ABSTRACT

The complex and dynamic process of tumorigenesis consists of three different stages such as initiation, progression, and metastasis. Each stage of tumorigenesis is supported by the surrounding stromal cells, extracellular matrix (ECM), and the physiological state of the tumor microenvironment (TME). Cancer-associated fibroblasts (CAF) occupy a vital and most prominent part of the TME in fostering tumorigenesis. Specifically, the dynamic interplay between the CAFs and the cancer cells is essential to stimulate the cancer heterogeneity, clonal evolution, and onset of chemoresistance in cancer cells ending in cancer cell proliferation and metastasis. Reciprocally, we find that cancer cells induce chemoresistance in cancer-associated fibroblasts. On continuous exposure of the conditioned media (CM) isolated from the breast cancer cells, we were able to induce the CAF characteristics in the normal human dermal fibroblasts. The resistant breast cancer cells were able to do so with great potential as compared to the parental cells. This is with concomitant increased secretion of TGF-β1 to the conditioned media from the resistant cells compared to the parental counterpart. The breast cancer cells through paracrine secretion of TGF-β1 stimulate epithelial to mesenchymal transition (EMT) in the neighboring CAFs. The resistant breast cancer cells have more potential to do so by upregulating the p44/42 MAPK signaling axis. In our second objective, we elucidated the significance of extracellular TGF-β1 in inducing autophagy and glycolytic surge in the CAFs. We found the marked upregulation of glycolysis in the hypoxic CAFs treated with TGF- β1. Synergistically, hypoxia and TGF- β1 induced autophagy in CAFs and concomitantly EMT. Mechanistically furthermore we observed that the autophagy in the CAFs promoted the glycolytic machinery of the CAFs via upregulation of MCT4, the membrane transporter. Blocking the TGF-β receptor and autophagy attenuated the glycolysis, EMT-like phenomena, and CAF phenotype in the CAFs. Finally, we have examined the role of exosomes, the extracellular vesicles secreted by the breast cancer cells in significant amounts in contributing to the remodeling of CAFs. We have isolated and characterized the exosomes from breast cancer cells in several established mechanisms. Therefore our studies may unlock new avenues for future studies and treatment options targeting the CAFs instead of cancer cell-centric formulation only. This may be helpful in understanding the reciprocal relationship between CAFs and cancer cells in inducing chemoresistance and strategically designing the CAF-specific therapeutics.

Keywords: Tumor microenvironment, Cancer-associated fibroblast, Breast cancer, autophagy, EMT, TGF-β, Chemoresistance, Hypoxia, and Exosomes.