疗有望在肿瘤治疗中取得突破。本文就卵巢癌细胞及其微环境之间的相互作用及微环境促进卵巢癌发生、发展的研究进展做一阐述。

关键词 卵巢癌;微环境;转移;外泌体

中图分类号 R737.31

文献标志码 A

卵巢癌是女性生殖系统第二大常见恶性肿瘤,由于筛查手段有限且早期症状不明显,60%~70%的患者就诊时已为进展期,在女性生殖系统肿瘤中致死率最高^[1]。虽然手术辅以顺铂、紫杉醇化疗对80%的卵巢癌患者有效,但大多数患者都会出现肿瘤复发。肿瘤细胞常以自分泌或旁分泌的方式影响微环境以促进自身生存发展。肿瘤微环境(tumor microenvironment, TME)是指肿瘤细胞所处的内环境,由基质细胞、免疫细胞、周围血管、淋巴管及细胞外基质(ECM)中的可溶性因子、胞外囊泡等组成^[2]。卵巢癌主要通过腹水跨体腔扩散,腹水中所含的T细胞和癌相关巨噬细胞等免疫细胞、胞外囊泡及其他类型非癌细胞也参与卵巢癌的增殖、转移和耐药^[3]。此外,由于卵巢癌常转移至网膜,网膜中丰富的结缔组织和脂肪成分也对卵巢癌的进展具有重要作用^[4]。因此,了解微环境与卵巢癌细胞之间的相互作用关系及其促进卵巢癌进展的相关机制,对今后开发新的卵巢癌治疗手段,提高临床诊治效果、改善患者预后具有重要意义。

1 基质细胞

1.1 癌相关成纤维细胞(cancer-associated fibroblasts, CAFs) 成纤维细胞是结缔组织中含最丰富的细胞。它可分泌I型、III型、IV型胶原蛋白、纤维连接素等ECM的重要组分,维持ECM的稳定^[5]。在多种生长因子的作用下,成纤维细胞可被活化,获得收缩能力参与组织修复过程,并在完成修复后发

生凋亡。CAFs可被癌细胞分泌的转化激活因子- $\beta 1$ (TGF- $\beta 1$)、血小板源性生长因子(PDGF)、碱性成纤维细胞生长因子(bFGF)和白细胞介素-6(IL-6)等激活,特异性表达 α -平滑肌肌动蛋白(α -SMA)和纤维激活蛋白(FAP)^[5-6]。与普通活化的成纤维细胞不同,CAFs不丢失活性表型,也不易发生凋亡。CAFs在恶性卵巢肿瘤中较良性卵巢肿瘤和正常卵巢组织中含量更丰富,且与肿瘤微血管、淋巴管的密度增加和肿瘤的网膜、淋巴结转移密切相关^[7]。体外实验发现,卵巢癌细胞通过产生TGF- $\beta 1$ 可上调成纤维细胞中活性氧及氯离子通道水平,诱导其转化为CAFs^[8]。另外,TGF- β 还可促进CAFs上调多能蛋白聚糖(VCAN)的表达,增强卵巢癌细胞的侵袭能力^[9]。CAFs分泌的IL-6促进卵巢上皮肿瘤的锚定非依赖性生长,增强其侵袭转移能力^[10]。更为有趣的是,IL-6还可抑制卵巢细胞的基础自噬,促进卵巢癌的形成^[10]。CAFs可产生肝细胞生长因子(HGF)降低癌细胞对各种抗癌药物的敏感性^[11]。此外,CAFs还通过异常重塑和过度沉积ECM成分,改变肿瘤的物理特性,增强间质屏障以阻碍化疗药物的传递^[12]。CAFs产生的谷胱甘肽和半胱氨酸也可促卵巢癌耐药,而CD8⁺T细胞通过释放干扰素 γ (IFN γ)上调 γ -谷氨酰转移酶和胱氨酸/谷氨酸反向转运体的转录,抑制谷胱甘肽和半胱氨酸水平,增加卵巢癌细胞对化疗药物的敏感性^[13]。进一步研究发现,CAFs和CD8⁺T细胞的数量分别与卵巢癌患者生存率呈负相关和正相关,因此利用化疗和免疫治疗之间的相互作用有助于改善卵巢癌患者预后^[13]。

1.2 间充质干细胞(mesenchymal stem cells, MSCs) MSCs是被招募至TME的基质细胞亚群,具有多向分化潜能。骨髓源性MSCs可促进小鼠移植瘤模型

基金项目 国家自然科学基金资助项目(81402420),天津市应用基础与前沿技术研究计划青年项目(15JCQNJC12400),天津市卫生计生委重点攻关项目(16KG25)

作者简介 王雅蕾(1977-),女,主管技师,硕士,研究方向:肿瘤复发转移机制;通信作者:齐丽莎, E-mail: lqi01@tmu.edu.cn。

中肿瘤的生长^[14]。将卵巢癌细胞与网膜中脂肪源性间充质干细胞(O-ADSCs)共培养后,其侵袭性和增殖能力都显著增加^[15]。卵巢癌细胞在经过O-ADSCs的条件培养基处理后,与细胞癌变、凋亡和肿瘤转移相关的9种蛋白表达增加,表明O-ADSCs可能通过旁分泌机制改变了卵巢癌细胞的蛋白组学特征促进其进展^[15]。MSCs可分泌IL-6,增强卵巢癌SKOV3细胞在免疫缺陷鼠的成瘤能力,而IL-6受体阻断抗体可抑制该作用^[16]。Pasquier等^[17]证实MSCs释放的CCL2和CCL5可诱导卵巢癌细胞分泌IL-6,进而导致卵巢癌发生耐药。这些研究表明,IL-6为未来针对肿瘤基质的抗癌治疗提供了潜在治疗靶点。体内、体外实验表明MSCs通过分泌血小板激活因子(PAF)激活PAF/PAFR通路,促进卵巢癌恶性进展^[18]。McLean等^[19]认为卵巢癌细胞和MSCs共作用可激活BMP信号通路,促进肿瘤进展。MSCs还可替代病毒成为有效的基因运载工具,MSCs可携带内皮抑素或IL-21特异性地作用于卵巢癌病灶,分别发挥抑制卵巢癌增殖和增强抗癌免疫的作用^[20-21],表明其在卵巢癌临床治疗上的巨大潜在价值,但如何将其转化应用于临床仍需探索。

2 免疫微环境

2.1 肿瘤相关巨噬细胞(tumor-associated macrophages, TAMs) 巨噬细胞是肿瘤微环境中含量最丰富的免疫细胞,根据环境中分子信号的不同可分为M1型(经典型)和M2型(转变型)。M1型细胞可通过表达促炎因子和IL-12、TNF- α 等免疫刺激因子抑制肿瘤进展^[22]。肿瘤细胞分泌的CCL2、CCL5、CXCL1和CFS等趋化因子可将M1或其前体单核细胞招募至肿瘤微环境,肿瘤微环境中的IL-4、IL-10和IL-13等可进一步促其分化为M2型细胞^[22]。肿瘤中极化的M2型细胞称为TAMs。Goossens等^[23]发现卵巢癌细胞可促进巨噬细胞膜胆固醇流出和脂筏消耗,使其转化成TAMs。TAMs的抗原呈递能力弱,但可通过多种方式促进肿瘤进展:TAMs可分泌EGF^[24]和TNF刺激肿瘤细胞的生长;可刺激肿瘤细胞分泌VEGF^[24]、PDGF^[25]等促进肿瘤血管生成;可产生各类基质金属蛋白酶(MMPs)促进肿瘤浸润迁移^[26];可分泌IL-10,在T细胞分化过程激活Foxp3,增加调节性T细胞(Treg)的比率,抑制免疫应答^[27]。最近一项研究发现,缺氧微环境促进卵巢癌上皮细胞分泌含microRNA-940(miR-940)的外泌体,巨噬细胞摄取外泌体递送的miR-940后发生M2极化,促进卵巢癌增殖和转移^[28]。TAMs释放的携带miRNA的外泌体通过靶向STAT3诱导Treg/Th17

细胞间的不平衡,发挥免疫抑制功能,促进卵巢癌的恶性进展和转移^[29]。有研究通过分析卵巢癌细胞和TAMs特异性转录组,建立了与临床预后相关的卵巢癌微环境的全转录组图谱,发现参与诱导STAT3分泌的细胞因子(包括IL-6、IL-10等),成纤维细胞生长因子(FGF)、WNT信号通路相关成分、信号素轴突(semaphorin axon)和肝配蛋白(ephlin guidance proteins)引导蛋白等都与卵巢癌复发有关^[30]。

2.2 肿瘤相关淋巴细胞(tumor-associated lymphocytes, TILs) TILs包括肿瘤基质和癌岛内的T细胞和Tregs。CD8⁺或CD4⁺T淋巴细胞通过T细胞受体(TCR)识别由树突状细胞呈递的癌抗原或过表达的自身抗原^[31],一旦TCR/MHC识别肿瘤抗原后活化的CD8阳性细胞毒性T细胞(CTL)可分泌穿孔素和颗粒酶,直接杀伤肿瘤细胞或通过FasL/Fas结合,诱导肿瘤细胞凋亡^[32-33]。T细胞还可分泌各种细胞因子或趋化因子激活其他类型免疫细胞。Treg、MDSCs和TAMs可通过分泌大量可溶性抑制因子抑制TILs功能^[27]。当MHC分子和共刺激配体表达下调,细胞程序性死亡-配体1(PD-L1)和细胞毒性T淋巴细胞相关抗原-4(CTLA-4)等抑制性受体上调时T细胞功能受抑制^[34]。PD-1是活性T细胞表达的抑制性免疫检测点受体,可与肿瘤细胞或基质细胞表达的PD-L1特异性结合^[35]。许多研究表明PD-L1的表达促进肿瘤微环境的免疫抑制功能;PD-L1在卵巢癌细胞系中高表达且与患者不良预后和CD8⁺TILs减少相关^[36];在动物模型将PD-L1沉默可减少卵巢癌的腹腔转移^[37];抗PD-1单抗Pembrolizumab、nivolumab及PD-L1抗体avelumab在复发性或难治性卵巢癌患者中的反应率为10%~20%^[38]。恶性卵巢癌中Tregs明显高于良性卵巢肿瘤和健康对照组,卵巢癌Ⅲ/Ⅳ期患者中Tregs的百分比高于Ⅰ/Ⅱ期患者,且其含量高则患者预后较差^[39]。这些研究表明Tregs可用以监测卵巢癌患者的免疫学状态。Tregs含量高的卵巢癌患者CTLA-4表达上调CD28表达下调,体外诱导的CD8阳性Tregs可通过TGF- β 1和IFN- γ 阻断CD4⁺T细胞的增殖,增加卵巢癌患者外周血中Tregs的数量并招募Tregs浸润肿瘤^[40]。

3 肿瘤血管生成(angiogenesis)

血管生成是肿瘤生长和转移的重要步骤,在缺氧、低血糖、机械压力或炎症等氧气和营养物质需求增加的状况下被激活。肿瘤和基质细胞可分泌多种促血管生成因子,其中以VEGF起主要作用。有学者提出VEGF的表达与卵巢癌患者的分级分期相关,虽然良性或交界性肿瘤中也有VEGF表达,

但其在癌中的表达更为明显^[41]。Kuerti 等^[42]发现卵巢癌中 VEGFC 水平较高的患者的总生存时间明显低于 VEGFC 水平低者,且 VEGFC 可作为鉴定高淋巴结转移风险患者的临床标志,针对 VEGFC 的特异性治疗方案可能对这类患者有益。最近研究表明,卵巢癌相关抗原 66(OVA66)过表达可激发癌细胞中 VEGF-VEGFR2 正反馈信号环,促进肿瘤血管生成和增殖^[43]。卵巢癌患者标本中 OVA66 的表达水平与 VEGF 水平有很强的正相关性,且 OVA66 在进展期卵巢癌中更为丰富^[43]。尽管目前抗血管生成治疗已在临床广泛应用,但已有报道称针对 VEGF 的靶向治疗在部分患者疗效欠佳甚至促进肿瘤进展。有学者认为除需在治疗前进行分子检测类型评估外,Notch 信号通路和 TAMs 也对 VEGF 靶向治疗疗效具有重要影响:卵巢癌上皮细胞可产生 DLL4 配体激活 Notch 通路,促进大血管的形成、降低癌细胞对抗 VEGF 治疗的敏感性^[44];TAMs 有促血管生成功能,还可分泌 Tie2 产生毛细血管样结构诱导肿瘤血管生成拟态。有研究发现,肿瘤坏死因子超家族-15(TNFSF15)在正常卵巢组织中可抑制血管生成但在卵巢癌中丢失,将沉默 TNFSF15 的卵巢癌细胞系 ID8 接种至小鼠体内可使肿瘤血管生成增加促进肿瘤生长,表明肿瘤细胞下调 TNFSF15 表达可能是卵巢癌新生血管形成的前提^[45]。

4 外泌体(Exosomes)

肿瘤微环境中大多细胞都可释放外泌体,介导肿瘤细胞和基质间或肿瘤细胞间蛋白质、脂质和核酸的转移^[46]。这些细胞间信息交流决定了肿瘤细胞生存和扩张的速度,在肿瘤进展中起重要作用。许多研究表明卵巢癌腹水中的外泌体与免疫抑制、侵袭性增加和化疗耐药有关^[47]。卵巢癌恶性腹水来源的外泌体可减弱外周血淋巴细胞的细胞毒作用,诱导淋巴细胞和树突状细胞的凋亡^[48],还可通过阻碍 T 细胞信号级联反应抑制 T 细胞的激活^[49]。卵巢癌患者血浆中的外泌体表达 IL-10 和 TGF- β 1 等免疫抑制因子可促进 Tregs 功能,抑制抗肿瘤免疫^[50]。Nakamura 等^[51]认为卵巢癌患者血清和腹水中携带 miRNA 的外泌体对卵巢癌的诊断、治疗和预后评估也具有重要价值。卵巢癌细胞可通过外泌体释放大量 miR-6126,调控与癌症转移相关的关键调节因子整合素 β 1^[52]。动物实验进一步证明癌细胞摄取 miR-6126 后肿瘤生长减缓,侵袭和转移能力降低^[52]。外泌体可介导 miR-21 从基质细胞转移至癌细胞,作用于凋亡肽酶激活因子 1(APAF1),诱导卵巢癌的紫杉醇耐药,如何抑制基质细胞来源的 miR-21

可能对复发性卵巢癌患者的治疗具有重要意义^[53]。

5 展望

卵巢癌尤其是化疗耐药和复发性病例的治疗仍是肿瘤学中的棘手问题。相对于经常发生突变的肿瘤细胞而言,基质成分较为稳定,靶向肿瘤的微环境是肿瘤治疗的可行策略。目前,TME 导向治疗和传统化疗的联合应用在卵巢癌的治疗中已取得一定成效。但另一方面卵巢癌微环境具有显著异质性,标准化治疗在患者不同亚组中可能引起不同程度的反应,因此仍需进一步研究,以求在卵巢癌的治疗中取得突破。

参考文献:

- [1] Siegel R L, Miller K D, Jemal A. Cancer statistics, 2019[J]. CA Cancer J Clin, 2019, 69(1):7
- [2] Chen F, Zhuang X E, Lin L Y, et al. New horizons in tumor microenvironment biology: challenges and opportunities [J]. BMC Med, 2015, 13(1):278
- [3] Von Strandmann E P, Reinartz S, Wager U A. Tumor-host cell interactions in ovarian cancer: pathways to therapy failure[J]. Trends Cancer, 2017, 3(2):137
- [4] Langyel E. Ovarian cancer development and metastasis[J]. Am J Pathol, 2010, 177(3): 1053
- [5] Tomasek J J, Gabbiani G, Hinz B, et al. Myofibroblasts and mechano-regulation of connective tissue remodelling [J]. Nat Rev Mol Cell Biol, 2002, 3(5):349
- [6] Raghu K, Michael Z. Fibroblasts in cancer[J]. Nat Rev Cancer, 2006, 6(5):392
- [7] Yuan Z, Huijuan T, Jing C, et al. Ovarian cancer-associated fibroblasts contribute to epithelial ovarian carcinoma metastasis by promoting angiogenesis, lymphangiogenesis and tumor cell invasion[J]. Cancer Lett, 2011, 303(1):47
- [8] Yao Q, Qu X, Yang Q, et al. CLIC4 mediates TGF- β 1-induced fibroblast-to-myofibroblast transdifferentiation in ovarian cancer[J]. Oncol Rep, 2009, 22(3):541
- [9] Yeung T L, Leung C S, Wong K K, et al. TGF- β modulates ovarian cancer invasion by upregulating CAF-derived versican in the tumor microenvironment[J]. Cancer Res, 2013, 73(16):5016
- [10] Thuwajit C, Ferraresi A, Titone R A, et al. The metabolic cross-talk between epithelial cancer cells and stromal fibroblasts in ovarian cancer progression: Autophagy plays a role[J]. Med Res Rev, 2018, 38(4):1235
- [11] Straussman R, Morikawa T, Shee K, et al. Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion[J]. Nature, 2012, 487(748):500
- [12] Sun Y. Translational horizons in the tumor microenvironment: harnessing breakthroughs and targeting cures[J]. Med Res Rev, 2015, 35(2):408
- [13] Wang W M, Kryczek I, Dostal L, et al. Effector T cells abrogate stroma-mediated chemoresistance in ovarian cancer[J]. Cell, 2016, 165(5):1092
- [14] Spaeth E L, Dembinski J L, Sasser A K, et al. Mesenchymal stem

- cell transition to tumor-associated fibroblasts contributes to fibrovascular network expansion and tumor progression[J]. *PLoS One*, 2009, 4(4):e4992
- [15] Zhang Y L, Dong W H, Wang J J, et al. Human omental adipose-derived mesenchymal stem cell-conditioned medium alters the proteomic profile of epithelial ovarian cancer cell lines *in vitro*[J]. *Oncotargets Ther*, 2017,10:1655
- [16] Ding D C, Liu H W, Chu T Y. Interleukin-6 from ovarian mesenchymal stem cells promotes proliferation, sphere and colony formation and tumorigenesis of an ovarian cancer cell line SKOV3 [J]. *J Cancer*, 2016, 7(13):1815
- [17] Pasquier J, Gosset M, Geyl C A, et al. CCL2/CCL5 secreted by the stroma induce IL-6/PYK2 dependent chemoresistance in ovarian cancer[J]. *Mol Cancer*, 2018,17(1):47
- [18] Gao T, Yu Y, Cong Q, et al. Human mesenchymal stem cells in the tumour microenvironment promote ovarian cancer progression: the role of platelet-activating factor[J]. *BMC Cancer*, 2018, 18(1):999
- [19] Mclean K, Gong Y, Choi Y, et al. Human ovarian carcinoma-associated mesenchymal stem cells regulate cancer stem cells and tumorigenesis via altered BMP production[J]. *J Clin Invest*, 2011, 121(8):3206
- [20] Jiang J, Chen W, Zhuang R, et al. The effect of endostatin mediated by human mesenchymal stem cells on ovarian cancer cells *in vitro* [J]. *J Cancer Res Clin Oncol*, 2010, 136(6):873
- [21] Hu W H, Wang J, He X F, et al. Human umbilical blood mononuclear cell-derived mesenchymal stem cells serve as interleukin-21 gene delivery vehicles for epithelial ovarian cancer therapy in nude mice[J]. *Biotechnol Appl Biochem*, 2011, 58(6):397
- [22] Sica A, Larghi P, Mancino A, et al. Macrophage polarization in tumour progression[J]. *Semin Cancer Biol*, 2008, 18(5):349
- [23] Goossens P, Rodriguez-Vita J, Etzerodt A, et al. Membrane cholesterol efflux drives tumor-associated macrophage reprogramming and tumor progression[J]. *Cell Metab*, 2019,29(6):1376
- [24] Yin M Z, Li X, Tan S, et al. Tumor-associated macrophages drive spheroid formation during early transcoelomic metastasis of ovarian cancer[J]. *J Clin Invest*, 2016, 126(11):4157
- [25] Yang Y L, Andersson P, Hosaka K, et al. The PDGF-BB-SOX7 axis-modulated IL-33 in pericytes and stromal cells promotes metastasis through tumour-associated macrophages [J]. *Nat Commun*, 2016, 7:11385
- [26] Ke X, Zhang S P, Wu M, et al. Tumor-associated macrophages promote invasion via toll-like receptors signaling in patients with ovarian cancer[J]. *Int Immunopharmacol*, 2016,40:184
- [27] Zhu Q Y, Wu X L, Wu Y E, et al. Interaction between Treg cells and tumor-associated macrophages in the tumor microenvironment of epithelial ovarian cancer[J]. *Oncol Rep*, 2016, 36(6):3472
- [28] Chen X, Ying X, Wang X J, et al. Exosomes derived from hypoxic epithelial ovarian cancer deliver microRNA-940 to induce macrophage M2 polarization[J]. *Oncol Rep*, 2017, 38(1):522
- [29] Zhou J R, Li X D, Wu X L, et al. Exosomes released from tumor-associated macrophages transfer miRNAs that induce a Treg/Th17 cell imbalance in epithelial ovarian cancer [J]. *Cancer Immunol Res*, 2018, 6(12):1578
- [30] Reinartz S, Finkernagel F, Adhikary T A, et al. A transcriptome-based global map of signaling pathways in the ovarian cancer microenvironment associated with clinical outcome[J]. *Genome Biol*, 2016, 17(1):108
- [31] Mittal D, Gubin M M, Schreiber R D, et al. New insights into cancer immunoediting and its three component phases—elimination, equilibrium and escape[J]. *Curr Opin Immunol*, 2014, 27(1):16
- [32] Melero I, Rouzaut A, Motz G T, et al. T-cell and NK-cell infiltration into solid tumors: a key limiting factor for efficacious cancer immunotherapy[J]. *Cancer Discov*, 2014, 4(5):522
- [33] Motz G T, Santoro S P, Wang L, et al. Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors[J]. *Nat Med*, 2014, 20(6):607
- [34] Higuchi T, Flies D B, Marjon N A, et al. CTLA-4 blockade synergizes therapeutically with PARP inhibition in BRCA1-deficient ovarian cancer[J]. *Cancer Immunol Res*, 2015, 3(11):1257
- [35] Topalian S L, Drake C G, Pardoll D M. Targeting the PD-1/B7-H1 (PD-L1) pathway to activate anti-tumor immunity [J]. *Curr Opin Immunol*, 2012, 24(2):207
- [36] Hwang W T, Adams S F, Tahirovic E, et al. Prognostic significance of tumor-infiltrating T cells in ovarian cancer: A meta-analysis[J]. *Gynecol Oncol*, 2012, 124(2):192
- [37] Abiko K, Mandai M, Hamanishi J, et al. PD-L1 on tumor cells is induced in ascites and promotes peritoneal dissemination of ovarian cancer through CTL dysfunction[J]. *Clin Cancer Res*, 2013, 19(6):1363
- [38] Varga A, Piha-Paul S A, Ott P A, et al. Antitumor activity and safety of pembrolizumab in patients (pts) with PD-L1 positive advanced ovarian cancer: Interim results from a phase Ib study[J]. *J Clin Oncol*, 2015, 33(15, S):194
- [39] Wu M, Chen X, Lou J, et al. Changes in regulatory T cells in patients with ovarian cancer undergoing surgery: Preliminary results [J]. *Int Immunopharmacol*, 2017, 47:244
- [40] Waldhauer I, Steinle A. NK cells and cancer immunosurveillance[J]. *Oncogene*, 2008, 27(45):5932
- [41] Mukherjee S, Pal M, Mukhopadhyay S, et al. VEGF expression to support targeted therapy in ovarian surface epithelial neoplasms[J]. *J Clin Diagn Res*, 2017, 11(4):C43
- [42] Kuerti S, Oliveira-Ferrer L, Milde-Langosch K, et al. VEGF-C expression attributes the risk for lymphatic metastases to ovarian cancer patients[J]. *Oncotarget*, 2017, 8(26):43218
- [43] Song F F, Chen Q, Rao W, et al. OVA66 promotes tumour angiogenesis and progression through enhancing autocrine VEGF-VEGFR2 signalling[J]. *EBioMedicine*, 2019, 41:156
- [44] Li J L, Sainson R C, Oon C E, et al. DLL4-Notch signaling mediates tumor resistance to anti-VEGF therapy *in vivo*[J]. *Cancer Res*, 2011, 71(18):6073
- [45] Deng W M, Gu X, Lu Y, et al. Down-modulation of TNFSF15 in ovarian cancer by VEGF and MCP-1 is a pre-requisite for tumor neovascularization[J]. *Angiogenesis*, 2012, 15(1):71
- [46] Han L, Xu J, Xu Q, et al. Extracellular vesicles in the tumor microenvironment: Therapeutic resistance, clinical biomarkers, and

- and PKM zeta in the monkey dentate gyrus and their relationships with aging and memory[J]. *J Neurosci*, 2012,32(21):7336
- [8] Knafo S, Sanchez-Puelles C, Palomer E A, et al. PTEN recruitment controls synaptic and cognitive function in Alzheimer's models[J]. *Nat Neurosci*, 2016, 19(3):443
- [9] Li S M, Jin M, Koeglsperger T, et al. Soluble a beta oligomers inhibit long-term potentiation through a mechanism involving excessive activation of extrasynaptic NR2B-Containing NMDA receptors[J]. *J Neurosci*, 2011, 31(18):6627
- [10] Tu S C, Okamoto S I, Lipton S A, et al. Oligomeric a beta-induced synaptic dysfunction in alzheimer's disease[J]. *Mol Neurodegener*, 2014, 9:48
- [11] Watts J C, Prusiner S B. β -Amyloid prions and the pathobiology of alzheimer's disease[J]. *Cold Spring Harb Perspect Med*, 2018, 8(5): pii: a023507
- [12] Rahman M M, Zetterberg H, Lendel C A. Binding of human proteins to amyloid-beta protofibrils[J]. *ACS Chem Biol*, 2015, 10(3):766
- [13] Reinders N R, Pao Y, Renner M C, et al. Amyloid-beta effects on synapses and memory require AMPA receptor subunit GluA3[J]. *Proc Natl Acad Sci U S A*, 2016, 113(42):E6526
- [14] Alfonso S, Kessels H W, Banos C C, et al. Synapto-depressive effects of amyloid beta require PICK1[J]. *Eur J Neurosci*, 2014, 39(7): 1225
- [15] Berchtold N C, Sabbagh M N, Beach T G, et al. Brain gene expression patterns differentiate mild cognitive impairment from normal aged and Alzheimer's disease[J]. *Neurobiol Aging*, 2014, 35(9):1961
- [16] Granger A J, Shi Y, Lu W, et al. LTP requires a reserve pool of glutamate receptors independent of subunit type[J]. *Nature*, 2013, 493 (7433):495
- [17] Whitcomb D J, Hogg E L, Regan P, et al. Intracellular oligomeric amyloid-beta rapidly regulates GluA1 subunit of AMPA receptor in the hippocampus[J]. *Sci Rep*, 2015, 5:10934
- [18] Wirth M, Madison C M, Rabinovici G D, et al. Alzheimer's disease neurodegenerative biomarkers are associated with decreased cognitive function but not beta-amyloid in cognitively normal older individuals[J]. *J Neurosci*, 2013, 33(13):5553
- [19] Yu W D, Polepalli J, Wagh D, et al. A critical role for the PAR-1/MARK-tau axis in mediating the toxic effects of A on synapses and dendritic spines[J]. *Hum Mol Genet*, 2012, 21(6):1384
- [20] Kopeikina K J, Polydoro M, Tai H, et al. Synaptic alterations in the rTg4510 mouse model of tauopathy[J]. *J Comp Neurol*, 2013, 521(6): 1334
- [21] Fa M, Puzzo D, Piacentini R, et al. Extracellular Tau oligomers produce an immediate impairment of LTP and memory[J]. *Sci Rep*, 2016, 6:19393
- [22] Regan P, Piers T, Yi J H, et al. Tau phosphorylation at serine 396 residue is required for hippocampal LTD [J]. *J Neurosci*, 2015, 35 (12):4804
- [23] Ittner A, Chua S W, Bertz J, et al. Site-specific phosphorylation of tau inhibits amyloid-beta toxicity in Alzheimer's mice[J]. *Science*, 2016, 354(6314):904
- [24] Tracy T E, Gan L. Acetylated tau in Alzheimer's disease: an instigator of synaptic dysfunction underlying memory loss: increased levels of acetylated tau blocks the postsynaptic signaling required for plasticity and promotes memory deficits associated with tauopathy[J]. *Bioessays*, 2017, 39(4): doi: 10.1002/bies.201600224
- [25] Tracy T E, Sohn P D, Minami S S, et al. Acetylated Tau obstructs KIBRA-mediated signaling in synaptic plasticity and promotes Tauopathy-Related memory loss[J]. *Neuron*, 2016, 90(2):245

(2019-08-13 收稿)

(上接第 291 页)

- targeting strategies[J]. *Med Res Rev*, 2017, 37(6, SI):1318
- [47] Worzfeld T, Von Strandmann E P, Huber M A, et al. The unique molecular and cellular microenvironment of ovarian cancer[J]. *Front Oncol*, 2017, 7(Suppl 5):24
- [48] Yokoi A, Yoshioka Y, Yamamoto Y, et al. Malignant extracellular vesicles carrying MMP1 mRNA facilitate peritoneal dissemination in ovarian cancer[J]. *Nat Commun*, 2017, 8:14470
- [49] Kelleher J, Balu-Iyer S, Loyall J A, et al. Extracellular vesicles present in human ovarian tumor microenvironments induce a phosphatidylserine-dependent arrest in the T-cell signaling cascade[J]. *Cancer Immunol Res*, 2015, 3(11):1269
- [50] Szajnik M, Czystowska M, Szczepanski M J, et al. Tumor-derived microvesicles induce, expand and up-regulate biological activities of human regulatory T cells (Treg)[J]. *PLoS One*, 2010, 5(7):e11469
- [51] Nakamura K, Sawada K, Yoshimura A, et al. Clinical relevance of circulating cell-free microRNAs in ovarian cancer[J]. *Mol Cancer*, 2016, 15(1):48
- [52] Kanlikilicer P, Rashed M H, Bayraktar R A, et al. Ubiquitous release of exosomal tumor suppressor miR-6126 from ovarian cancer cells[J]. *Cancer Res*, 2016, 76(24):7194
- [53] Au Yeung C L, Co N N, Tsuruga T, et al. Exosomal transfer of stroma-derived miR21 confers paclitaxel resistance in ovarian cancer cells through targeting APAF1[J]. *Nat Commun*, 2016, 7:11150

(2019-03-18 收稿)