Advances in Clinical Medicine 临床医学进展, 2019, 9(4), 606-612
Published Online April 2019 in Hans. http://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2019.94092

Hans汉斯

Breast Cancer-Associated Fibroblasts: A New Target for Breast Cancer Therapy

Junjie Li[1], Hui Li[1], Qiming Long[1], Ye Yang[2*]

[1]Department of Breast Surgery, Sichuan Cancer Hospital, Chengdu Sichuan
[2]Department of Medical Oncology, Sichuan Cancer Hospital, Chengdu Sichuan
Email: *yangye43@163.com

Received: Apr. 9th, 2019; accepted: Apr. 23rd, 2019; published: Apr. 30th, 2019

Abstract

Tumor microenvironment is composed of tumor cells, tumor supporting cells, cell matrix and cytokines. Among these, cancer-associated fibroblasts (CAFs) are the most abundant in tumor microenvironment and play an important role in tumorigenesis, angiogenesis, proliferation, invasion and metastasis. This has prompted some researchers to study the molecular and cellular characteristics of CAFs and explore their potential applications in cancer prevention and treatment. There are a lot of studies on the definition, origin and effect of CAFs on cancer cells. In this paper, we summarize the differences in the definition of CAFs, the diversity of their sources, and the possible mechanisms in the treatment of breast cancer, and the future research directions in this field are also predicted.

Keywords

Breast Cancer, Cancer-Associated Fibroblasts, Tumor Microenvironment

乳腺癌相关成纤维细胞：乳腺癌治疗的新靶点

李俊杰[1]，李　卉[1]，龙启明[1]，杨　业[2*]

[1]四川省肿瘤医院乳腺外科中心，四川 成都
[2]四川省肿瘤医院肿瘤内科，四川 成都
Email: *yangye43@163.com

收稿日期：2019年4月9日；录用日期：2019年4月23日；发布日期：2019年4月30日

*通讯作者。

文章引用：李俊杰，李卉，龙启明，杨业. 乳腺癌相关成纤维细胞：乳腺癌治疗的新靶点[J]. 临床医学进展, 2019, 9(4): 606-612. DOI: 10.12677/acm.2019.94092

摘　要

肿瘤微环境是由肿瘤细胞、肿瘤支持细胞、细胞基质、细胞因子等构成。其中肿瘤相关成纤维细胞(Cancer-Associated Fibroblasts, CAFs)在肿瘤微环境中含量最为丰富，其在肿瘤的形成、肿瘤血管生成、增殖、侵袭和转移等事件过程中起着重要作用。这促使一些研究人员对CAFs的分子和细胞特征进行研究，探索其在预防和治疗癌症方面的潜在应用。目前有大量关于CAFs的定义、起源以及其对肿瘤细胞的作用的研究。在此，本文总结了目前CAFs定义的分歧，来源的多样性，以及其在乳腺癌治疗中的可能机制，并对该领域未来研究方向做出了分析。

关键词

乳腺癌，肿瘤相关成纤维细胞，肿瘤微环境

1. 引言

乳腺癌是目前女性发病率最高的恶性肿瘤，也是全世界女性癌症死亡的主要原因之一[1] [2] [3]。和所有恶性肿瘤类似，早诊早治对乳腺癌的治疗效果影响显著。雷洛昔芬或他莫昔芬等抗雌激素药物在乳腺癌的预防方面起着积极作用；大量新药上市也为乳腺癌治疗效果的改善做出了贡献；高患病风险女性乳腺预防切除也降低了乳腺癌发生[4]。手术、放化疗、内分泌治疗、靶向治疗等是乳腺癌主要的治疗手段。对晚期乳腺癌而言，治疗目的主要是提高生活质量和延长患者寿命。乳腺癌是存在着高度异质性的恶性肿瘤，乳腺癌细胞主要通过局部浸润或者经血管、淋巴管转移到骨、肺，肝脏和脑等部位[5]。转移是连续的、复杂的多步骤过程，具有高度侵袭性的癌细胞亚群首先通过降解细胞外基质，继而通过血液或淋巴系统，转移到远处器官组织[6]。以往认为乳腺癌细胞的转移是其晚期表现，但不断有新的证据表明，乳腺癌在早期就可以出现全身转移[7]。大量科研工作者正不断深入探索其可能机制，如有研究表明乳腺癌肺转移与富含半胱氨酸(SPARC)的蛋白质酸、基质金属蛋白酶 2 (MMP2)、白细胞介素-2 受体 α、血管细胞黏附分子 1 (VCAM1)等有密切关系。乳腺癌骨转移与结缔组织生长因子(CTGF)、白介素-11 (IL-11)有紧密关系；而乳腺癌脑转移由唾液酸转移酶介导。以上种种证据都表明乳腺癌转移不仅与自身细胞特性有关还与其微环境有着密切关系[8]。自 1889 年“种子和土壤”学说被提出来以来，大量的证据表明肿瘤组织自身特性和肿瘤微环境在肿瘤的产生、进展过程中都起着重要作用。肿瘤微环境包括细胞成分和非细胞成分；主要由成纤维细胞、免疫细胞、内皮细胞、细胞外基质等组成。而成纤维细胞是含量最多肿瘤微环境成分；其具有多种作用，包括分泌趋化因子、细胞因子、细胞外基质，参与免疫调控、上皮细胞分化，影响肿瘤的发生、发展[9]。大量证据表明乳腺癌相关成纤维细胞在乳腺癌的发生以及发展过程中起着重要作用，下面对其进行综述。

2. 肿瘤相关成纤维细胞定义？

目前对 CAFs 的定义尚不明确。尽管肿瘤相关成纤维细胞有许多标志物，但特异性不高。肿瘤相关成纤维细胞高表达肾小球足突细胞膜黏蛋白、平滑肌肌动蛋白(α-SMA)、p53、CD10、基质金属蛋白酶

(MMPs)、成纤维细胞活化蛋白(FAP)，但韧粘素、血小板源性生长因子(PDGFR)和 Caveolin-1 (Cav-1)表达缺失[6]。有研究者将肿瘤相关成纤维细胞定义为形态为梭形的 α-SMA 阳性的肿瘤组织成纤维细胞。然而，α-SMA 并不是肿瘤相关成纤维细胞特异性表达，在正常的成纤维细胞、纤维结缔组织病的骨骼肌中也可以观察到其表达[10]。

成纤维细胞是肿瘤微环境细胞中最丰富的细胞类型。Gabbiani 等在人伤口愈合过程中首次发现肿瘤相关成纤维细胞[11]。肿瘤相关成纤维细胞是成纤维细胞的一个亚群，其通过分泌各种趋化因子、细胞因子，及降解细胞外基质蛋白促进肿瘤的进展和转移[12]。正常组织中，成纤维细胞增殖指数低；伤口愈合过程以及在肿瘤组织中，成纤维细胞被激活，增殖加快并分泌大量的细胞外基质成分，同时获得收缩功能。肿瘤组织中，这些细胞被称为活化的成纤维细胞，肿瘤周围成纤维细胞、肿瘤相关成纤维细胞、肿瘤或癌相关成纤维细胞[13]。活化的成纤维细胞大量分泌各种生长因子，这些因子被活化的成纤维细胞用于与癌细胞以及其他基质细胞进行信息交流。基因芯片和蛋白质组学分析发现，与正常乳房成纤维细胞(Normal breast fibroblasts, NBFs)相比，CAFs 遗传和表观遗传信息均发生变化[14] [15]。CAFs 表现出一些癌症特异性的变化，如缺陷的 p53 基因、存活素蛋白高表达，增殖标志物 Ki-67、PCNA 高表达；对顺铂和紫外光抵抗增强[16]。CAFs 可以通过 NF-kB 介导肿瘤细胞增强炎症谱，同时通过释放生长因子(FGFs、TGF-b、HGF、SDF1 等)，细胞因子(CXCL12，IL-6 等)，雌激素等促进血管生成与肿瘤生长。CAFs 可以富集免疫细胞(如：Foxp3 T 细胞和髓系衍生抑制细胞)到肿瘤微环境中，这些免疫细胞可以抑制 T 细胞、自然杀伤细胞功能。清除 CAFs 可以减少肿瘤相关巨噬细胞，髓系抑制性细胞在肿瘤组织中的聚集。相关动物实验表明，CAFs 能通过抑制 Th1 细胞因子从而抑制 Th1 的免疫反应，同时增强免疫抑制 Th2 细胞因子促进肿瘤生长[17]。

3. 乳腺癌相关成纤维细胞的起源

乳腺癌相关成纤维细胞的来源是多样性的，目前已知主要有三种来源。一是肿瘤组织内静息间质成纤维细胞转化为乳腺癌相关成纤维细胞。三维共培养实验表明，成纤维细胞与乳腺癌细胞共培养时可分化成乳腺癌相关成纤维细胞，同时可反作用于肿瘤细胞，对其产生促进作用[18] [19]。在异种移植乳腺癌动物模型中，也有相同发现[20]。这些结果显示 CAFs 是通过旁分泌作用将正常乳腺间质成纤维细胞向 CAFs 发生转变。例如，TGF-β 可诱导体外培养的乳腺成纤维细胞产生 α-SMA，进而将成纤维细胞转变成 CAFs。研究发现正常成纤维细胞与 CAFs 相比，CAFs 中的许多基因表达上调，如：肝细胞生长因子(HGF)、成纤维细胞生长因子(FGF)、转化生长因子 β (TGFβ)、基质细胞衍生因子 1 (SDF-1)、效应物细胞蛋白酶受体 1 (EPR-1)]、细胞因子巨噬细胞集落刺激因子(GM-CSF)、癌基因(K-ras)等。这些基因产物中有许多是具有促进侵袭和转移的作用[21]。在胰腺癌与肝癌的相关研究中发现：胰腺和肝脏中的正常成纤维细胞可被胰腺癌和肝癌细胞诱导获得表达 α-SMA 的 CAFs [22] [23]。其次是来自特循环祖细胞，如成纤维细胞和骨髓间充质干细胞(MSCs)。研究显示，成纤维细胞表达造血干细胞、单核细胞和成纤维细胞谱系标志物。骨髓间充质干细胞可以分化为活跃的表达 α-SMA 的成纤维细胞，并已被证实能迁移到肿瘤部位并分化为 CAFs。这些现象在胶质瘤、乳腺癌、胰腺癌和胃癌的相关研究中均被发现[24] [25] [26] [27]。值得注意的是间充质干细胞可分为肿瘤相关的间充质干细胞(tumour-associated MSCs, TA-MSCS)，和非 CAF 细胞类型；TA-MSCS 具有较高的自我更新能力和低表达 CAF 相关的标记物，如波形蛋白、成纤维细胞活化蛋白(FAP)和 S100A4 (也称为成纤维细胞特异性蛋白-1)，其机制尚待进一步研究[28]。这些发现有力地表明 MSCs 是 CAF 的来源之一。第三个来源是乳腺上皮细胞，内皮细胞，脂肪细胞向肌纤维母细胞转分化。上皮间质转化(EMT)是癌症进展的重要过程，转化生成的成纤维细胞，增强肿瘤迁移、侵袭能力[28] [29]。大量证据表明内皮细胞间质转化(EndMT)可以产生肿瘤相关成纤维细胞[30] [31]。此外，

利用转基因小鼠的研究表明，通过 EndMT 可产生高达 40% CAFs，肿瘤组织在不同癌变阶段 CAFs 构成比也不同[32]。局部细胞转化似乎是最主要的来源，远处细胞迁移浸润也是肿瘤相关成纤维细胞的组成部分。总之，这些发现表明乳腺癌相关的成纤维细胞可能有不同的起源。

4. 乳腺癌相关成纤维细胞在乳腺癌发生和进展中的作用

大量研究表明乳腺癌相关成纤维细胞在乳腺癌的发生、进展过程中起着促进作用。当普通成纤维细胞与乳腺癌细胞系 MDA-MB-231 共同培养时，普通成纤维细胞可分化形成 CAFs 亚型，同时分泌肝细胞生长因子[10]。基因表达谱分析显示，与正常成纤维细胞相比，乳腺癌相关成纤维细胞有明显不同的基因表达模式，乳腺癌亚型不同其成纤维细胞的基因表型也明显不同[15]。有趣的是，正常乳腺成纤维细胞基因表达变异反而高于乳腺癌相关成纤维细胞，这表明正常乳腺成纤维细胞存在潜在异质性。与激素受体阳性和三阴性乳腺癌相比，HER-2 过表达乳腺癌在骨架和整合素信号通路方面，其相关基因出现明显上调。HER-2 阳性乳腺癌相关成纤维细胞可显著增强 T47D 乳腺癌细胞系侵袭、迁移能力，这表明乳腺癌相关成纤维细胞的特异性可以作用于乳腺癌细胞[33] [34]。在另一项研究中，1,25 二羟维生素 D3 对乳腺癌相关成纤维细胞转录作用的影响明显不同于正常成纤维细胞。1,25 二羟维生素 D3 下调乳腺癌相关成纤维细胞增殖相关基因(NRG1, Wnt5a, PDGFC)表达，上调免疫调节基因表达(nfkb1a, TREM-1)。在正常成纤维细胞组，其诱导基因参与抗凋亡、解毒、抗菌防御系统和抗氧化应激保护系统[35]。研究发现正常乳腺组织纤维细胞与乳腺癌相关成纤维细胞相比，CAFs 中的许多基因表达上调，如：肝细胞生长因子(HGF)、转化生长因子 β (TGFβ)、细胞因子巨噬细胞集落刺激因子(GM-CSF)、成纤维细胞生长因子(FGF)、基质细胞衍生因子 1 (SDF-1)、效应物细胞蛋白酶受体 1 (EPR-1)、癌基因(K-ras)等，这些基因产物中大都具有促进侵袭和转移的作用[36] [37]。从原代提取的成纤维细胞的基因表达在体外培养可能会改变。目前尚不清楚肿瘤成纤维细胞的遗传或表观遗传学的变化是乳腺癌发生和发展的前提还是结果[38]。所以还需要对不同类型乳腺癌成纤维细胞遗传学信息进一步研究。

乳腺癌治疗是涉及手术、放化疗、内分泌、靶向的综合治疗。乳腺癌免疫表型决定了其治疗方式的选择；这些措施包括针对雌激素途径的内分泌治疗(如三苯氧胺、芳香化酶抑制剂和氟维司群)、化疗(如蒽环类、紫杉、铂类)和靶向治疗(如抗 HER-2 药物、mTOR 抑制剂、CDK4/6 抑制剂) [39]。早期筛查和不断发展的治疗手段显著改善了乳腺癌预后，但耐药性仍然是乳腺癌治疗中的难题。而乳腺癌相关成纤维细胞可能有助于解决治疗抵抗的问题。体外研究表明，乳腺癌相关成纤维细胞可以通过激活 MAPK、PI3K/Akt 通路和磷酸化 ERα 调节三苯氧胺耐药[40]。在 MCF-7 与成纤维共培养试验中，可以观察到 MCF-7 细胞线粒体使用 CAFs 产生的乳酸或酮体进行代谢[41]。蛋白质组学分析表明，在正常氧环境中，乳腺癌相关成纤维细胞的特征物性标志 Cav-1 缺失可导致 CAFs 糖酵解酶转录水平升高[41] [42]。研究表明，成纤维细胞生长因子可以使三阴乳腺癌细胞在与 EGFR 抑制剂吉非替尼共培养的环境中存活[43]。这可能是过度表达表皮生长因子受体(EGFR)的乳腺癌细胞使用 EGFR 抑制剂没有临床效果的原因所在。通过这些实验，我们可以从中探索乳腺癌治疗新思路。

乳腺癌相关成纤维细胞是乳腺癌微环境中含量最多的细胞成分，在乳腺癌的发生、转移、脉管形成过程中起着重要作用。但对乳腺癌相关成纤维细胞的定义、起源和生物学异质性等重要特征的认识仍有待深入。目前包括乳腺癌在内的抗肿瘤治疗几乎都是仅仅针对肿瘤细胞治疗，这是极其片面的。因为肿瘤是全身性疾病，肿瘤的播散、转移与“种子和土壤”两者都有着密切关系。有关乳腺癌微环境中关键成分的研究可能会进一步阐明癌细胞及其微环境之间的复杂关系，并从中发现治疗乳腺癌的新靶点。

参考文献

[1] Siegel, R.L., Miller, K.D. and Jemal, A. (2018) Cancer Statistics, 2018. *CA*: *A Cancer Journal for Clinicians*, **68**, 7-30.

https://doi.org/10.3322/caac.21442

[2] Anderson, B., Yip, C., Smith, R., Shyyan, R., Sener, S., Eniu, A., *et al*. (2008) Guideline Implementation for Breast Healthcare in Low-Income and Middle Income Countries: Overview of the Breast Health Global Initiative Global Summit 2007. *Cancer*, **113**, 2221-2243. https://doi.org/10.1002/cncr.23844

[3] Han, S., Guo, Q. and Wang, T., *et al*. (2013) Prognostic Significance of Interactions between ER Alpha and ER Beta and Lymph Node Status in Breast Cancer Cases. *Asian Pacific Journal of Cancer Prevention*, **14**, 6081-6084. https://doi.org/10.7314/APJCP.2013.14.10.6081

[4] Peng, J., Sengupta, S. and Jordan, V.C. (2009) Potential of Selective Estrogen Receptor Modulators as Treatments and Preventives of Breast Cancer. *Anti-Cancer Agents in Medicinal Chemistry*, **9**, 481-99. https://doi.org/10.2174/187152009788451833

[5] Brenton, J.D., Carey, L.A., Ahmed, A.A. and Caldas, C. (2005) Molecular Classification and Molecular Forecasting of Breast Cancer: Ready for Clinical Application? *Journal of Clinical Oncology*, **23**, 7350-7360. https://doi.org/10.1200/JCO.2005.03.3845

[6] Luo, H., Tu, G., Liu, Z. and Liu, M. (2015) Cancer-Associated Fibroblasts: A Multifaceted Driver of Breast Cancer Progression. *Cancer Letters*, **361**, 155-163. https://doi.org/10.1016/j.canlet.2015.02.018

[7] Tchou, J., Kossenkov, A.V., Chang, L., Satija, C., Herlyn, M., Showe, L.C. and Pure, E. (2012) Human Breast Cancer-Associated Fibroblasts Exhibit Subtype Specific Gene Expression Profiles. *BMC Medical Genomics*, **5**, 39. https://doi.org/10.1186/1755-8794-5-39

[8] Bergamaschi, A., Tagliabue, E., Sorlie, T., Naume, B., Triulzi, T., Orlandi, R., Russnes, H.G., Nesland, J.M., Tammi, R., Auvinen, P., *et al*. (2008) Extracellular Matrix Signature Identifies Breast Cancer Subgroups with Different Clinical Outcome. *The Journal of Pathology*, **214**, 357-367. https://doi.org/10.1002/path.2278

[9] Quail, D.F. and Joyce, J.A. (2013) Microenvironmental Regulation of Tumor Progression and Metastasis. *Nature Medicine*, **19**, 1423-1437. https://doi.org/10.1038/nm.3394

[10] Campbell, I., Qiu, W. and Haviv, I. (2011) Genetic Changes in Tumour Microenvironments. *The Journal of Pathology*, **223**, 450-458. https://doi.org/10.1002/path.2842

[11] Moinfar, F., Man, Y.G., Arnould, L., Bratthauer, G.L., Ratschek, M. and Tavassoli, F.A. (2000) Concurrent and Independent Genetic Alterations in the Stromal and Epithelial Cells of Mammary Carcinoma: Implications for Tumorigenesis. *Cancer Research*, **60**, 2562-2566.

[12] Gabbiani, G., Ryan, G.B. and Majne, G. (1971) Presence of Modified Fibroblasts in Granulation Tissue and Their Possible Role in Wound Contraction. *Experientia*, **27**, 549-550. https://doi.org/10.1007/BF02147594

[13] Hasebe, T., Tamura, N., Okada, N., Hojo, T., Akashi-tanaka, S., Shimizu, C., Tsuda, H., Shibata, T., Sasajima, Y., Iwasaki, M., *et al*. (2010) p53 Expression in Tumor-Stromal Fibroblasts Is Closely Associated with the Nodal Metastasis and Outcome of Patients with Invasive Ductal Carcinoma Who Received Neoadjuvant Therapy. *Human Pathology*, **41**, 262-270. https://doi.org/10.1016/j.humpath.2009.07.021

[14] Dvorak, H.F. (1986) Tumors: Wounds that Do Not Heal. Similarities between Tumor Stroma Generation and Wound Healing. *The New England Journal of Medicine*, **315**, 1650-1659. https://doi.org/10.1056/NEJM198612253152606

[15] Bhowmick, N.A., Neilson, E.G. and Moses, H.L. (2004) Stromal Fibroblasts in Cancer Initiation and Progression. *Nature*, **432**, 332-337. https://doi.org/10.1038/nature03096

[16] Bauer, M., SU, G., Casper, C., HE, R., Rehrauer, W. and Friedl, A. (2010) Heterogeneity of Gene Expression in Stromal Fibroblasts of Human Breast Carcinomas and Normal Breast. *Oncogene*, **29**, 1732-1740. https://doi.org/10.1038/onc.2009.463

[17] Hawsawi, N.M., Ghebeh, H., Hendrayani, S.F., Tulbah, A., Al-Eid, M., Al-Tweigeri, T., Ajarim, D., Alaiya, A., Dermime, S. and Aboussekhra, A. (2008) Breast Carcinoma—Associated Fibroblasts and Their Counterparts Display Neoplastic-Specific Changes. *Cancer Research*, **68**, 2717-2725. https://doi.org/10.1158/0008-5472.CAN-08-0192

[18] Mao, Y., Keller, E.T., Garfield, D.H., Shen, K. and Wang, J. (2013) Stromal Cells in Tumor Microenvironment and Breast Cancer. *Cancer and Metastasis Reviews*, **32**, 303-315. https://doi.org/10.1007/s10555-012-9415-3

[19] Pula, B., Jethon, A., Piotrowska, A., Gomulkiewicz, A., Owczarek, T., Calik, J., Wojnar, A., Witkiewicz,W., Rys, J., Ugorski, M., *et al*. (2011) Podoplanin Expression by Cancer-Associated Fibroblasts Predicts Poor Outcome in Invasive Ductal Breast Carcinoma. *Histopathology*, **59**, 1249-1260. https://doi.org/10.1111/j.1365-2559.2011.04060.x

[20] Ronnov-Jessen, L., Petersen, O.W., Koteliansky, V.E. and Bissell, M.J. (1995) The Origin of the Myofibroblasts in Breast Cancer. Recapitulation of Tumor Environment in Culture Unravels Diversity and Implicates Converted Fibroblasts and Recruited Smooth Muscle Cells. *Journal of Clinical Investigation*, **95**, 859-873. https://doi.org/10.1172/JCI117736

[21] Kojima, Y., Acar, A., Eaton, E.N., Mellody, K.T., Scheel, C., Ben-Porath, I., Onder, T.T., Wang, Z.C., Richardson,

A.L., Weinberg, R.A., *et al*. (2010) Autocrine TGF-Beta and Stromal Cell-Derived Factor-1 (SDF-1) Signaling Drives the Evolution of Tumor-Promoting Mammary Stromal Myofibroblasts. *PNAS*, **107**, 20009-20014. https://doi.org/10.1073/pnas.1013805107

[22] Omary, M.B., Lugea, A., Lowe, A.W. and Pandol, S.J. (2007) The Pancreatic Stellate Cell: A Star on the Rise in Pancreatic Diseases. *Journal of Clinical Investigation*, **117**, 50-59. https://doi.org/10.1172/JCI30082

[23] Yin, C., Evason, K.J., Asahina, K. and Stainier, D.Y. (2013) Hepatic Stellate Cells in Liver Development, Regeneration, and Cancer. *Journal of Clinical Investigation*, **123**, 1902-1910. https://doi.org/10.1172/JCI66369

[24] Barth, P.J., Ebrahimsade, S., Ramaswamy, A. and Moll, R. (2002) $CD34^+$ Fibrocytes in Invasive Ductal Carcinoma, Ductal Carcinoma in Situ, and Benign Breast Lesions. *Virchows Archiv*, **440**, 298-303. https://doi.org/10.1007/s004280100530

[25] Jung, Y., *et al*. (2013) Recruitment of Mesenchymal Stem Cells into Prostate Tumours Promotes Metastasis. *Nature Communications*, **4**, Article No. 1795. https://doi.org/10.1038/ncomms2766

[26] Mishra, P.J., *et al*. (2008) Carcinoma-Associated Fibroblast—Like Differentiation of Human Mesenchymal Stem Cells. *Cancer Research*, **68**, 4331-4339. https://doi.org/10.1158/0008-5472.CAN-08-0943

[27] Zhu, Q., *et al*. (2014) The IL-6-STAT3 Axis Mediates a Reciprocal Crosstalk between Cancer-Derived Mesenchymal Stem Cells and Neutrophils to Synergistically Prompt Gastric Cancer Progression. *Cell Death & Disease*, **5**, e1295. https://doi.org/10.1038/cddis.2014.263

[28] Weber, C.E., *et al*. (2015) Osteopontin Mediates an MZF1-TGF-β1-Dependent Transformation of Mesenchymal Stem Cells into Cancer-Associated Fibroblasts in Breast Cancer. *Oncogene*, **34**, 4821-4833. https://doi.org/10.1038/onc.2014.410

[29] Shi, Y., Du, L., Lin, L. and Wang, Y. (2017) Tumour-Associated Mesenchymal Stem/Stromal Cells: Emerging Therapeutic Targets. *Nature Reviews Drug Discovery*, **16**, 35-52. https://doi.org/10.1038/nrd.2016.193

[30] Zeisberg, E.M., Potenta, S., Xie, L., Zeisberg, M. and Kalluri, R. (2007) Discovery of Endothelial to Mesenchymal Transition as a Source for Carcinoma-Associated Fibroblasts. *Cancer Research*, **67**, 10123-10128. https://doi.org/10.1158/0008-5472.CAN-07-3127

[31] Kalluri, R. and Weinberg, R.A. (2009) The Basics of Epithelial-Mesenchymal Transition. *Journal of Clinical Investigation*, **119**, 1420-1428. https://doi.org/10.1172/JCI39104

[32] Massague, J. (2008) TGF-β in Cancer. *Cell*, **134**, 215-230. https://doi.org/10.1016/j.cell.2008.07.001

[33] Trimmer, C., Sotgia, F., Whitaker-Menezes, D., Balliet, R.M., Eaton, G., Martinez-Outschoorn, U.E., Pavlides, S., Howell, A., Iozzo, R.V., Pestell, R.G., *et al*. (2011) Caveolin-1 and Mitochondrial SOD2 (MnSOD) Function as Tumor Suppressors in the Stromal Microenvironment: A New Genetically Tractable Model for Human Cancer-Associated Fibroblasts. *Cancer Biology & Therapy*, **11**, 383-394. https://doi.org/10.4161/cbt.11.4.14101

[34] Witkiewicz, A.K., Dasgupta, A., Sammons, S., Er, O., Potoczek, M.B., Guiles, F., Sotgia, F., Brody, J.R., Mitchell, E.P. and Lisanti, M.P. (2010) Loss of Stromal Caveolin-1 Expression Predicts Poor Clinical Outcome in Triple Negative and Basal-Like Breast Cancers. *Cancer Biology & Therapy*, **10**, 135-143. https://doi.org/10.4161/cbt.10.2.11983

[35] Witkiewicz, A.K., Dasgupta, A., Sotgia, F., Mercier, I., Pestell, R.G., Sabel, M., Kleer, C.G., Brody, J.R. and Lisanti, M.P. (2009) An Absence of Stromal Caveolin-1 Expression Predicts Early Tumor Recurrence and Poor Clinical Outcome in Human Breast Cancers. *The American Journal of Pathology*, **174**, 2023-2034. https://doi.org/10.2353/ajpath.2009.080873

[36] Pula, B., Wojnar, A., Werynska, B., Ambicka, A., Kruczak, A., Witkiewicz, W., Ugorski, M., Podhorska-Okolow, M. and Dziegiel, P. (2013) Impact of Different Tumour Stroma Assessment Methods Regarding Podoplanin Expression on Clinical Outcome in Patients with Invasive Ductal Breast Carcinoma. *Anticancer Research*, **33**, 1447-1455.

[37] Schoppmann, S.F., Berghoff, A., Dinhof, C., Jakesz, R., Gnant, M., Dubsky, P., Jesch, B., Heinzl, H. and Birner, P. (2012) Podoplanin-Expressing Cancer-Associated Fibroblasts Are Associated with Poor Prognosis in Invasive Breast Cancer. *Breast Cancer Research and Treatment*, **134**, 237-244. https://doi.org/10.1007/s10549-012-1984-x

[38] Martinez-Outschoorn, U.E., Pavlides, S., Whitaker-Menezes, D., *et al*. (2010) Tumor Cells Induce the Cancer Associated Fibroblast Phenotype via Caveolin-1 Degradation: Implications for Breast Cancer and DCIS Therapy with Autophagy Inhibitors. *Cell Cycle*, **9**, 2423-2433. https://doi.org/10.4161/cc.9.12.12048

[39] Orimo, A. and Weinberg, R.A. (2007) Heterogeneity of Stromal Fibroblasts in Tumors. *Cancer Biology & Therapy*, **6**, 618-619. https://doi.org/10.4161/cbt.6.4.4255

[40] Qiao, A., Gu, F., Guo, X., *et al*. (2016) Breast Cancer-Associated Fibroblasts: Their Roles in Tumor Initiation, Progression and Clinical Applications. *Frontiers of Medicine*, **10**, 33-40. https://doi.org/10.1007/s11684-016-0431-5

[41] Paulsson, J., Sjoblom, T., Micke, P., Ponten, F., Landberg, G., Heldin, C.H., Bergh, J., Brennan, D.J., Jirstrom, K. and

Ostman, A. (2009) Prognostic Significance of Stromal Platelet-Derived Growth Factor Beta-Receptor Expression in Human Breast Cancer. *The American Journal of Pathology*, **175**, 334-341. https://doi.org/10.2353/ajpath.2009.081030

[42] Pontiggia, O., Sampayo, R., Raffo, D., Motter, A., Xu, R., Bissell, M.J., Joffe, E.B. and Simian, M. (2012) The Tumor Microenvironment Modulates Tamoxifen Resistance in Breast Cancer: A Role for Soluble Stromal Factors and Fibronectin through β1 Integrin. *Breast Cancer Research and Treatment*, **133**, 459-471. https://doi.org/10.1007/s10549-011-1766-x

[43] Pavlides, S., Tsirigos, A., Vera, I., Flomenberg, N., Frank, P.G., Casimiro, M.C., Wang, C., Fortina, P., Addya, S., Pestell, R.G., *et al*. (2010) Loss of Stromal Caveolin-1 Leads to Oxidative Stress, Mimics Hypoxia and Drives Inflammation in the Tumor Microenvironment, Conferring the "Reverse Warburg Effect": A Transcriptional Informatics Analysis with Validation. *Cell Cycle*, **9**, 2201-2219. https://doi.org/10.4161/cc.9.11.11848