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Chemotherapy-induced metastatic switch is mediated by extracellular vesicles expressing CD44

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Abstract:

Tumor cell heterogeneity is primarily dictated by mutational changes, sometimes leading to clones that undergo a metastatic switch. However, little is known about tumor heterogeneity following chemotherapy perturbation. Here we studied the possible involvement of tumor-derived extracellular vesicles, often referred to as tumor-derived microparticles (TMPs), as mediators of the metastatic switch in the tumor microenvironment by hindering cell adhesion properties. Specifically, we show that highly metastatic or chemotherapy-treated breast cancer cells shed an increased number of TMPs compared to their respective controls. We found that these TMPs substantially reduce cell adhesion and disrupt actin filament structure, therefore increasing their biomechanical force pace, further implicating tumor cell dissemination as part of the metastatic cascade. Our results demonstrate that these pro-metastatic effects are mediated in part by CD44 which is highly expressed in TMPs obtained from highly metastatic cells or cells exposed to chemotherapy when compared to cells with low metastatic potential.

Consequently, when we inhibited CD44 expression on TMPs by a pharmacological or a genetic approach, increased tumor cell adhesion and re-organized actin filament structure were observed. We also demonstrated that breast cancer patients treated with paclitaxel chemotherapy exhibited increased CD44-expressing TMPs. Overall, our study provides further insights into the role of TMPs in promoting metastasis, an effect which is augmented when tumor cells are exposed to chemotherapy.

Although significant progress has been made in the last decades towards the development of novel anti-cancer therapies for the treatment of advanced metastatic disease, most cancer types are still incurable, with metastasis being the main cause of death. In breast cancer, the most frequently diagnosed cancer in women, approximately half a million cancer deaths due to metastasis are reported per year. Although a minority of breast cancer patients are diagnosed with stage IV advanced metastatic incurable disease, approximately 30% of all breast cancer will develop metastasis within months and years after diagnosis. Metastasis is a multi-step process that includes cancer cell dissemination from the primary tumor, intravasation to the blood or lymphatic system, survival in the circulation, extravasation to a target organ, and seeding and proliferation at a distant site.

These effects require a tight regulation of the cellular machinery that supports tumor cell detachment from the primary tumor and their binding to the metastatic site. Microparticles have recently emerged as having a potentially significant role in tumor progression and metastasis. Microparticles belong to heterogeneous double layered membrane-coated particles exerted from cells, called extracellular vesicles (EVs). EVs encompass lipids, proteins, mRNA, non-coding RNA, and DNA. EVs have been mostly studied in the context of intercellular communication, whereby they transfer cargo between cells, including signaling proteins and RNA, as well as stimulate cells by membrane binding. There are three main family members of EVs: apoptotic bodies (1000–4000 nm in diameter), microparticles (100–1000 nm in diameter), and exosomes (20–100 nm in diameter). EVs have been shown to affect cancer progression in various ways. These effects are associated with integrins expressed by EVs, which direct them to specific organs. In melanoma, EVs derived from tumors contribute to the mobilization of myeloid cells to the pre-metastatic site and support metastasis. Such pre-metastatic niche formation has been recently reported to be enhanced in response to chemotherapy. At the primary tumor site, EVs promote tumor progression by transferring oncogenic proteins such as EGFRvIII between glioblastoma cells. Thus, EVs play a significant role in tumor growth and metastasis.

Metastasis is the main cause of death in cancer patients and is still a major obstacle for the success of therapy.

Biography:

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