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在线全文

肝脏微环境细胞在肿瘤肝定植转移过程的作用及意义*

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【摘要】 肿瘤转移是引起肿瘤患者死亡的主要原因，是临床上面临的重要挑战。肿瘤转移是个多步骤的复杂过程，肿瘤细胞历经离开原发部位，内渗进入血管，随血液远行，从血管外渗到远处器官，最终在靶器官定植(colonization）而生长成为转移性癌灶。肿瘤转移具有一定的靶器官亲嗜倾向，肝脏是肿瘤的常见转移部位，对肝脏有亲嗜倾向的肿瘤包括眼葡萄膜黑色素瘤、结直肠癌、胰腺癌等。肝脏解剖结构造成的血流动力学特点(例如压力小、血流慢)常常使得肿瘤细胞在肝脏易于瘀滞而利于定植，但肿瘤是否能在肝脏成功定植主要取决于肿瘤细胞与肝脏微环境(特别是肝固有细胞成分)的相互作用。肝脏微环境的固有细胞主要包括肝细胞、肝血窦内皮细胞(liver sinusoidal endothelial cells, LSECs)、肝星状细胞(hepatic stellate cells, HSCs)、枯否细胞(Kupffer cells, KCs) 等。本文将讨论肝脏的固有细胞在肿瘤肝定植转移中的作用及意义。

【关键词】 肝转移定植　肝细胞　肝血窦内皮细胞　肝星状细胞　枯否细胞

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【**Abstract**】 Metastasis, a main cause of death in tumor patients, is a complicated process that involves multiple steps, presenting a major clinical challenge. Tumor cells break the physical boundaries of a primary tumor, intravasate into the lumina of blood vessels, travel around through blood circulation, extravasate into distant organs, colonize the host organs, and eventually develop into the foci of metastatic cancer. The metastasis of tumor cells exhibits organ-tropism, i.e., tumor cells preferentially spread to specific organs. Liver is a common site for metastasis. The pattern of metastasis in uveal melanoma, colorectal carcinoma, and pancreatic ductal adenocarcinoma shows organ-tropism for liver. The anatomical structure of liver determines its hemodynamic characteristics, e.g., low pressure and slow blood flow, which tend to facilitate the stasis and colonization of tumor cells in the liver. Besides the hemodynamic features, the metastatic colonization of liver depends largely on the interaction between tumor cells and the hepatic microenvironment (especially liver-resident cellular components). Resident cells of the hepatic microenvironment include hepatocytes, liver sinusoidal endothelial cells (LSECs), hepatic stellate cells (HSCs), Kupffer cells (KCs), etc. Herein, we discussed the role and significance of liver-resident cells in the metastatic colonization of tumor in the liver.

【**Key words**】 Metastatic colonization of liver　Hepatocyte　Liver sinusoidal endothelial cells　Hepatic stellate cells　Kupffer cells

肿瘤转移是个多步骤的复杂过程，一部分肿瘤细胞离开原发部位，内渗进入血管，成为循环肿瘤细胞(circulating tumor cells, CTCs)随血液远行，从血管外渗到远处器官，最终在靶器官定植。肝脏因其丰富的血流，是胃肠道恶性肿瘤〔如结直肠癌(colorectal cancer, CRC)、胃癌(gastric cancer, GC)和胰腺癌〕、葡萄膜黑色素瘤(uveal melanoma, UM)，以及乳腺癌等肿瘤发生转移的主要部位[1]。肝转移是导致肿瘤患者死亡的主要原因。大部分肿瘤细胞进入血液后，由于机械剪切力的胁迫和免疫细胞的攻击以及缺乏营养等因素发生死亡，只有极少数的肿瘤细胞能够存活并在肝脏形成转移灶[2]。

“种子和土壤”假说形象地描述了肿瘤细胞与靶器官之间的联系，肿瘤转移的形成是作为“种子”的肿瘤细胞和为之提供适合生存“土壤”的微环境之间相互作用的综合结果[3-4]。肿瘤细胞与肝脏中的肝细胞、肝血窦内皮细胞(liver sinusoidal endothelial cell, LSEC)、肝星状细胞(hepatic stellate cell, HSC)、枯否细胞(Kupffer cell, KC)相互影响，共同调控肝脏微环境，重塑肿瘤细胞侵袭、黏附、渗出，血管新生等过程[5]。肿瘤细胞与肝微环境之间的交互作用可能涉及诸如肿瘤细胞分泌的外泌体、细胞因子与肝脏微环境细胞的黏附等因素，引起肿瘤细胞的增殖、运动能力和肝脏微环境的应答包括炎症反应的激活、免疫耐受等特性的改变。阐明肿瘤肝转移过程中的分子机制将有助于发现靶向干预的策略。本文将探讨肝脏微环境中四种固有细胞成分在肿瘤肝转移中的作用及其意义。

1 LSEC

LSEC是肝脏内最早接触肿瘤细胞的肝脏固有细胞。当LSEC激活后，其分泌的肿瘤坏死因子(tumor

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necrosis factor, TNF)、一氧化氮和活性氧等可通过Fas-FasL途径诱导细胞死亡，LSEC 是阻挡肿瘤细胞入侵肝脏的屏障。随着肿瘤细胞持续的输入，LSEC 的作用转变为促进肿瘤细胞在肝脏定植。LSEC促进肿瘤发生肝转移的机制主要包括黏附[6]、血管生成[7]、免疫调节[8]等。LSEC与CRC 细胞之间形成黏着斑，增加两者之间的黏附，一方面促使CRC细胞表达c-Met获得更强的侵袭能力[9]，增强肿瘤细胞跨内皮迁移的能力和逃避常驻KC和NK细胞的细胞毒作用；另一方面促使肝脏内皮纤连蛋白沉积[10]，共同促进CRC细胞发生肝转移。 LSEC能促进肿瘤诱导血管生成，侵入窦周隙的CRC细胞与LSEC形成连续的转移内血管，形成肿瘤-肝界面处与窦状内皮细胞共生生长，被称为组织学上的“替代”或“窦状”生长模式[11]。肿瘤细胞分泌的白细胞介素(interleukin, IL)-23 被LSEC摄取使之分泌TNF-α，进一步引起LSEC纤丝状肌动蛋白(F-actin)聚合和基质金属蛋白酶(matrix metalloproteinase, MMP)9的水平增加，促使LSEC形成细胞间隙连接，肿瘤细胞通过间隙连接在肝脏浸润生长，从而促进肝转移[12]。UM细胞分泌的血管内皮细胞生长因子(vascular endothelial growth factor, VEGF)-C刺激内皮细胞形成血管新生，促进UM细胞在肝脏形成转移结节[13]。此外，LSEC对肝脏微环境的免疫抑制作用也是促进肿瘤肝转移的一个重要方面，LSEC可诱导调节性T细胞在肝内形成免疫抑制的微环境[14]。通过外源性的干预方式能调节肝脏内的免疫微环境从而影响肿瘤细胞在肝脏定植。例如，经静脉注射装载了蜂毒肽的纳米颗粒，被LSEC摄取，促进LSEC表达 CD80、CD86和MHC-Ⅱ，并释放细胞因子IL-1α、IL-18、CXCL9、CXCL10等，招募$CD4^+$ T细胞、$CD8^+$ T细胞和细胞毒性T淋巴细胞至肝脏共同抑制肿瘤细胞(图1)。蜂毒肽纳米颗粒能激活LSEC，调动肝内免疫微环境，从而抑制肿瘤肝转移[15]。LSEC还可以通过其他机制促进转移[16]，例如，LSEC细胞被肿瘤细胞劫持，成为肿瘤细胞和$FAP\alpha^+$ HSC之间的桥梁，强化HSC旁分泌FGF2/FGFR1/ERK-1/-2/EGR1通路，促使肿瘤细胞发生上皮间充质转化(epithelial-mesenchymal transition, EMT)[17]。因此，LSEC未能防止肿瘤细胞渗出，而是通过多种方式积极参与转移过程。

2 KC

KC约占所有肝内细胞10%，是肝脏内长期驻留型巨噬细胞，主要存在于肝窦[18]。KC可能对肿瘤肝转移有双重的作用，肿瘤细胞到达肝脏的24 h内，KC能吞噬肿瘤细胞，激活的KC能通过释放细胞因子和趋化因子活化自然杀伤细胞和中性粒细胞，杀伤肿瘤细胞。随着时间的推移和肿瘤细胞的增加，KC可分泌肝细胞生长因子、VEGF和MMP等细胞因子促进肿瘤细胞的增殖和血管生成以及加速肿瘤细胞入侵肝实质，KC的功能转变为促进肿瘤的作用[19-21]。尽管如此，肿瘤细胞在到达肝脏前已通过外

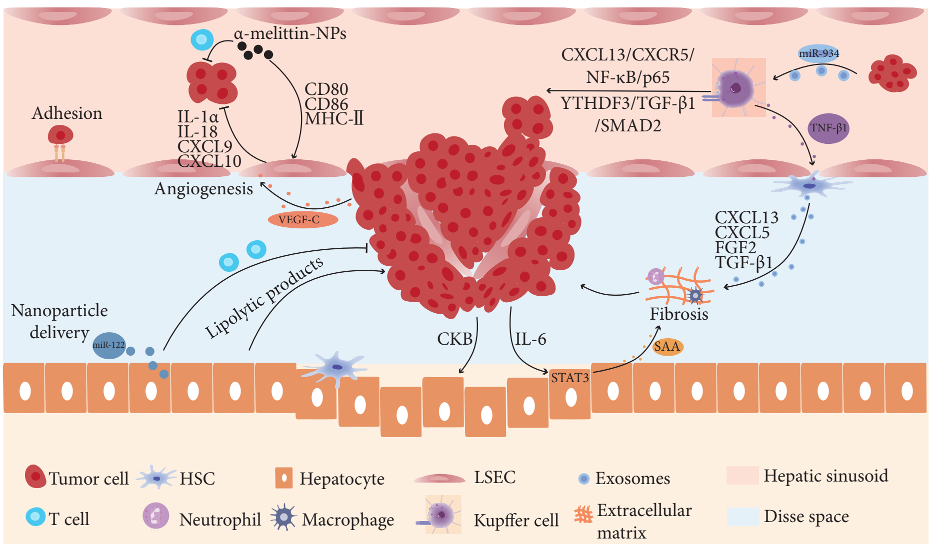

图 1 肝固有细胞对肿瘤细胞肝定植转移的作用

Fig 1 The contribution of liver-resident cells to the metastatic colonization of tumor cells in liver

IL: interleukin; CXCL: C-X-C motif chemokine ligand; CXCR: C-X-C motif chemokine receptor; CD: cluster of differentiation; MHC: major histocompatibility complex; CKB: creatine kinase, brain-type; SAA: serum amyloid A; FGF: fibroblast growth factor; TGF: transforming growth factor; NF-κB: noncanonical nuclear factor-kappa B; VEGF-C: vascular endothelial growth factor C; HSC: hepatic stellate cell; LSEC: liver sinusoidal endothelial cells; YTHDF3: YTH N6-methyladenosine RNA binding protein F3; SMAD2: mothers against decapentaplegic homolog 2; STAT3: signal transducer and activator of transcription 3; TNF: tumor necrosis factor.

泌体构建转移前微环境(pre-metastasis niche)。胰腺癌细胞来源的外泌体特异性地被KC摄取,外泌体携带的迁移抑制因子(migration inhibitory factor, MIF)促使KC释放TGF-β, TGF-β激活HSC而使之产生纤连蛋白,纤连蛋白沉积使得骨髓来源的巨噬细胞和中性粒细胞被招募而聚集于肝脏,从而形成转移前微环境[22-23]。在肿瘤细胞定植后生长阶段,KC还通过血管紧张素Ⅱ受体(angiotensin Ⅱ subtype 1a receptor, AT1a)分泌TGF-β1,促进肝脏胶原沉积,从而促进肝脏转移灶的形成[24]。KC还参与调控肝脏转移灶免疫微环境(图1),例如在CRC,外泌体携带的miR-135a-5p被KC吞噬,通过LATS2-YAP-MMP7轴介导细胞黏附和CD30-TRAF2-NF-κB介导免疫抑制信号[25];外泌体来源的miR-934诱导巨噬细胞发生M2极化,并显著增加KC分泌细胞因子CXCL13,通过CXCL13-CXCR5-NF-κB/p65正反馈环路增强肿瘤细胞的侵袭能力,从而促进CRC肝转移[26]。KC还能影响肿瘤细胞的特性,例如,KC摄取胃癌细胞衍生的外泌体,所含的miR-151a-3p通过N6-甲基腺苷(m^6A)阅读器YTHDF3 以 m^6A依赖的方式减少类泛素蛋白修饰分子SUMO1的翻译,使得转录因子SP3发生SUMO化修饰的水平降低,减少了SP3的转录抑制活性从而促进KC的TGF-β1信号转导,激活SMAD2/3途径,增强胃癌细胞的干细胞样特性来促进胃癌肝转移[27]。然而,CRC细胞外泌体携带的血管生成素样蛋白(angiopoietin-like protein 1, ANGPTL1)被KC摄取后,通过抑制JAK2-STAT3通路下调抑制KC分泌MMP9,阻止肝脏血管外渗,而抑制肝转移[28]。综上所述,KC调控肿瘤转移的过程受肿瘤细胞所处阶段、KC的M1/M2极化状态、是否发生免疫抑制有关,KC可发挥多种甚至相反的作用影响肿瘤转移,而KC对促进肝转移作用很大程度上取决于其摄取的外泌体所携带的内容物,通过调控外泌体装载的内容物或可用于治疗肿瘤[29-31]。

3　HSC

HSC约占非实质肝细胞的15%,位于窦周隙的HSC通常处于静止状态,合成少量的可溶性胶原纤维而利于维持肝脏结构[32]。KC摄取胰腺癌外泌体后分泌TGF-β, TGF-β进一步激活HSC,活化的HSC(activated HSC, aHSC)可以触发类似炎症刺激和肝脏损伤修复的过程,合成纤连蛋白等细胞外基质促进纤维化,生成镜下可见纤维素网格[33-34]。这种纤维素网格易于阻隔血液循环中的髓性细胞、免疫细胞,因此可认为是转移前微环境的一个组成部分,为肿瘤细胞的定植准备适宜的环境(图1)。此外, HSC活化后分泌的趋化因子CXCL5通过CXCR2促进肿瘤细胞分泌外泌体,携带核仁蛋白HSPC111,改变肿瘤相关成纤维细胞(cancer-associated fibroblasts, CAF)脂质代谢,上调乙酰辅酶A的水平,乙酰辅酶A进一步促进CXCL5上调,与肿瘤细胞之间形成正反馈环路[35],促进肿瘤细胞肝定植转移。在CRC, aHSC分泌趋化因子CCL20,通过CCL20/CCR6/ERK1/2/Elk-1/miR-181a-5p正反馈环路促进肿瘤细胞定植后增殖[36]。笔者课题组发现aHSC分泌Ⅰ型胶原(collagen Ⅰ),Ⅰ型胶原可激活UM上的盘状结构受体1(discoidin domain receptor 1, DDR1),从而上调STAT3依赖的SOX2表达而增强肿瘤干细胞干性,促进UM细胞肝定植转移,用小分子化合物抑制DDR1活性或者沉默DDR1的表达阻断aHSC产生的胶原可显著抑制肝转移[37-38]。综上所述,肿瘤细胞分泌的外泌体和(或)细胞因子直接或间接激活HSC,导致纤连蛋白在细胞外基质沉积,促进肿瘤细胞黏附和转移定植,抑制HSC活化能减少肝脏微环境纤维和胶原堆积,从HSC的角度理解肝转移分子机制并发现潜在的干预策略。

4　肝细胞

肝细胞占肝脏细胞总数的60%,肝质量的80%,是肝脏中数量最多的实质细胞[39]。肝细胞含有大量的线粒体和内质网,产生白蛋白、凝血因子等血浆蛋白和其他化学物质[40]。肝细胞是肝脏代谢的主要场所[41]。肝细胞脂类代谢发生异常,可促进乳腺癌和黑色素瘤发生肝转移[42],其机制涉及肿瘤细胞诱导邻近的肝细胞的三酰甘油发生脂解作用,脂解产物经脂肪酸转运蛋白1进入肿瘤细胞经由线粒体氧化代谢过程促进肿瘤细胞生长。此外,转移至肝脏的CRC细胞处于缺氧的环境释放肌酸激酶B(CKB),CKB在微环境中的ATP的作用下催化肌酸形成磷酸肌酸,磷酸肌酸经SLC6A8转运子被CRC细胞摄取,以反馈性支持CRC细胞在肝脏缺氧环境下的能量需求,从而促进CRC细胞生存[43]。肿瘤微环境来源的细胞因子也是调控肝脏微环境的重要因素。在*IL*-6敲除小鼠原位接种胰腺癌细胞,发现肿瘤微环境来源的IL-6 激活肝细胞STAT3信号通路(图1),促使肝细胞释放血浆淀粉样蛋白A1和A2,招募髓系细胞在肝内停留,并激活HSC促使肝脏微环境纤维化,形成促进肿瘤转移的微环境,进而促进转移定植和生长[44]。肝细胞内信号通路的紊乱也是影响肿瘤肝转移的因素,肿瘤细胞周围的肝细胞内Hippo通路失活,促进黑色素瘤细胞在肝内的转移灶生长[45]。来自肝微环境的肝细胞生长因子(hepatocyte growth factor, HGF)通过激活CRC细胞c-Met/PI3K/AKT/mTOR信号通路诱导胆固醇生物合成,促进CRC在肝脏定植转

移[46]。肝脏的炎症微环境改变能促进肿瘤肝转移，如，中性粒细胞受到细胞因子刺激，释放富含DNA和颗粒蛋白的中性粒细胞胞外诱捕网（neutrophil extracellular traps，NETs），其所含的DNA与肿瘤细胞的跨膜蛋白CCDC25特异性结合，激活ILK-β-parvin-RAC1-CDC42信号通路从而增强肿瘤细胞运动能力，促进乳腺癌和CRC等肿瘤细胞转移至肝脏[47]。 基于对肝转移分子机制的认识，研究者尝试利用肝细胞建立靶向治疗的策略。SENDI等[48]利用半乳糖靶向脂质磷酸钙（galactose-targeted lipid calcium phosphate，Gal-LCP）纳米制剂递送miR-122至肝细胞，抑制肿瘤转移相关的关键基因，提高CRC肝转移灶内$CD8^+/CD4^+$ T细胞而减少免疫抑制细胞的浸润，从而抑制肝转移。通过腺病毒特异性在肝细胞表达糖基化磷脂酰肌醇锚定膜蛋白（Meflin），可抑制肝脏纤维化微环境，从而改善CRC肝转移模型小鼠的生存[49]。

总的来说，肿瘤细胞和肝脏内的实质细胞、非实质细胞以及招募的免疫细胞和炎症细胞发生复杂的相互作用（表1），这些细胞成分、分泌的细胞因子以及细胞外基质

表 1 肝微环境细胞、肿瘤细胞与定植肝转移的关键分子及其可能机制

Table 1 Hepatic cell components, key molecules, and the putative mechanisms involved in liver metastasis

Cellular component in liver	Tumor	Key molecules	Mechanisms	References
LSEC	CRC	FAPα; FGFBP1	Tumor cell–derived FGFBP1 induces FAPα expression by enhancing the paracrine FGF2/FGFR1/ERK1/-2/EGR1 signaling pathway in HSC. FAPα promotes CXCL5 secretion in HSC, which activates CXCR2 to promote the EMT of tumor cells and the recruitment of myeloid-derived suppressor cells.	[17]
LSEC	HCC	IL-23	Cancer cells induce LSEC intracellular gap formation via proinflammatory paracrine of TNF-α. TNF-α triggered depolymerization of F-actin and induce MMP9, ICAM1, and CXCL expression in LSEC.	[12]
KC	PDAC	MIF	Uptake of PDAC-derived exosomes containing MIF by Kupffer cells causes fibrotic microenvironment via upregulation of TGF-β secretion and fibronectin production by HSC, enhancing the recruitment of bone marrow-derived macrophages.	[22]
KC	CRC	Angiotensin Ⅱ	Angiotensin Ⅱ-AT1a signaling enhances TGF-β1 expression in Kupffer cells. The formation of liver metastasis is correlated with collagen deposition in the metastatic area, which is dependent on AT1a signaling.	[24]
KC	CRC	MiR-135a-5p	KCs phagocytose exosomes containing highly expressed miR-135a-5p from the blood circulation into the liver. Exosomal miR-135a-5p initiates the LATS2-YAP-MMP7 axis to promote the occurrence of CRC liver metastasis.	[25]
KC	GC	MiR-151a-3p	MiR-151a-3p carried by sEVs targets YTHDF3 to decrease the transcriptional inhibitory activity of SP3 by reducing SUMO1 translation in a m6A-dependent manner, contributing to TGF-β1 transactivation in KC. TGF-β1 subsequently activates the SMAD2/3 pathway and enhances the stem cell-like properties of incoming GC cells.	[27]
KC	CRC	ANGPTL1	Exosomal ANGPTL1 attenuates CRC liver metastasis and impedes vascular leakiness by downregulating MMP9 level in KC through inhibiting the JAK2-STAT3 signaling pathway.	[28]
HSC	CRC	HSPC111	Exosomal HSPC111 alteres lipid metabolism of CAFs by phosphorylating ATP-citrate lyase (ACLY), which upregulates the level of acetyl-CoA. The accumulation of acetyl-CoA further promotes CXCL5 expression and secretion by increasing H3K27 acetylation in CAFs. Moreover, CXCL5-CXCR2 axis reinforces exosomal HSPC111 excretion from CRC cells and promotes liver metastasis.	[35]
HSC	CRC	MiR-181a-5p	FUS mediates packaging of miR-181a-5p into CRC EVs, which in-turn persistently activates HSC by targeting SOCS3 and activating the IL6/STAT3 signaling pathway. Activated HSC can secrete the chemokine CCL20 and further activate a CCL20/CCR6/ERK1/2/Elk-1/miR-181a-5p positive feedback loop, resulting in the reprogramming of the TME and the formation of pre-metastatic niches in CRLM.	[36]
HSC	UM	TGF-β1	UM cells secrete TGF-β1 which induces quiescent HSC into aHSCs which secretes collagen type Ⅰ. Such a remodeling of extracellular matrix, in turn, activates DDR1, strengthening survival through upregulating STAT3-dependent Mcl-1 expression, enhancing stemness via upregulating STAT3-dependent SOX2, and promoting clonogenicity in cancer cells.	[37]
Hepatocyte	PDAC	IL-6	Depending on the release of IL-6 into the circulation by non-malignant cells, hepatocytes coordinate myeloid cell accumulation and fibrosis within the liver by activating STAT3 signaling and production of SAA, leading to increased susceptibility of the liver to metastatic seeding and outgrowth.	[44]
Hepatocyte	CRC	MiR-122; MMPs	Delivery of nano-formulation miR-122 into hepatocytes is associated with 1) an increased $CD8^+/CD4^+$ T-cell ratio and decreased infiltration of MDSCs; 2) downregulation of key genes involved in metastatic and cancer inflammation pathways, including several proinflammatory factors, matrix metalloproteinases, and other extracellular matrix degradation enzymes.	[48]
Hepatocyte	CRC	GREM1; ISLR	Stromal GREM1 inhibits BMP signaling, while ISLR acts in the opposite way. A GREM1-neutralizing antibody or fibroblast Islr overexpression reduces CRC tumoroid growth and promotes Lgr5+ intestinal stem cell differentiation. AAV8-mediated delivery of Islr to hepatocytes increases BMP signaling and improves survival.	[49]

LSEC: liver sinusoidal endothelial cell; CRC: colorectal cancer; FAPα: fibroblast activation protein alpha; FGFBP1: fibroblast growth factor binding protein 1; FGF: fibroblast growth factor; FGFR: fibroblast growth factor receptor; ERK: extracellular signal-regulated kinase; EGR: early growth response; EMT: epithelial-mesenchymal transition; HCC: hepatocellular carcinoma; IL: interleukin; TNF: tumor necrosis factor; NF-κB: noncanonical nuclear factor-kappa B; MMP: matrix metalloproteinase; ICAM: intracellular adhesion molecule; KC: Kupffer cell; MIF: migration inhibitory factor; TGF: transforming growth facto; HSC: hepatic stellate cell; AT1a: angiotensin Ⅱ subtype receptor 1a; LATS: large tumor suppressor; YAP: yes-associated protein; TRAF: TNF receptor-associated factors; GC: gastric cancer; sEVs: small extracellular vesicles; SUMO: small ubiquitin-related modifier; ANGPTL1: angiopoietin like 1; JAK: Janus kinase; HSPC111: hypothetical protein HSPC111; ACLY: ATP-citrate lyase; CXCL: C-X-C motif chemokine ligand; CXCR: C-X-C motif chemokine receptor; FUS: fused in Sarcoma; SOCS: suppressor of cytokine signaling; CCL: C-C motif chemokine ligand; CCR: C-C motif chemokine receptor; ERK: extracellular regulated MAP kinase; Elk-1: ETS transcription factor ELK1; TME: tumour microenvironment; CRLM: liver metastasis of colorectal cancer; UM: uveal melanoma; DDR1: discoidin domain receptor tyrosine kinase 1; SOX2: sex-determining region Y-box 2; PDAC: pancreatic ductal adenocarcinoma; SAA: serum amyloid A; CD: cluster of differentiation; MDSCs: myeloid-derived suppressor cells; GREM1: gremlin 1; ISLR: immunoglobulin superfamily containing leucine rich repeat; BMP: bone morphogenetic protein; Lgr5: leucine rich repeat containing G protein coupled receptor; AAV8: adeno-associated virus 8; YTHDF3: YTH N6-methyladenosine RNA binding protein F3; SMAD2: mothers against decapentaplegic homolog 2; STAT3: signal transducer and activator of transcription 3.

等非细胞成分形成了独特的肝脏微环境。肝脏固有细胞以各自的特点形成对肿瘤细胞肝定植转移多角度和多维度的调控,深度认识这些调控作用也许能为阻断肿瘤发生肝转移提供新思路。

因体外培养条件的单一性、机体环境的系统性和复杂性,上述提及的部分研究尽管受限于细胞水平或小鼠模型,与肿瘤在人体肝脏定植的复杂分子机制还存在差距,但深化了人们对肿瘤肝定植转移的分子机制的认识。加强基础研究与临床转化研究的联系,通过多学科的交叉研究,推动基础研究的成果应用于临床,有望发现有效的靶向干预措施,阻断肿瘤发生肝转移,最终使患者受益。

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利益冲突　所有作者均声明不存在利益冲突

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