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乳腺癌中脂肪组织的特异性作用

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摘要: 乳腺癌的发生和发展受周围脂肪组织微环境的深刻影响。脂肪组织不仅为乳腺癌细胞提供机械支撑, 而且由于乳腺癌细胞与脂肪细胞间紧密的解剖学接触, 使得其局部的肿瘤相关脂肪细胞数量和雌激素水平都较其他恶性实体肿瘤显著升高。本文系统综述了脂肪组织促进恶性肿瘤进展的普遍机制, 并重点阐述了其在乳腺癌微环境中的特异性作用。通过与其他肥胖相关癌症进行对比分析, 本文旨在深化对“脂肪-癌细胞”互作网络的理解, 为乳腺癌的精准治疗提供新的理论依据。

关键词: 乳腺癌; 肥胖; 脂肪组织; 肿瘤相关脂肪细胞

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The specific roles of adipose tissue in breast cancer

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Abstract: Breast cancer has surpassed lung cancer to become the most prevalent malignancy worldwide, characterized by high heterogeneity and complex pathological mechanisms. Epidemiological evidence firmly establishes obesity as a significant risk factor for breast cancer, particularly in postmenopausal women, correlating with poor prognosis and increased metastasis. Adipose tissue, far from being merely an energy storage depot, is recognized as the body's largest endocrine organ. While adipose tissue contributes to the progression of various cancers including hepatic, colorectal, and pancreatic cancers through shared mechanisms such as chronic inflammation and metabolic dysregulation, the breast presents a unique anatomical landscape where epithelial cells are deeply embedded within a fat-rich stroma. This review aims to synthesize the general mechanisms by which adipose tissue promotes tumorigenesis and, more importantly, to dissect the specific, intimate crosstalk between breast cancer cells and the surrounding adipose microenvironment, highlighting the distinct roles of cancer-associated adipocytes (CAAs) and local estrogen biosynthesis. Adipose tissue exerts a pro-tumorigenic influence across multiple cancer types through systemic low-grade chronic inflammation, insulin/IGF-1 signaling dysregulation, and altered adipokine secretion (e.g., increased leptin and decreased adiponectin). However, adipose-tumor crosstalk in breast cancer is uniquely direct and sustained. Specifically, breast cancer cells induce adjacent mature adipocytes to undergo de-differentiation into CAAs. This process, regulated by factors such as Wnt, TGF- β , and adrenomedullin (AM), transforms adipocytes into fibroblast-like cells with reduced lipid droplets and activated pro-inflammatory phenotypes. CAAs undergo metabolic reprogramming, accelerating lipolysis via ATGL and HSL activation to release free fatty acids (FFAs). These FFAs are taken up by cancer cells for β -oxidation, fueling rapid proliferation and membrane synthesis. Furthermore, CAAs secrete a myriad of cytokines (e.g., IL-6, CCL2), which not only activate STAT3 and ERK1/2 pathways to enhance tumor invasiveness but also recruit immune cells, notably promoting the polarization of macrophages towards the immunosuppressive M2 phenotype.

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A defining feature of the breast cancer-adipose nexus, particularly in ER-positive postmenopausal cases, is the profound upregulation of local estrogen synthesis. Adipose tissue serves as the primary source of estrogen via the aromatase enzyme (CYP19A1). This process is amplified by intricate positive feedback loops within the tumor microenvironment: obesity-induced inflammation elevates PGE2 and TNF- α , while tumor-derived oncostatin M (OSM) activates the JAK/STAT3 pathway in adipocytes. These signals converge to upregulate CYP19A1 expression, resulting in significantly higher level of local estrogen than circulating system, thereby driving hormone-dependent tumor growth. Current clinical translation efforts, including microphysiological systems (MPS) and 3D bioprinting, are improving our ability to model these interactions, while radiomic tools like MRI proton density fat fraction (PDFF) offer non-invasive risk assessment. Despite these advances, the causal hierarchy and dynamic regulation of the adipose-tumor dialogue remain to be fully elucidated. Future research must leverage single-cell multi-omics and spatial transcriptomics to map the heterogeneity of the tumor-adipose interface and clarify the metabolic fate of adipocyte-derived lipids. Ultimately, targeting the specific signaling axes of CAAs, such as the blockage of pro-inflammatory cytokines or the inhibition of specific metabolic enzymes, without disrupting systemic metabolic homeostasis, represents a promising frontier for developing novel, personalized therapeutic strategies for breast cancer.

Key words: breast cancer; obesity; adipose tissue; tumor-associated adipocytes

乳腺癌是全球女性中最常见的恶性肿瘤之一,具有高度的异质性和复杂的病理机制。乳腺癌已超过肺癌,成为全球最常见的癌症^[1]。尽管在化疗、内分泌治疗、靶向治疗方面取得了一定进展,但其复发和转移仍然是临床上的主要挑战。

肥胖被定义为体内脂肪的过度积累,是乳腺癌的重要危险因素之一,尤其在绝经后女性中,这种相关性更加显著^[2,3]。根据最新的全球统计调查,全球已有超过11.1亿的肥胖成年女性,并且人数还在持续增长^[4]。肥胖不仅改变全身激素水平和代谢状态,还重塑了肿瘤微环境,成为乳腺癌发生、进展和预后的关键影响因素。

脂肪组织是最大的内分泌器官之一,分别平均占成年男性和成年女性体重的26%和38%^[5]。白色脂肪组织是最丰富、最具特征的脂肪组织类型,其通过分泌多种细胞因子、激素和外泌体等,深度参与包括乳腺癌在内的多种疾病的病理过程^[6]。脂肪组织也与肝癌、结肠癌、子宫内膜癌、食管癌、卵巢癌和胰腺癌的进展有关^[7]。乳腺有着特殊的解剖与微环境基础,乳腺上皮和导管小叶直接镶嵌在脂肪组织中,故发生癌变时,乳腺肿瘤细胞与脂肪细胞是近距离、持续相互作用的,前者可以促使邻近脂肪细胞去分化并成为肿瘤相关脂肪细胞(cancer-associated adipocytes, CAAs),反过来后者分泌促炎因子和生长因子支持肿瘤生长^[8]。乳腺周围的脂肪组织非常丰富且可以大量表达芳香化酶,将雄激素转化为雌激素,使得肿瘤局部雌激素水平显著高于循环水平,尤其是绝经后且雌激素受体阳性型(ER⁺)的乳腺癌更依赖脂肪组织的内分泌功能^[9]。本文将总

结脂肪组织促进相关恶性肿瘤的共有机制,并深入探讨其在乳腺癌中的特异性作用。

1 脂肪组织对肿瘤的共同作用机制

多种癌症与肥胖或脂肪组织表现出密切关联,主要由激素分泌异常、慢性炎症和代谢紊乱等机制介导^[10]。在全球范围内,肥胖被认为是慢性代谢综合征以及乳腺癌、肝癌、结肠癌、子宫内膜癌、食管癌、卵巢癌和胰腺癌的风险因素^[11]。脂肪组织对这些不同类型癌症的共同作用机制涉及炎症因子、脂肪因子、胰岛素/胰岛素样生长因子1(insulin-like growth factor 1, IGF-1)信号、免疫调节、脂肪酸代谢重编程、血管生成和细胞外基质重塑等多个方面(表1)。

1.1 慢性炎症的诱导

脂肪组织的扩张伴随着巨噬细胞的浸润和促炎因子的释放,导致全身性低度炎症,并通过激活NF- κ B和STAT3通路促进乳腺癌、肝癌和结肠癌的发生^[12]。在慢性炎症的背景下,NF- κ B和STAT3作为重要的转录因子,分别在放大微环境炎症信号与驱动肿瘤细胞恶性演进中发挥重要作用。NF- κ B的激活诱导了TNF- α 、IL-6等核心促炎细胞因子的过表达,这些因子不仅在局部微环境中促进肿瘤细胞的增殖,还能通过血液循环影响远处组织的肿瘤发生^[13]。同样,过度激活的STAT3不仅上调细胞周期以维持细胞存活,更通过特异性结合并驱动下游正五聚蛋白3(pentraxin 3, PTX3)及基质金属蛋白酶7(matrix metalloproteinase 7, MMP7)等关键基因的转录,直接促发肿瘤侵袭边缘的基质重塑与恶

表1 脂肪组织对肿瘤共同作用机制

Table 1 Common mechanisms of adipose tissue-mediated tumorigenesis and progression

因子类别	主要信号通路	作用机制	相关肿瘤
炎症因子(IL-6、TNF-α等)	NF-κB、JAK/STAT3	引发慢性炎症,激活促增殖、促存活信号;诱导胰岛素抵抗	乳腺癌、结直肠癌、肝癌
瘦素	JAK/STAT3、MAPK/PI3K	瘦素水平上调,促进细胞增殖和转移	乳腺癌、结直肠癌、肝癌、子宫内膜癌、卵巢癌
脂联素	LKB1/AMPK	脂联素水平下降,失去抑制增殖的保护作用	乳腺癌、胰腺癌、食管癌
胰岛素/IGF-1	PI3K/AKT、MAPK/ERK	高胰岛素/IGF-1激活下游通路,促进增殖、抗凋亡	子宫内膜癌、乳腺癌、前列腺癌等
免疫调节	PD-1/PD-L1	增加M2巨噬细胞、MDSCs、Tregs,抑制CD8 ⁺ T细胞和NK细胞活性	各类肥胖相关肿瘤,尤其胃肠道及实体瘤
脂肪酸代谢重编程	PPAR、TLR、AMPK等	WAT释放FFAs供给癌细胞能量和膜原料;促进炎症介质合成;改变肿瘤细胞代谢模式	乳腺癌、肝癌、胰腺癌
血管生成和转移	VEGF/JAK/STAT3、FGF-2/FGFR和PI3K/AKT	脂肪细胞分泌促血管生成因子,促进肿瘤血管生成和血行转移	乳腺癌、肝癌、胰腺癌
细胞外基质重塑	MAP3K和NF-κB	脂肪组织通过释放MMPs和细胞因子,破坏基底膜,便于肿瘤细胞侵袭和转移	结肠癌、卵巢癌和乳腺癌

注:脂肪组织通过内分泌功能(分泌炎症因子、脂肪因子等)及代谢重编程对多种肥胖相关肿瘤施加影响的主要信号通路及作用机制。IL-6,白细胞介素-6;TNF-α,肿瘤坏死因子-α;IGF-1,胰岛素样生长因子-1;MDSCs,髓源性抑制细胞;Tregs,调节性T细胞;WAT,白色脂肪组织;FFAs,游离脂肪酸;VEGF,血管内皮生长因子;FGF-2,成纤维细胞生长因子-2;MMPs,基质金属蛋白酶。

Note: The major signaling pathways and mechanisms through which adipose tissue exerts effects on various obesity-related tumors via endocrine functions (secretion of inflammatory factors, adipokines, etc.) and metabolic reprogramming. IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; IGF-1, insulin-like growth factor 1; MDSCs, myeloid-derived suppressor cells; Tregs, regulatory T cells; WAT, white adipose tissue; FFAs, free fatty acids; VEGF, vascular endothelial growth factor; FGF-2, fibroblast growth factor 2; MMPs, matrix metalloproteinases.

性转移^[14,15]。

1.2 脂肪酸代谢重编程

脂肪组织可通过跨内皮机制调控长链脂肪酸的双向转运,向肿瘤微环境中释放游离脂肪酸和甘油三酯;这些底物被肝癌和胰腺癌等细胞摄取后,通过β-氧化等途径,满足肿瘤细胞对能量和生物合成前体的高需求,从而增强其增殖和存活能力^[16]。在肝癌等脂质依赖型肿瘤中,组织间液中富集的脂质和脂蛋白不仅直接为癌细胞供能,还会诱导肿瘤微环境中的巨噬细胞丧失免疫监视功能,并向免疫抑制表型转化,这种由异常脂质驱动的免疫细胞重塑,进一步促进了肿瘤的侵袭与演进^[17]。而胰腺癌细胞则对这种外源性脂质表现出明显的代谢适应特征;在营养受限的微环境中,胰腺癌细胞通过调节自身的能量代谢网络,将摄取的脂质转化为维持生存的主要能量来源,这种对脂质产能途径的依赖,构成了其在代谢压力下持续增殖与扩散的病理基础,从而使胰腺肿瘤细胞能够在营养匮乏的微环境中生存并扩散^[18]。

1.3 胰岛素/IGF-1信号通路

胰岛素抵抗和高胰岛素血症是肥胖相关代谢综

合征的核心特征,二者均与多种癌症的发展密切相关,尤其是在乳腺癌、结肠癌和子宫内膜癌中,全身性慢性炎症加剧胰岛素抵抗,导致代偿性高胰岛素水平,进而激活IGF-1信号通路^[19-21]。在乳腺癌中,胰岛素不仅通过IGF-1通路促进乳腺癌细胞增殖,还能通过影响肿瘤微环境,促进乳腺癌细胞的转移^[22]。在结肠癌中,胰岛素抵抗与肿瘤的生长和转移相关,并且肥胖导致的高胰岛素水平可以通过激活PI3K/AKT等信号通路,增强结肠癌细胞的增殖能力^[23,24]。对于子宫内膜癌,高胰岛素状态被认为是核心的驱动因素之一,特别是在肥胖患者中,代偿性分泌的过量胰岛素能够通过过度激活PI3K/AKT/mTOR等经典致癌信号通路,强烈刺激子宫内膜细胞的异常增殖与恶性转化^[25]。此外,肥胖伴随的胰岛素抵抗还会促发内源性雌激素的异常蓄积,由此引发代谢与内分泌协同失调,进一步加剧子宫内膜发生恶性转化的风险^[26,27]。

1.4 瘦素的促癌作用

瘦素是一种由脂肪组织分泌的细胞因子,在多种癌症的发展中起着重要作用。在乳腺癌中,瘦素显著增强了癌细胞的增殖和迁移能力,并且通过调

节JAK/STAT通路,增强癌细胞对表皮生长因子(epidermal growth factor,EGF)刺激的敏感性^[28,29]。在肝癌细胞中,瘦素水平升高通过影响细胞周期和凋亡信号通路,促进肝癌细胞的生存与扩散^[30]。在结肠癌中,瘦素的促增殖作用同样显著,其通过激活PI3K/AKT通路,进一步增强了结肠癌细胞的存活率和迁移能力^[31]。瘦素在子宫内膜癌和卵巢癌中的作用也引起了广泛关注。在肥胖个体中,瘦素的水平普遍较高,这与子宫内膜癌和卵巢癌的发生风险密切相关^[32]。这种关联可能与瘦素对内分泌环境的影响以及其在肿瘤微环境中促进炎症反应的作用有关,进而影响癌症的发生和发展^[33]。

1.5 脂联素的抗癌效应

脂联素是由脂肪细胞分泌的一种重要的细胞因子,具有显著的抗癌效果。尤其是在胰腺癌和食管癌中,脂联素水平的降低与不良预后密切相关。这一现象可能与其通过激活AMPK信号通路来抑制肿瘤生长有关^[34]。在胰腺癌中,脂联素通过促进AMPK的磷酸化,抑制癌细胞的增殖和迁移,而脂联素的缺失会导致胰腺癌细胞的生长加速,这进一步支持了脂联素在抑制胰腺癌中的关键作用^[35]。在食管癌方面,低脂联素水平同样与肿瘤的进展、复发及转移等风险增加密切相关^[36]。此外,脂联素还通过抑制肿瘤微环境中NF- κ B和STAT3的活化,降低炎症反应,发挥抗癌作用^[37]。

1.6 免疫调节和免疫抑制机制

脂肪组织内的免疫细胞浸润,包括调节性T细胞(regulatory T cell,Treg)、髓源性抑制细胞(myeloid-derived suppressor cells,MDSCs)和M2型巨噬细胞,已被证明能抑制抗肿瘤免疫反应。这些细胞在乳腺癌、肝癌和胰腺癌等多种癌症中均有显著的浸润和积累^[38]。

首先,在细胞层面上,微环境中的抑制性免疫细胞群通过旁分泌网络协同发挥作用。Treg细胞通过分泌抑制性细胞因子,如IL-10和TGF- β 抑制效应T细胞的功能,协助肿瘤细胞逃避免疫监视^[39]。其次,MDSCs通过分泌一系列免疫抑制性因子,如一氧化氮和活性氧来抑制T细胞和NK细胞的功能;在肝癌和胰腺癌中,MDSCs的大量存在不仅促进了肿瘤细胞的生长与转移,更显著降低了患者对免疫治疗的应答率^[40]。同时,M2型巨噬细胞通过分泌免疫抑制因子,进一步巩固了促癌微环境的构建,其在

胰腺癌中的高浸润水平往往预示着患者的极差临床预后,凸显了其在癌症进展中的关键地位^[41]。此外,在分子层面,脂肪组织微环境可上调免疫检查点分子PD-1/PD-L1等表达,导致CD8⁺T淋巴细胞耗竭加速与细胞毒性下降,促进结肠癌和食管癌免疫逃逸的发生^[42]。这种由脂肪驱动的免疫抑制状态,不仅与结肠癌和食管癌的高侵袭性和不良预后密切相关,更削弱了患者对PD-1/PD-L1免疫检查点抑制剂的治疗反应^[43]。

1.7 血管生成和转移的调节

在乳腺癌、肝癌和胰腺癌的肿瘤微环境中,脂肪组织是血管内皮生长因子(vascular endothelial growth factor,VEGF)和成纤维生长因子(fibroblast growth factor,FGF)的重要来源。VEGF是一种强效的血管生成因子,在乳腺癌、肝癌和胰腺癌的进展过程中其表达显著上调,并通过激活VEGF/JAK/STAT3信号通路,促进肿瘤血管的形成,从而为肿瘤细胞提供必要的养分和氧气,支持其快速生长和扩散^[44]。FGF的大量分泌同样源于肿瘤与脂肪细胞的恶性串扰:肿瘤细胞主要通过旁分泌途径释放TNF- α 进而激活邻近脂肪细胞内的NF- κ B信号通路,从而显著诱导脂肪细胞上调FGF的表达与分泌,从而促进肿瘤相关血管生成。机制上,脂肪细胞分泌的FGF通过激活肿瘤细胞中的FGF-2/FGFR和PI3K/AKT信号通路,促进肿瘤细胞的增殖和迁移,这种机制可能与肥胖相关的炎症反应密切相关^[45-47]。

1.8 细胞外基质重塑

细胞外基质(extracellular matrix,ECM)与基底膜是阻挡肿瘤细胞扩散的重要物理屏障,而基质金属蛋白酶(matrix metalloproteinases,MMPs)作为降解ECM的核心酶,大量来源于微环境中的脂肪组织^[48]。在肿瘤进展中,微环境中的慢性炎症会显著放大脂肪组织对ECM的破坏作用。例如,TNF- α 可通过激活NF- κ B信号通路,诱导脂肪细胞过度表达MMPs^[49]。同时,局部蓄积的IL-1和IL-6等促炎因子也可进一步诱导MMPs分泌,加速基底膜降解,直接为肿瘤的侵袭转移打开通道。该机制在结肠癌和卵巢癌中尤为典型:由于常侵犯或定植于肠系膜、大网膜等富脂组织,肿瘤与脂肪的强烈炎症串扰导致MMPs高度富集。这种由脂肪介导的ECM重塑直接驱动了肿瘤的高侵袭性,并与不良预后

密切相关^[50]。

2 脂肪组织对乳腺癌的特异性作用机制

尽管肥胖与多种肿瘤相关,但乳腺癌具有独特的解剖学特征:乳腺上皮细胞直接镶嵌于富含脂肪的基质中。这种物理上的紧密接触使得乳腺癌细胞与脂肪细胞之间存在更直接、持续的双向串扰,主要表现为CAAs的形成及局部雌激素生物合成的异常活跃^[51]。

2.1 CAAs的促癌作用

CAAs是乳腺肿瘤微环境的重要组成部分。乳腺癌细胞通过分泌多种信号分子,如Wnt家族成员、TGF- β 、肾上腺髓质素(adrenomedullin, AM)等,诱导邻近的正常脂肪细胞发生去分化。这些经过炎症性与代谢重编程的脂肪细胞即为CAAs。在CAAs形成过程中,伴随着脂滴耗竭与成熟标志物表达的下调,CAAs逐渐丧失了成熟脂肪细胞的固有特征,转而表现出体积较小、类似成纤维细胞的形态,并伴随IL-6、TNF- α 及IL-1 β 等经典促炎细胞因子的大量表达与释放^[52]。CAAs形成的调控因子包括Runx1、NCoA3、YAP/TAZ等。Runx1通过下调脂滴相关蛋白Plin1促进脂肪细胞向CAAs转变,增强肿瘤细胞的迁移和侵袭能力^[53]。NCoA3的上调激活NF- κ B信号通路,诱导脂肪组织炎症反应,促进肿瘤相关炎症微环境的建立^[54]。YAP/TAZ信号的激活也促进CAAs的形成和肿瘤微环境的恶性重塑,抑制该通路可逆转脂肪细胞功能障碍,抑制肿瘤进展^[55,56]。完成了上述表型重塑的CAAs,则通过旁分泌反作用于肿瘤细胞及免疫系统。一方面CAAs通过分泌SAA1、FUCA2、CSF2、LIF和CXCLs等细胞因子,激活多种信号通路如STAT3、ERK1/2、NF- κ B,促进肿瘤干性特征的获得,尤其在三阴性乳腺癌中表现出促进肿瘤侵袭和转移的关键作用^[57-60]。另一方面,CAAs参与肿瘤免疫调节,通过分泌C-C基序趋化因子配体2(C-C motif chemokine ligand 2, CCL2)招募单核细胞和巨噬细胞,促进巨噬细胞向M2型的极化,形成免疫抑制微环境^[61](图1)。

CAAs的促癌机制在临床病理与预后中也得到了印证。在临床上,CAAs的形态和数量与患者的体质指数、绝经状态、肿瘤类型及预后密切相关^[62]。CAAs的脂滴体积缩小与患者不良生存期相关,而CAAs丰富的肿瘤微环境通常伴随炎症和转移相关

通路上调,针对CAAs的治疗策略包括靶向其促炎因子分泌、脂肪代谢通路及其与肿瘤细胞的信号交流,成为乳腺癌治疗的新兴方向^[63]。

2.2 局部雌激素水平显著升高

雌激素受体阳性乳腺癌高度依赖雌激素信号,因而更依赖脂肪组织的内分泌功能。乳腺周围的脂肪组织非常丰富且可大量表达芳香化酶CYP19A1(cytochrome P450 family 19 subfamily A member 1),将雄激素转化为雌激素,使得局部雌激素水平显著高于循环水平,直接驱动了肿瘤的恶性进展^[64]。在肥胖状态下,局部微环境中升高的促炎因子前列腺素E2(prostaglandin E2, PGE2)通过cAMP/PKA通路促进CYP19A1的合成,而TNF- α 通过激活环氧合酶-2来增强PGE2的合成,进一步放大PGE2促CYP19A1合成的作用。作为肿瘤微环境中关键的促炎与趋化因子,抑瘤素M(oncostatin M, OSM)和CCL2分别通过激活脂肪细胞的JAK/STAT3通路和ERK1/2信号通路,上调CYP19A1基因表达,进而增加脂肪细胞内CYP19A1的合成及雌激素分泌,这些雌激素继而激活乳腺癌细胞的雌激素受体通路,促进ER⁺乳腺癌细胞增殖^[65-67](图2)。上述局部雌激素合成网络对绝经后女性尤为关键:由于卵巢功能衰退,脂肪组织接替成为雌激素的主要来源。若患者同时叠加肥胖,乳腺局部的慢性炎症将进一步恶化;免疫浸润与前述促炎因子的持续蓄积会双重强化芳香化酶活性,最终维持高雌激素的促癌微环境^[68]。

3 临床转化研究

乳腺癌微环境中的脂肪组织与肿瘤细胞间存在复杂交互关系,微生理系统(microphysiological system, MPS)模型的建立显著推动了基础发现的临床转化。该模型利用人类乳腺组织和脂肪衍生干细胞构建多细胞共培养系统,模拟真实的肿瘤微环境,使得肿瘤细胞迁移及代谢互作的动态观察成为可能,为靶向治疗策略的筛选提供了平台^[69]。脂肪源性干细胞(adipose-derived stem cells, ASCs)是驻留于脂肪组织基质内的多能间充质干细胞,具备强大的自我更新、成脂分化及旁分泌功能。基于此,ASCs在乳腺癌术后脂肪移植重建中展现出改善软组织损伤的巨大潜力;更重要的是,患者体内ASCs的增殖及分化能力在接受化疗后基本未受损,表明ASCs作为临床脂肪移植细胞源具有可行性^[70]。在

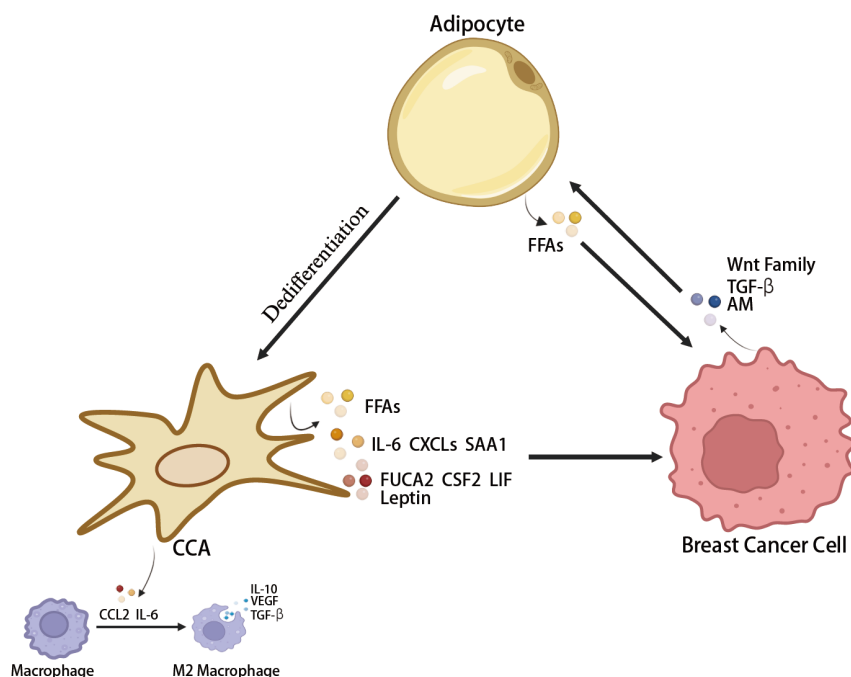


图1 肿瘤相关脂肪细胞 (CAAs) 的形成及其与乳腺癌细胞和免疫微环境的相互作用

乳腺癌细胞通过分泌Wnt家族蛋白、转化生长因子- β (TGF- β) 和肾上腺髓质素 (AM) 等信号分子, 诱导邻近的成熟脂肪细胞发生去分化 (dedifferentiation), 转变为具有成纤维细胞特征的肿瘤相关脂肪细胞 (CAAs)。CAAs通过代谢重编程释放游离脂肪酸 (FFAs) 供肿瘤细胞利用, 并分泌IL-6、CXCLs、SAA1、FUCA2、CSF2、LIF和瘦素 (Leptin) 等多种细胞因子, 促进乳腺癌的恶性进展。此外, CAAs还通过分泌CCL2和IL-6招募单核细胞并诱导其向M2型巨噬细胞极化; M2型巨噬细胞随即分泌IL-10、血管内皮生长因子 (VEGF) 和TGF- β , 进一步营造免疫抑制微环境。

Figure 1 Formation of cancer-associated adipocytes (CAAs) and their crosstalk with breast cancer cells and the immune microenvironment

Breast cancer cells induce dedifferentiation of adjacent mature adipocytes into fibroblast-like cancer-associated adipocytes (CAAs) by secreting signaling molecules such as Wnt family members, transforming growth factor- β (TGF- β), and adrenomedullin (AM). CAAs undergo metabolic reprogramming to release free fatty acids (FFAs) for tumor cell utilization and secrete a variety of cytokines, including interleukin-6 (IL-6), CXCLs, serum amyloid A1 (SAA1), fucosidase, alpha-L-fucosidase 2 (FUCA2), colony stimulating factor 2 (CSF2), leukemia inhibitory factor (LIF), and leptin, thereby promoting the malignant progression of breast cancer. Furthermore, CAAs recruit monocytes and induce their polarization into M2 macrophages via the secretion of CCL2 and IL-6. These M2 macrophages subsequently secrete IL-10, vascular endothelial growth factor (VEGF), and TGF- β , further establishing an immunosuppressive microenvironment.

乳腺癌术后放疗患者中, 脂肪移植能够减轻放射性损伤, 增加组织厚度, 改善重建效果和生活质量^[71]。脂肪组织的影像学指标也值得关注, 如利用3T MRI的质子密度脂肪分数 (proton density fat fraction, PDFF) 测定乳腺脂肪含量, 该定量指标与传统乳腺影像密度指标高度相关, 为乳腺癌风险评估提供了无创、定量的手段^[72, 73]。然而, 脂肪组织在乳腺癌中的双重作用及其潜在促瘤机制仍需进一步阐明, 尤其是脂肪组织炎症状态、脂肪细胞亚型多样性与肿瘤细胞代谢重编程的关系, 未来对这些机制的深入解析, 将为开发更有效的临床干预策

略奠定基础^[74, 75]。

4 未来展望

现有研究已勾勒出脂肪组织促进乳腺癌发展的轮廓, 但破解其时空动态特征与因果链条仍是未来的核心任务。首先, 应结合单细胞多组学与空间转录组学技术, 系统描绘肿瘤-脂肪组织界面中以CAAs及浸润免疫细胞为代表的多细胞亚群及信号网络的异质性与动态演化。其次, 需通过稳定同位素示踪、脂质组学及代谢通量分析等手段, 深入挖掘脂肪组织代谢重编程的具体特征, 明确其释放的炎

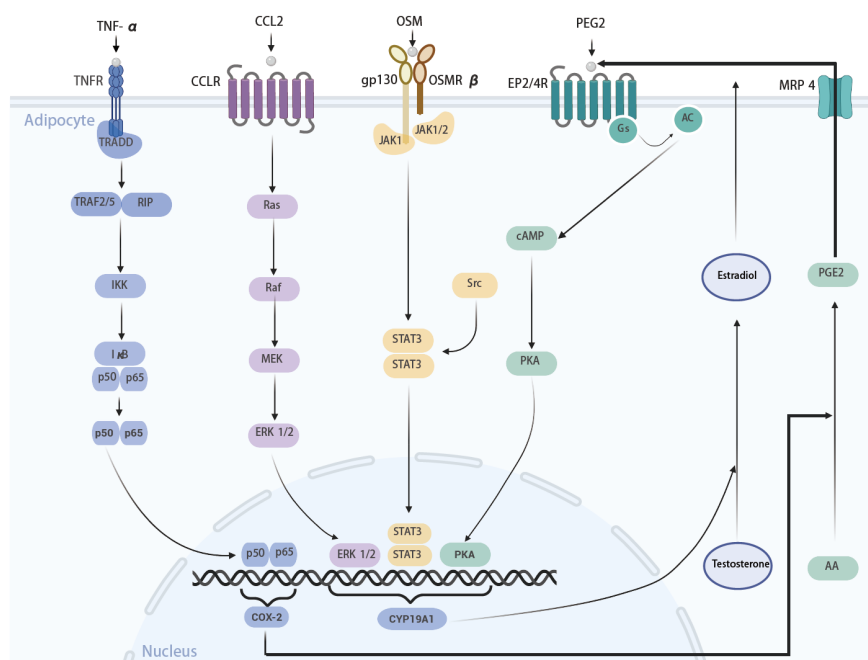


图2 炎症微环境下脂肪细胞芳香化酶CYP19A1的转录调控及局部雌激素合成的正反馈环路

该图展示了在肥胖或炎症状态下,脂肪细胞内促进CYP19A1表达和雌激素合成的主要信号通路。TNF- α 通路:TNF- α 结合受体后激活NF- κ B(p50/p65)通路,入核促进环氧合酶-2(COX-2)的表达,COX-2催化花生四烯酸(AA)生成前列腺素E2(PGE2)。PGE2通路:PGE2输出细胞后以自分泌/旁分泌方式结合EP2/4R受体,激活cAMP/PKA信号轴,诱导CYP19A1转录。CCL2和OSM通路:CCL2和OSM分别通过ERK1/2和JAK/STAT3信号通路,上调CYP19A1的表达。这些通路共同导致脂肪细胞内芳香化酶水平升高,将睾酮(testosterone)大量转化为雌二醇(estradiol),高浓度的雌二醇反过来通过雌激素受体进一步刺激肿瘤生长,形成恶性循环。

Figure 2 Transcriptional regulation of CYP19A1 in adipocytes under inflammatory conditions and the positive feedback loop of local estrogen synthesis

This figure illustrates the key signaling pathways that drive CYP19A1 expression and estrogen synthesis within adipocytes under obese or inflammatory conditions. TNF- α pathway: TNF- α binds to receptors to activate the NF- κ B(p50/p65) pathway, which translocates to the nucleus to promote cyclooxygenase-2 (COX-2) expression: COX-2 subsequently catalyzes the conversion of arachidonic acid (AA) into prostaglandin E2 (PGE2). PGE2 pathway: secreted PGE2 binds to EP2/4R receptors in an autocrine/paracrine manner, activating the cAMP/PKA signaling axis to induce CYP19A1 transcription. CCL2 and OSM pathways: CCL2 and OSM directly upregulate the expression of the CYP19A1 gene via the ERK1/2 and JAK/STAT3 signaling pathways, respectively. These converging pathways lead to elevated aromatase levels in adipocytes, resulting in the robust conversion of testosterone to estradiol. High levels of local estradiol further stimulate tumor growth, creating a vicious cycle.

性因子和脂肪酸等在肿瘤细胞中的代谢过程及与信号转导通路的耦合机制。再次,应重点探究脂肪介导的炎症趋化网络在免疫调控中的作用,阐明其驱动免疫逃逸与耐药的核心机制。最后,建立更具仿生特性的类器官、微流控“肿瘤-脂肪芯片”及人源化动物模型,为关键分子机制的验证及潜在靶点的转化应用提供有力支撑。未来,跨学科、多组学与功能验证相结合的研究策略,将有助于全面揭示脂肪组织与肿瘤之间的复杂互作,为代谢-免疫联合调控的抗肿瘤策略提供新的理论依据与干预方向。

从临床应用的角度看,实现成果转化的关键瓶颈在于如何在干预肿瘤微环境的同时维持全身代谢稳态。未来的治疗策略不应仅局限于单一通路,而应开发能够精准阻断“脂肪-肿瘤”恶性串扰且副作用可控的组合疗法。通过跨学科技术融合与机制的深度解析,靶向脂肪微环境有望成为改善乳腺癌患者预后的新高地。因此,在全面权衡脂肪组织生理和病理双重效应的基础上,开发兼顾“抗肿瘤”与“保代谢”的精准干预策略,将是未来推动乳腺癌治疗进步的关键所在。

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