Diverting epithelial-to-mesenchymal transition to transform cancer cells to adipocytes: A promising strategy to stop metastasis

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Besides epigenetic and genetic alterations, cancer cell plasticity, characterized as the capacity of tumor cells to deviate dynamically between a differentiated state and an undifferentiated state, constitutes a significant mechanism playing a pivotal role in intra-tumor heterogeneity, survival, growth, invasion, metastatic potential and treatment resistance [1]. Epithelial-to mesenchymal transition (EMT), the process by which epithelial cells are transformed to mesenchymal cells, may induce tumor cell plasticity promoting drug resistance, metastatic dissemination and poor survival [2]. Whilst EMT is important in primary cancer cell invasion, its reverse process, mesenchymal-to epithelial transition (MET), plays a role in the metastatic outgrowth of tumor cells in distant tissues. Physiologically, EMT as well as MET contribute to embryogenesis, wound healing and organ fibrosis. However, both processes are tightly regulated to ensure tissue integrity and homeostasis. Because EMT and MET are clearly implicated in drug resistance and metastasis, targeting EMT (and MET)-associated pathways is considered an important therapeutic strategy in malignancies [3].

In an interesting study by Ishay-Ronen et al. in Cancer Cell, the researchers developed a new therapeutic approach using EMT [4]. In a time frame of cellular plasticity acquired during EMT, they diverted EMT by trans-differentiating metastatic breast cancer cells into mature, post-mitotic and functional fat cells through a combination of the anti-diabetic drug rosiglitazone (a selective and potent agonist of peroxisome proliferator-activated receptor γ, PPARγ) and Bone Morphogenetic Protein 2 (belonging to the transforming growth factor-β [TGF-β], BMP2) as shown in Fig. 1 [5]. PPARγ is a transcription factor which is expressed mainly in adipose tissue regulating genes involved in adipocyte differentiation, fatty acid uptake and storage, as well as glucose uptake. Most importantly, compared to their positive controls the 3T3-L1 cells, the adipocytes stemming from the EMT-transformed breast cancer cells represent bona fide fat cells in a post-mitotic cell cycle arrest. Notably, these fat cells presented comparable features with 3T3-L1 cells such as: 1) enhanced formation of intracellular lipid droplets; 2) expression of adipocyte markers C/EBPα, fatty acid binding protein 4 and PPARγ; 3) secretion of the adipokine adiponectin; 4) expression of RETN (resistin) observed in white adipose tissue and not UCP1 (Uncoupling protein 1 or thermogenin) which is expressed in brown adipose tissue; 5) similar transcriptomic profiles and fat cell metabolic signatures and 6) loss of mesenchymal phenotype [4]. Most importantly, these adipocytes were in post-mitotic cell cycle arrest and manifested decreased expression of oncogenic and enhanced expression of tumor-suppressive genes [4]. The presence of TFG-β, which is considered a potent inducer of EMT but negative regulator of adipogenesis, decreased the efficacy of the combination therapy (rosiglitazone plus BMP2). Nevertheless, in the presence of Transforming Growth Factor-β (TGF-β), the pharmacologic inhibition of MEK/ERK activation using a MEK-inhibitor, PD98059, enabled an efficient adipogenic process of EMT-transformed breast tumor cells (Fig. 1), potentiating thus a normal adipocyte function to such a degree that the addition of BMP2 was not important [4].

In in vivo short-term mouse models of breast cancer, the research team demonstrated that rosiglitazone in combination with a MEK-inhibitor decreased invasiveness and restricted tumor mass. The cancer-transformed adipocytes were mainly situated to the border between physiologic and cancer tissue, the exact location where tumor cells undergo EMT [4]. Furthermore, the cocktail treatment with rosiglitazone and trametinib, a FDA-approved MEK-inhibitor, has been shown to target transitioning invasive tumor cells with increased plasticity forcing them to transform into adipocytes and preventing the metastatic spread in mice implanted with GFP-expressing MDA-MB 231 LM2 human breast cancer cells prone to metastasize to the lungs [4]. The researchers reported a >10-fold decrease in lung metastases compared to controls which did not receive treatment [4]. Potential challenges of the proposed therapeutic strategy include its time duration, novel mechanisms of resistance, the role of the immune system [5] and the potential side-effects of rosiglitazone (and PPARγ agonists) [6].

In medical literature, very few examples can be cited where therapy was used for the differentiation of tumor cells. The most remarkable example is the use of all-tans retinoic acid which induces differentiation of immature granulocytes (promyelocytes) into mature granulocytes and apoptosis in acute promyelocytic leukemia, a subtype of acute myeloid leukemia which has been transformed from a highly fatal disease to a clinically more manageable one [7]. In carcinomas, there is a paucity of differentiation treatment to revert tumor cells to physiologic epithelial cells, which
can show decreased cell proliferation and elevated sensitivity to chemotherapy in preclinical models [5].

Therefore, the study by Ishay-Ronen et al. opens up a new window of cancer therapy for solid tumors by irreversible trans-differentiation of invasive mesenchymal tumor cells to mature adipocytes, and deserves further investigation and clinical translation.

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