柳素玲，复旦大学生物医学研究院和肿瘤医院双聘、二级教授，博士研究生导师。中组部海外高层次人才引进计划青年项目获得者；国家“优秀青年”科学基金获得者；科技部中青年科技创新领军人才计划获得者，国家万人计划获得者。分别于中国科学技术大学生物系获得学士学位，美国俄亥俄州立大学获得博士学位；随后加入美国密歇根大学癌症研究中心从事博士后研究工作，接着被聘为研究助理教授。2005—2008年获美国苏珊–库门癌症基金会博士后奖，2006年获美国癌症协会默克学者奖，2010年获美国癌症协会苏珊–库门学者奖，2014年获USCACA-NFCR学术奖，2018年获得中国肿瘤青年科学家奖，2019年获上海市医学领军人才称号，2020年入选复旦大学“卓越2025”-卓识人才计划，2020年获上海市科技创新行动计划优秀学术带头人称号，2020年获药明康德生命化学研究奖，2020年获上海市领军人才称号。课题组长期从事乳腺癌干细胞异质性调控分子机制和精准靶向研究。近5年来，作为通讯作者在*Nature Cell Biology*、*Advanced Science*、*Nature Communications*、*Science Advances*、*Cancer Research*、*Clinical Cancer Research*、*Molecular Cancer*等国际杂志上共发表论文27篇。累计发表SCI论文81篇，论文总他引超过18 000次。共获得国际专利五项，申请中国专利五项(两项已获批)。

脂肪间充质干细胞对乳腺癌进展的影响

董浩楠　柳素玲*

(复旦大学附属肿瘤医院肿瘤研究所&生物医学研究院，上海医学院，上海市乳腺肿瘤重点实验室，上海 200032)

摘要　肥胖会导致包括癌症在内的多种恶性疾病。流行病学研究表明，过度肥胖会增加患乳腺癌的风险，并使患者的预后恶化。肥胖患者脂肪组织功能障碍的特点是白色脂肪细胞的肥大和增生。脂肪间充质干细胞是从白色脂肪组织中分离出来的一种间充质干细胞，具有很强的增殖和分化能力。脂肪间充质干细胞作为乳腺癌潜在的肿瘤启动子，通过激活多种细胞内信号促进肿瘤进展和侵袭。然而，关于脂肪间充质干细胞与乳腺癌细胞相互作用的报道并不一致，其可能的分子机制还有待进一步探讨。该综述将重点总结近年来脂肪间充质干细胞影响乳腺癌进展的相关研究，以期为乳腺癌的治疗提供新的策略。

关键词　脂肪间充质干细胞; 乳腺癌; 肿瘤微环境

The Effects of Adipose-Derived Mesenchymal Stem Cells on Breast Cancer Progression

DONG Haonan, LIU Suling*

(*Fudan University Shanghai Cancer Center and Institutes of Biomedical Sciences, Shanghai Medical College, Key Laboratory of Breast Cancer in Shanghai, Shanghai 200032, China*)

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*通讯作者。Tel: 15256086161, E-mail: suling@fudan.edu.cn

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*Corresponding author. Tel: +86-1526086161, E-mail: suling@fudan.edu.cn

Abstract Obesity can cause a variety of malignant diseases including cancer. Epidemiology shows that excessive obesity will increase the risk of breast cancer and worsen the prognosis. Adipose tissue dysfunction in obese patients is characterized by hypertrophy and hyperplasia of white adipose cells. Adipose-derived mesenchymal stem cells are a kind of mesenchymal stem cells isolated from white adipose tissue, which have strong proliferation and differentiation abilities. As a potential tumor promoter of breast cancer cells, adipose-derived mesenchymal stem cells support tumor progression and invasion by activating multiple intracellular signals. However, there are conflicting reports on the interaction between adipose-derived mesenchymal stem cells and breast cancer cells, and the possible molecular mechanisms remain to be further explored. This review will focus on recent studies on the effects of adipose-mesenchymal stem cells on breast cancer progression, with the aim of providing novel strategies for breast cancer therapy.

Keywords adipose-derived mesenchymal stem cells; breast cancer; tumor microenvironment

在过去的20年里, 肥胖已经成为一个全球性的健康问题, 它可以导致多种恶性疾病, 如乳腺癌。流行病学研究表明, 肥胖可严重影响乳腺癌的患病风险、预后和进展[1-2]。脂肪间充质干细胞(adipose-derived mesenchymal stem cells, ADSCs)是一种从脂肪组织中分离出来的间充质干细胞, 具有较强的增殖能力和定向分化潜能[3]。归巢能力使ADSCs聚集在肿瘤区域, 参与肿瘤微环境的形成[4]。ADSCs作为乳腺癌的肿瘤启动子, 通过复杂的信号交换影响乳腺癌的发生与进展, 其中涉及细胞增殖、侵袭、迁移和上皮–间质转化等生物学过程。最近的研究发现, ADSCs也可以通过分泌相关的脂肪因子来增强乳腺癌的干性, 尽管关于ADSCs外泌体的研究展现出矛盾的结果[5-6]。本文将从ADSCs的生物学特性出发, 重点回顾近年来有关ADSCs影响乳腺癌进展的具体机制的报道。

1 ADSCs的生物学特性

间充质干细胞(mesenchymal stem cells, MSCs)最初是从骨髓中分离出来的, 后来在包括脂肪在内的各种组织中被发现[7]。MSCs具有很强的增殖能力和定向分化潜能, 并能通过归巢到炎症或损伤部位, 促进组织修复、组织再生和血管生成[7]。与骨髓间充质干细胞相比, ADSCs的来源更丰富, 具有寿命更长、增殖能力更强的特点[7]。ADSCs最初是由ZUK等[8-9]从白色脂肪组织中分离出来的, 并被发现可以分化为多种间充质细胞, 包括脂肪细胞、成骨细胞和成软骨细胞等, 因而ADSCs在再生医学领域中备受关注。

1.1 ADSCs的分离与定义

血管基质组分(stromal vascular fraction, SVF)是通过密度梯度离心法获得的脂肪组织内所含细胞的异质性集合, 包括四个细胞亚群: 内皮祖细胞(endothelial progenitor cells, EPCs, $CD31^+CD34^+CD45^-$)、成熟内皮细胞(endothelial cells, ECs, $CD31^+CD34^-CD45^-$)、周细胞($CD31^-CD34^-CD45^-CD146^+$)、动脉外膜外脂肪基质细胞($CD31^-CD34^+CD45^-$)[10-11]。其中, 周细胞亚群所占比例(不到1%)最小, 通常认为周细胞是ADSCs的前体细胞[12]。周细胞和ADSCs均因其成脂分化潜能而被认为是理想的脂肪组织的重建细胞系[10-11]。国际脂肪治疗与科学联合会(International Federation for Adipose Therapeutics and Science, IFATS)和国际细胞治疗学会(International Society for Cellular Therapy, ISCT)将ADSCs定义为$CD34^+$ SVF亚群[13]。然而, 在脂肪移植后, $CD34^+$细胞的比例在不同患者之间表现出差异, 这与脂肪移植物保留的程度有关[13]。

1.2 ADSCs的表面标志物

ADSCs的表面标记物因来源部位的差异而不同, 但普遍认为间充质表面标记物, 如CD29、CD44和CD37均为阳性, 而造血和内皮标志物, 如CD31和CD45为阴性[14]。此外, 对CD34在ADSCs中的表达存在不同的报道。CD34是一种高度糖基化的糖蛋白, 选择性地表达在一些造血干细胞与祖细胞的表面, 参与多种生物学过程, 包括干细胞增殖、炎症因子分泌、细胞间黏附与肿瘤转移等[15-18]。TRIVANOVIĆ等[14]从正常的乳腺组织与肿瘤区域的脂肪组织中分离出ADSCs, 发现前者CD34为阳性, 而后者CD34为阴性。相反, YANG等[19]的分析证明CD34在正常乳腺脂肪组织的ADSCs中表达很少。CD34表达的差异可能归因于ADSCs在不同环

境中处于不同的分化状态, CD34在ADSCs及以正常乳腺组织和乳腺癌组织中的作用都有待进一步被阐明。

2 ADSCs参与肿瘤微环境的形成与重塑

作为MSCs的成员, ADSCs具有归巢能力, 即可以向损伤细胞或肿瘤细胞迁移与聚集, 从而参与炎症或肿瘤微环境的形成[20-21]。KIDD等[22]发现在乳腺癌中, 脂肪和骨髓来源的间充质干细胞均可被诱导至肿瘤微环境中。除ADSCs外, 肿瘤微环境还包括肿瘤细胞及其周围的正常组织, 以及免疫细胞、癌症相关成纤维细胞(cancer-associated fibroblasts, CAFs)、内皮细胞、细胞外基质(extracellular matrix, ECM)和各种分泌因子[23]。微环境中不同细胞之间复杂的相互作用对肿瘤进展至关重要, 因此了解ADSCs在肿瘤微环境中的具体作用将有助于理解ADSCs对乳腺癌进展的影响。

肿瘤微环境中肿瘤细胞与基质细胞、内皮细胞、免疫细胞之间的作用均可为肿瘤的恶性生长提供有利条件。炎症或肿瘤微环境中的ADSCs能够分泌或表达PDGF、VEGF、c-Kit等生长因子及其受体, 诱导内皮细胞增殖, 促进肿瘤血管网络的形成, 从而支持肿瘤细胞的恶性增殖[24-26]。此外, ADSCs可通过细胞因子和趋化因子的信号调节免疫细胞的功能。例如, ADSCs可通过旁分泌将脂肪驻留巨噬细胞的表型从促炎型M1重塑为抗炎型M2[27], 其中巨噬细胞M1与M2表型的转换对维持乳腺癌干细胞(breast cancer stem cell, BCSC)干性等必不可少[23]。BAHRAMI等[28]发现, 乳腺癌微环境中的ADSCs能够影响自然杀伤(natural killer, NK)细胞中激活性受体与抑制性受体的表达, 调节NK细胞的肿瘤免疫抑制作用。FAKHIMI等[29]证实ADSCs能够诱导效应T细胞中Helios、CD73与CD39的表达, 赋予T细胞免疫抑制的表型, 从而有利于乳腺肿瘤的生长。因此, ADSCs可以塑造肿瘤的免疫微环境并为肿瘤的免疫逃逸提供可能。

细胞外基质是肿瘤微环境中重要的非细胞组分, 包括纤连蛋白、层黏连蛋白、透明质酸等基质蛋白或多糖, 在肿瘤侵袭与转移中具有重要的作用[30]。作为一种动态的细胞外结构, ECM的降解和重组依赖于特定的酶, 例如基质金属蛋白酶(matrix metalloproteinases, MMPs)。已有实验表明ADSCs可表达表面标志物CD44, 以锚定部分MMP从而影响ECM的重组[4]。此外, KLOPP等[31]发现ADSCs有利于肿瘤生长、ECM沉积与新血管生成, 并可促进促结缔组织增生反应。后者可导致基底膜的破裂与ECM的重塑, 是癌细胞浸润的基质反应, 这一反应需要MMPs的活性[32]。在乳腺癌中, 骨髓间充质干细胞(bone marrow-derived mesenchymal cells, BM-MSCs)的EGF/EGFR/Akt信号轴是促进促结缔组织增生反应的一条典型途径[33]。因此, 有充足的理由相信ADSCs可通过激活促结缔组织增生反应而为乳腺癌的进展创造合适的微环境。ADSCs与肿瘤微环境中其他成分间的串扰可为乳腺癌的发生和进展提供多种有利条件, 这一方面还需要进一步探索。

3 ADSCs对乳腺癌的影响

乳腺癌是全世界女性中最常见的恶性肿瘤。流行病学研究表明, 肥胖可严重影响乳腺癌的患病风险、预后和进展[1-2]。一般而言, 肥胖与晚期的乳腺癌特征(包括更大的体积、更高的分级、远处转移和更低的总生存率)相关[34-35]。肥胖患者的脂肪组织功能障碍以白色脂肪细胞的肥大和增生为特征, 可导致游离脂肪酸、甘油三酯水平升高, 以及胰岛素抵抗等病理生理变化。此外, 扩散的脂肪组织可分泌激素、炎症因子和脂肪因子, 因而产生局部或全身效应[36-37]。

脂肪组织是人类乳腺的主要组成部分之一, 脂肪组织主要由脂肪间充质干细胞、前体细胞和成熟脂肪细胞组成[38]。如上所述, ADSCs可被刺激并归巢至乳腺肿瘤区域, 参与肿瘤微环境的形成。ADSCs可以影响乳腺癌进展中的多个过程, 包括增殖、迁移与侵袭、上皮–间质转化(epithelial-mesenchymal transition, EMT)等(表1和表2)。ADSCs作为乳腺癌的肿瘤启动子, 主要通过分泌细胞因子、生长因子等物质影响乳腺癌的表型(图1), 或通过与微环境内的其他基质细胞和免疫细胞相互作用而间接调节乳腺癌[39]。下面将从增殖、迁移与侵袭、EMT三个方面总结ADSCs对乳腺癌进展的影响。

3.1 ADSCs对乳腺癌细胞增殖的影响

关于ADSCs是否能促进乳腺癌的生长, 目前报道不太一致。KUCEROVA等[41,45]的研究表明, 除SK-BR-3细胞系外, ADSCs能促进多种乳腺癌细

表1 ADSCs在体外细胞实验中对乳腺癌细胞的影响

Table 1 The effects of ADSCs on breast cancer cells *in vitro*

年份 Year	ADSC来源 ADSC origin	ADSC表面标志物 ADSC surface biomarkers	乳腺癌细胞系 BC cell lines	对乳腺癌细胞的影响 Effects on BC cells	参考文献 Reference
2010	Human whole fat	$CD29^+CD44^+CD90^+CD105^+$ $CD14^-CD34^-CD45^-$	MCF-7; MDA-MB-231	Migration and invasion↑ ADSCs differentiate to CAFs	[40]
2011	Human lipoaspirates	$CD44^+CD73^+CD90^+CD105^+$ $CD14^-CD34^-CD45^-$	MCF-7; T-47D; MDA-MB-361	Proliferation↑	[41]
2012	Human breast	$CD29^+CD73^+CD90^+$ $CD105^+CD166^+$ $CD31^-CD144^-CD14^-$ $CD45^-HLA\text{-}DR^-$	MCF-7	Proliferation↑	[33]
2012	Human lipoaspirates	$CD29^+CD44^+CD105^+$ $CD34^-CD45^-$	MCF-7	Migration↑; angiogenesis↑	[42]
2012	Human breast	$CD13^+CD29^+CD44^+CD71^+$ $CD105^+HLA\text{-}I^+$ $CD4^-CD10^-CD14^-CD34^-$ $CD38^-HLA\text{-}DR^-$	MCF-7	Proliferation↑; migration↑	[43]
2012	Human whole fat	—	4T1 (murine); BT-474; MCF-7; T47D	Proliferation↑; EMT↑	[44]
2013	Human lipoaspirates	$CD29^+CD44^+CD90^+CD105^+$ $CD14^-CD34^-CD45^-$	SK-BR-3	Proliferation↓; migration↑ EMT↑; chemosensitivity↑	[45]
2013	Human lipoaspirates	$CD29^+CD44^+CD105^+$ $CD31^-CD34^-HLA\text{-}DR^-$	MCF-7	Proliferation↑; migration↑ (ADSC-CM)	[46]
2014	Human breast	$CD44^+CD73^+CD90^+CD105^+$ $CD11a^-CD33^-CD45^-CD235a^-$	MCF-7	Proliferation↑ (direct co-culture); proliferation↓ (indirect co-culture)	[14]
2015	Abdominal lipoaspirates	$CD73^+CD90^+CD105^+$	MCF-7; MDA-MB-231	Viability↑	[47]
2017	—	—	MDA-MB-231	Pro-angiogenic behavior↑; endothelial sprouting↑; ADSCs differentiate into myofibroblasts	[48]
2017	Human breast cancer	$CD90^+CD29^+CD105^+$ $CD31^-CD34^-CD45^-$	MDA-MB-231	Doxorubicin resistance↑ (ADSC-CM)	[49]
2017	Mouse inguinal fat	$CD90^+c\text{-}Kit^+$	4T1	Viability↑; proliferation↑	[26]
2018	Lipoaspirate	—	MCF-7; MDA-MB-231	Viability↓; migration↓ (ADSC-CM)	[50]
2019	—	—	4T1	Migration↑; invasion↑	[51]
2019	Abdominal liposuction aspirates	—	MCF-7	Tumor-sphere formation↑	[52]
2020	—	$CD90^+CD44^+CD105^+$	MCF-7; MDA-MB-231	Metastasis↓; EMT↓	[53]

ADSCs: 脂肪间充质干细胞; BC: 乳腺癌; CAF: 癌症相关成纤维细胞; EMT: 上皮–间质转化; ADSC-CM: ADSC条件培养基。

ADSCs: adipose-derived mesenchymal stem cells; BC: breast cancer; CAF: cancer-associated fibroblast; EMT: epithelial-to-mesenchymal transition; ADSC-CM: ADSC-conditioned medium.

胞系的增殖。然而, TRIVANOVIC等[14]使用从正常与乳腺肿瘤组织中获得的ADSCs制备条件培养基, 发现其能有效抑制MCF-7细胞的生长和增殖。ROWAN等[55]指出ADSCs不能促进三阴性乳腺癌细胞系MDA-MB-231的增殖, 但可以增强ER^+亚型MCF-7与BT-474细胞系的增殖能力。ADSCs对乳

表2 ADSCs在体内实验中对乳腺癌进展的影响

Table 2 The effects of ADSCs on breast cancer progression *in vivo*

年份 Year	ADSC来源 ADSC origin	ADSC表面标志物 ADSC surface biomarkers	乳腺癌细胞系 BC cell lines	对乳腺癌的影响 Effects on BC	参考文献 Reference
2012	Murine (endogenous)	$CD13^+CD29^+CD44^+$ $CD71^+CD105^+HLA\text{-}I^+$ $CD4^-CD10^-CD14^-$ $CD34^-CD38^-HLA\text{-}DR^-$	E0771; MCF-7	Circulating ADSCs↑; ADSCs incorporate into tumor vasculature	[43]
2012	Human breast	$CD29^+CD44^+CD105^+$ $CD34^-CD45^-$	HMT-3522 S3 (preinvasive); HMT-3522 T4-2 (invasive); MDA-MB-231	Tumor growth↑; tumor invasiveness↑; no effect on preinvasive BCCs	[42]
2013	Human lipoaspirates	$CD13^+CD34^+CD140b^+$ $CD31^-CD45^-$	HCC1937; MDA-MB-436; ZR75-1	Tumor growth↑; metastatic spread↑; EMT↑	[54]
2014	Human abdominal lipoaspirates	$CD29^+CD34^+CD73^+$ $CD90^+CD105^+$ $CD44^{low}CD45^{low}$	BT-474; MCF-7; MDA-MB-231	EMT↑; migration and metastasis↑	[55]
2014	Lipoaspirates; breast tissues	—	Kbr	ADSCs integrate into the tumor microenvironment↑; vascularize↑	[56]
2015	Abdominal lipoaspirates	$CD73^+CD90^+CD105^+$	MCF-7; MDA-MB-231	Tumor weight↑; metastatic occurrence↑	[47]
2016	—	—	4T1	Tumor size↓; survival rate↑ (TNF-α preactivated ADSCs with irradiation) Metastasis↓; apoptosis↑ (TNF-α preactivated ADSCs)	[57]
2017	—	$CD166^+CD73^+CD90^+$ $CD29^+CD105^+$ $CD31^-CD45^-CD34^-$ $CD11b^-HLA\text{-}DR^-$	MCF-7; ZR-75-30; MDA-MB-231	Angiogenesis↑; proliferation↑ (MCF-7; ZR-75-30)	[58]
2017	Mouse inguinal fat tissues	$CD90^+c\text{-}Kit^+$	4T1	Tumor volume↑; vessel formation↑	[26]
2019	Abdominal liposuction aspirates	—	MCF-7	Tumor tropism↑; stem-like properties↑	[52]
2020	Mouse abdominal fat	$CD29^+CD44^+CD73^+CD105^+CD106^+$ $SCA\text{-}1^+CD90^+CD45^-CD34^-$ $CD31^-CD11b^-(CD90^{high}ADSC)$; $CD29^+CD44^+CD73^+CD105^+CD106^+$ $SCA\text{-}1^+CD45^-CD34^-$ $CD31^-CD11b^-CD90^-(CD90^{low}ADSC)$	E0771	$CD90^{high}ADSCs$ could be converted into $CD90^{low}ADSCs$; tumor growth↓ ($CD90^{low}ADSC$)	[59]

ADSC: 脂肪间充质干细胞; BC: 乳腺癌; EMT: 上皮–间质转化; TNF-α: 肿瘤坏死因子-α。

ADSC: adipose-derived mesenchymal stem cell; BC: breast cancer; EMT: epithelial-to-mesenchymal transition; TNF-α: tumor necrosis factor-α.

腺癌细胞增殖影响的差异可能取决于分泌因子的性质。乳腺癌细胞增殖能力的增强主要与细胞因子、趋化因子以及潜在的脂肪因子相关。例如, ADSCs能通过分泌趋化因子CXCL1与CXCL8促进肿瘤组织中血管的生成, 以增强乳腺癌细胞的生长能力[58]。相反, 乳腺癌细胞增殖的抑制则可能与ADSCs分泌的外泌体相关, 这些外泌体包含多种miRNA, 能够抑制乳腺癌细胞中一些关键基因的表达。最近的研究表明, 从ADSCs中提取的微囊泡(microvesicels)具有抗乳腺癌的能力[60]。此外, ADSCs对乳腺癌细胞

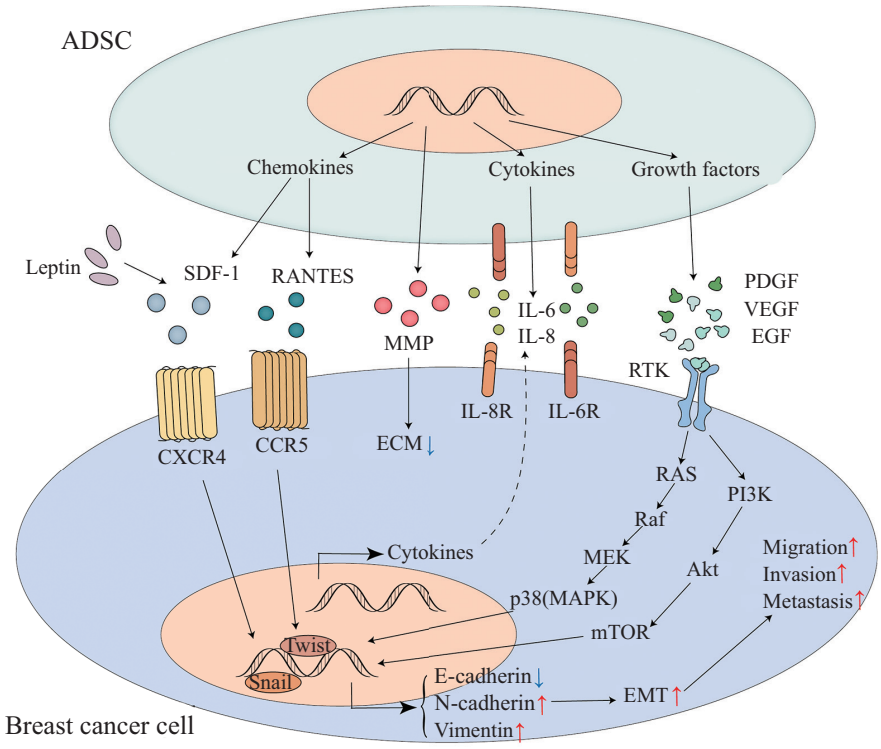

图1 ADSCs对乳腺癌细胞的EMT、迁移与侵袭的影响和调控机制

Fig.1 The effects and regulation mechanisms of ADSCs on the EMT, migration and invasion of breast cancer cells

增殖不同的效果可能也受到ADSCs自身异质性或环境特异性的影响。例如, LI等[59]根据CD90表达的差异, 将从小鼠腹部脂肪组织中分离得到的ADSCs鉴定为$CD90^{high}$ADSCs与$CD90^{low}$ADSCs, 发现$CD90^{high}$ADSCs能够向$CD90^{low}$ADSCs转化, 并且后者能够抑制乳腺癌的生长。

3.2 ADSCs对乳腺癌细胞迁移与侵袭的影响

乳腺癌细胞的迁移与侵袭是导致患者高死亡率的主要因素之一。ADSCs可通过分泌趋化因子和细胞因子以增强乳腺癌细胞的迁移与侵袭能力。CXCR4是最重要的趋化因子受体之一, 在包括肿瘤细胞的多种细胞中表达[61]。SDF-1, 又名为CXCL12, 可以与CXCR4结合并介导多种下游信号通路, 因此SDF1/CXCR4信号轴在乳腺癌的恶性进展中发挥着重要作用[61]。此前的研究表明, ADSCs可通过SDF-1依赖性途径促进体内乳腺癌细胞的增殖[62]。最近, DUAN等[63]报道瘦素(leptin)通过激活SDF-1/CXCR4信号轴促进乳腺癌的骨转移。这暗示ADSCs可能通过瘦素等脂肪因子参与激活SDF-1/CXCR4甚至促进其他趋化因子−趋化因子受体的相互作用, 从而影响乳腺癌的进展。RANTES, 或又称CCL5, 是ADSCs释放的另一种促炎趋化因子[64]。KARNOUB等[64]指出乳腺癌细胞可刺激ADSCs产生RANTES, RANTES反过来增强乳腺癌细胞的运动性, 从而有利于其侵袭与转移。此外, ADSCs可分泌一些白细胞介素例如IL-6和IL-8, 从而参与乳腺癌的侵袭与迁移[65-67]。ECM与肿瘤的迁移与侵袭密切相关, 而ADSCs可通过分泌部分MMP参与ECM的降解与重组。例如, 乳腺癌细胞可诱导ADSCs分泌MMP-11, 而MMP-11反过来促进乳腺癌细胞的迁移[68]。迁移与侵袭是肿瘤转移的必要条件, 其中乳腺癌的主要转移部位有骨、肺、肝脏与脑[69]。ADSCs是否存在于这些区域并通过塑造肿瘤转移前微环境或通过内分泌系统释放相关的因子以诱导乳腺癌的靶向转移需要更详细的探讨。

3.3 ADSCs对乳腺癌细胞上皮−间质转化的影响

EMT是乳腺癌进展中的一个必要过程, 在肿瘤细胞向更具侵袭和转移性的表型转变的过程中发挥关键的作用[70]。EMT涉及多种信号通路, 包括转化生长因子(transforming growth factor, TGF)、骨形态发生蛋白、成纤维细胞生长因子、表皮生长因子受体、肝细胞生长因子(hepatocyte growth factor, HGF)、Wnt/β-catenin和Notch信号通路[71]。在EMT的过程

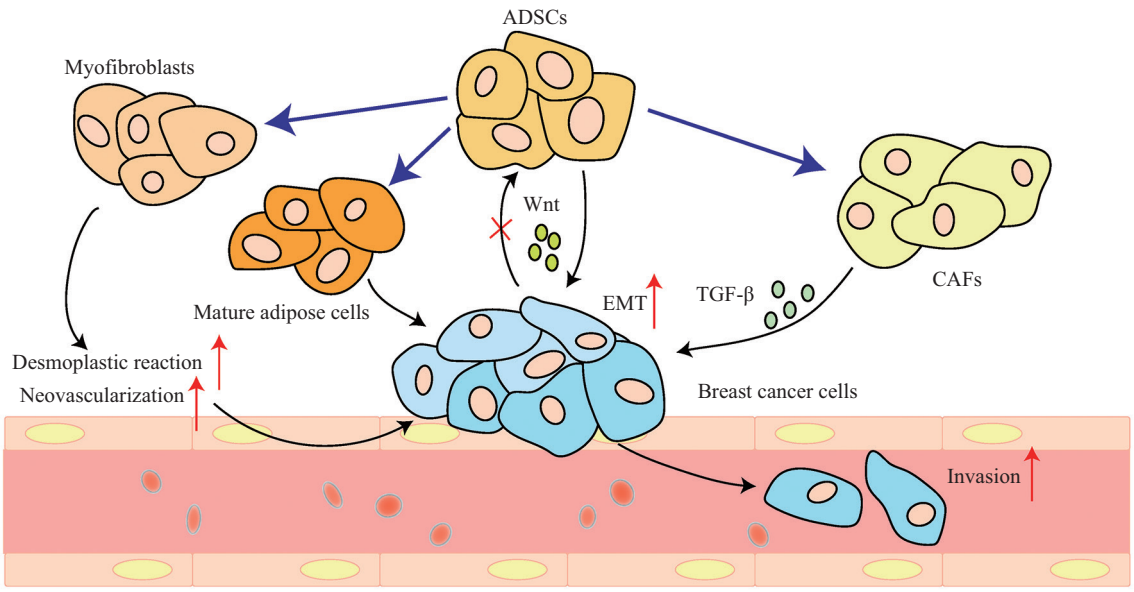

图2 ADSCs的分化对乳腺癌进展的影响

Fig.2 The impact of ADSCs differentiation on breast cancer progression

中, 癌细胞出现细胞形态和分子表达量的改变, 具体表现为上皮标志物(E-钙黏蛋白、闭锁蛋白等)的表达量减少, 间质标志物(N-钙黏蛋白、波形蛋白、纤黏连蛋白等)的表达量增加。此外, 与EMT相关的转录因子如Snail、Zeb、Twist和其他表观遗传修饰也与EMT反应相关[72]。在乳腺癌微环境中, ADSCs诱导乳腺癌细胞的EMT依赖于多种途径, 如PI3K/Akt/mTOR信号通路、p38(MAPK)信号级联[45,73-74], 或是瘦素的过度表达[75]。

ADSCs对乳腺癌细胞EMT和迁移的影响可通过Wnt信号通路介导。经典的Wnt的信号依赖于下游的转录共激活因子β-catenin的蛋白酶水解活性的周转(proteolytic turnover)。Wnt/β-catenin信号的突变常发生在癌细胞中, 该通路的持续激活赋予癌细胞自我更新和生长的能力, 并可影响肿瘤的治疗耐药性[76]。过去的研究表明, ADSCs释放的外泌体可通过Wnt信号通路诱导乳腺癌细胞的EMT和迁移[46]; 乳腺肿瘤的衍生因子可通过抑制Wnt信号的转导, 促进ADSCs转化为癌症相关成纤维细胞[50]。此外, 癌症相关成纤维细胞分泌的TGF-β可通过下游的SMAD信号诱导乳腺癌的EMT, 并能使暴露于乳腺癌胞外囊泡的ADSCs分化为肌成纤维细胞[77], 从而促进肿瘤微环境中的促结缔组织增生反应[48]。因此, ADSCs的分化潜能可以影响EMT和乳腺癌的侵袭性(图2)。近期研究表明, 表没食子儿茶素没食子酸酯(epigallocatechin gallate, EGCG; 绿茶茶多酚的一种主要成分)能在三阴性乳腺癌中抑制ADSCs向成熟脂肪细胞分化, 并抑制STAT3介导的侵袭性[78]。然而, ADSCs具有分化为多种细胞类型的能力, 通过ADSCs的定向分化调控乳腺癌进展的分子机制仍需更深入的探索。

作为间充质干细胞的成员, ADSCs可分泌干细胞因子(stem cell factor, SCF), 从而参与乳腺癌细胞的增殖、分化等过程。已有的研究表明, SCF能够结合酪氨酸激酶受体c-Kit并诱导丝裂原活化蛋白激酶(mitogen activated protein kinase, MAPK)通路的激活, 诱导磷酸化蛋白激酶移位至细胞核并刺激转录因子的活性, 从而影响细胞增殖、凋亡与分化[79]。E2F是SCF/c-Kit信号调控的下游转录因子之一, 其表达异常通常与肿瘤进展、转移以及抗肿瘤药物耐药性相关[80-81]。XU等[51]发现, ADSCs分泌的SCF通过下游的c-Kit/p38(MAPK)/E2F1信号级联减少乳腺癌细胞内miR-20b的合成。miR-20b的下调可激活其靶基因*HIF-1α*与*VEGFA*的表达, 并诱导乳腺癌细胞的EMT与转移。然而, 早期的研究表示miR-20b能通过抑制肿瘤抑制因子PTEN的表达, 在体内与体外促进乳腺癌细胞的增殖[82]。miR-20b对乳腺癌细胞影响的差异可能受微环境异质性的调控。因此, 以ADSCs作为乳腺癌细胞迁移、侵袭与转移的潜在治疗靶点还需要更全面详细的探究。

4 ADSCs对乳腺癌干细胞的影响

肿瘤干细胞(cancer stem cells, CSCs), 又称肿瘤

起始细胞, 是肿瘤组织中的小亚群, 具有自我更新、产生分化的肿瘤细胞谱系的能力[83]。由于CSCs与肿瘤转移和治疗抵抗密切相关, 因此靶向CSCs的治疗策略为完全消除癌细胞提供了可能。根据标志物的不同, 乳腺癌干细胞一般可分为两类: 间充质样BCSC($CD24^{-}CD44^{+}$)与上皮样BCSC($ALDH^{+}$)[84]。BCSC的可塑性体现在上皮与间充质状态之间的转换, 例如在转移定居时, 乳腺癌干细胞经历从间充质到上皮的转变, 这一过程依赖于EMT以及该过程的逆转[23]。因此, EMT是乳腺癌干细胞维持自我更新能力与干性的重要机制之一。

已有的实验表明, ADSCs对乳腺癌细胞干性的获得与维持具有正向的调控作用。GOTO等[5]发现, ADSCs的降脂蛋白(adipsin)能够增强乳腺癌球体的形成能力, 促进肿瘤生长, 增强BCSC的干细胞特性。经脂肪因子内脂素(visfatin)预处理并与MDA-MB-231细胞共培养的ADSCs能够增强乳腺癌细胞的增殖、转移与干性[85]。最近的研究指出, ADSCs能够与癌细胞融合形成肿瘤干细胞样细胞, 从而具有更高的致瘤性[86]。MIRANDA等[87]使用ADSCs条件培养基培养MCF-7与MDA-MB-231细胞系, 发现细胞周期蛋白B1(cyclin B1)表达水平的升高与凋亡执行蛋白caspase-7的激活。此外, 利用ADSCs条件培养基培养的乳腺癌细胞的迁移能力得到增强, 且间充质样BCSC($CD44^{+}CD24^{-/low}$)的比例增加。这些结果可能表明, ADSCs可通过增强细胞增殖, 诱导乳腺癌细胞的选择性压力, 从而在MCF-7与MDA-MB-231细胞中产生具由自我更新与侵袭性的干细胞表型。

相反的是, ADSCs分泌的外泌体可能会阻碍BCSCs干性的维持。SEO等[6]发现, 来自ADSCs条件培养基的外源性miR-503-3p对乳腺癌细胞的增殖以及BCSCs的自我更新具有抑制作用。miR-503-3p下调乳腺癌干细胞标志物的表达, 并能限制乳腺癌异种移植肿瘤的生长。此外, MOHD等[53]发现, 与MCF-7、MDA-MB-231等乳腺癌细胞系共培养的ADSCs能够分泌不同的外泌体miRNA, 它们通过抑制乳腺癌的转移与EMT来调节基本的信号通路与细胞周期使乳腺癌细胞进入休眠停滞状态。这暗示ADSCs相关的miRNA在诱导乳腺癌干性、转移与休眠等方面具有关键作用, 识别与筛选这些miRNA标记物或许有助于鉴定乳腺癌不同的转移模式、预测乳腺癌患者的复发情况。

5 ADSCs在乳腺癌治疗中的作用

5.1 ADSCs对乳腺癌化疗的影响

近年来, 研究人员在乳腺癌的诊断与治疗方面已取得较大的进展, 但乳腺癌的治疗抵抗仍然是一个不可忽视的挑战。乳腺癌对治疗的抗性主要受肿瘤微环境与自身异质性的影响[88-89]。

化疗是目前乳腺癌治疗中应用较多的方法。乳腺癌细胞的化疗耐药性的形成涉及多种生长因子或信号通路。例如, EGFR、HER2/neu、PI3K或其他生长因子信号与他莫昔芬(tamoxifen)、吉非替尼(gefitinib)等常见乳腺癌化疗药物的耐药性相关[90-91]。然而, 有关ADSCs对乳腺癌化疗耐药性的报道并不充分。部分报道指出ADSCs具有抗药性的特征, 乳腺癌细胞可通过分泌细胞因子与ADSCs相互作用, 从而使乳腺癌细胞自身获得耐药性[49,92]。相反, KUCREOVA等[45]发现, 与ADSCs共培养后的SK-BR-3细胞表现出化疗敏感性。LU等[93]发现, ADSCs能够通过C-端Src激酶(Csk)-结合蛋白(Cbp)的表达增加乳腺癌细胞系MCF-7/ADR(一种多药耐药乳腺癌细胞模型)的耐药性和细胞增殖。对ADSCs影响乳腺癌化疗耐药性的具体机制进行更全面的研究将有助于ADSCs成为乳腺癌化疗评估的标准之一。

5.2 ADSCs对乳腺癌放疗的影响

放疗是包括乳腺癌在内的多种恶性肿瘤的传统治疗方法, 其能够显著提高患者的生存率, 尽管会对周围正常组织造成损伤。与化疗耐药性相似, 乳腺癌细胞对放射具有一定的抵抗性。肥胖被认为是导致乳腺癌放疗抵抗的因素之一, 其可能依赖代谢失调与相关信号通路的改变来增强乳腺癌细胞对放射的抵抗[94]。因此, 乳腺癌微环境中的ADSCs可能通过分泌相关的生长因子以介导肥胖相关的放疗抵抗。例如, YANG等[95]的早期实验表明, ADSCs会在放射过程中被乳腺癌招募至其微环境中, 并通过IGF-1信号增强乳腺癌的放疗抵抗。最近的研究指出ADSCs分泌的脂肪因子在放疗抵抗中发挥关键的作用。SABOL等[96]发现在放射处理后, ADSCs能够增强瘦素的分泌, 促进ER^{+}亚型乳腺癌细胞中的IL-6与Notch信号通路的激活, 从而增强乳腺癌细胞的放射抵抗。此外, SABOL等[97]在之前的研究中指出, 阻断ADSCs中瘦素的表达能够抑制乳腺癌细胞的转移, 因此靶向瘦素相关信号可能成为乳腺癌转移的诊断与治疗的新选择。

5.3 ADSCs-EVs在乳腺癌治疗中的应用

细胞外囊泡(extracellular vesicles, EVs)是一种由细胞在生理或病理条件下释放的膜性细胞结构, 包含蛋白质、miRNA等多种物质, 参与肿瘤微环境中的细胞间通讯。ADSCs具有分泌EVs以及归巢至肿瘤部位的能力, 因而可通过ADSCs的定向基因改造使其具有精准的肿瘤靶向能力与较强的抗肿瘤活性。LI等[59]将具有抗肿瘤活性的miR-16-5p装载于$CD90^{low}$ADSCs-EVs中, 能减弱乳腺癌细胞的增殖与迁移, 抑制乳腺肿瘤的生长。利用ADSCs-EVs递送抗肿瘤药物或分子具有低免疫原性、靶向特异性等优点, 因此是一种极具潜力的抗肿瘤策略。但ADSCs在临床上的应用仍有很多需要克服的困难, 例如EVs在肿瘤进展中的双重功能、EVs递送药物或分子的选择、EVs类药物的剂量效应等问题, 因此需要一系列更深入的临床研究。

5.4 ADSCs与乳腺癌术后的乳房重建

自体脂肪移植是重建手术中常用的方法。ADSCs来源丰富, 且具有自我更新以及分化为特定细胞的能力, 能够改善组织的血管分布与愈合能力, 并最低限度地引发炎症反应, 因而在乳腺癌术后的乳房重建中发挥重要的作用[98]。利用ADSCs进行乳房重建的关键在于脂肪移植物的存活率, 实验表明ADSCs能够分泌多种抗凋亡因子以增强其活力[99]。然而, 乳腺癌治疗过程中的放疗与化疗对ADSCs的存活与分化功能可能具有负面影响。人工设计脂肪移植物有助于ADSCs在重建手术的广泛应用, 目前其主要挑战在于如何提高血管的生成与维持ADSCs的分化潜能。此外, 通过优化ADSCs的微环境从而促进其血管生成以提高乳腺癌放疗中脂肪移植物的存活率也是一种可行的方法。因此, 系统阐明放射和化学疗法对ADSCs的影响将改善ADSCs在乳腺癌术后的乳房重建中的应用。

6 总结与展望

ADSCs是一类具有较强增殖能力、定向分化潜能的间充质干细胞。ADSCs能够通过与微环境中的其他基质细胞、免疫细胞相互作用, 或与乳腺癌细胞直接进行信号交流, 在乳腺癌进展中发挥促进或抑制的功能。然而, ADSCs对乳腺癌细胞增殖、干性等的影响不一致的报道从侧面说明这一领域研究的局限性, 趋化因子、细胞因子、外泌体等物质共同组成的复杂调控网络需要更全面详细的探讨。此外, 有关ADSCs释放的脂肪因子如何影响乳腺癌的进展有待更多的发现。此外, ADSCs在乳腺癌的治疗中也发挥关键的作用, 探究ADSCs如何影响乳腺癌的治疗抵抗性具有重要的意义。总之, 对ADSCs影响乳腺癌进展的深入理解将有助于降低其在相关领域中的潜在应用风险。

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