ABSTRACT

Polyploid giant cells form a significant fraction of a chemoresistant cell population. These cells are generated in response to stress signals including anticancer treatments like chemotherapy and radiotherapy. Polyploid giant cells (PGCs) have been linked to a number of pro-tumorigenic properties like increased genomic instability, epithelial-mesenchymal transition, stemness, metastasis and chemoresistance. They exhibit senescence and release several cytokines and growth factors in the tumor microenvironment due to senescence-associated secretory phenotype. In this study, we have explored how these giant cells modulate other cancer cells in the tumor microenvironment. Chemoresistant cell lines were generated from parental breast cancer cell lines which showed better cell viability and enhanced cell survival due to a decrease in apoptotic tendency and increase in EMT. Polyploid giant cells developed from the chemoresistant cell lines exhibited senescence and showed an upregulation of senescence markers. The conditioned medium of PGCs induced a reduction in proliferation efficiency of breast cancer cells in a dose-dependent manner. PGCs inhibited the cell cycle progression at G1 phase as revealed by the cell cycle analysis and hypophosphorylated state of retinoblastoma protein. A protein expression profile showed downregulation of cyclin D1 which was upregulated at the mRNA level. Dephosphorylation of 4EBP1 and its master regulator mTOR was found to be responsible for reduced proliferation efficiency via cap-dependent translation inhibition of cyclin D1 in breast cancer cells. Reduced proliferation or tumor dormancy has been linked to cancer progression in the recent research. We found an upregulation of stemness markers and mesenchymal markers in the breast cancer cells after treatment with PGC-media. The PGC-media induced formation of larger colonies in soft agar colony formation assay. The Wnt pathway was found to be activated after treatment with PGC-media. Upon its inhibition, the tumorigenic potential of cells decreased along with reduced stemness and EMT. Hence, PGCs modulated the pro-tumorigenic properties of neighboring cells which could be responsible for tumor progression. Therefore, targeting polyploid giant cells can reduce their pro-tumorigenic effects thereby resulting in better treatment strategies. So an understanding of the interplay between polyploid giant cells and the tumor microenvironment needs some serious consideration.

Keywords: Polyploid Giant Cells, Tumor Microenvironment, Cell Proliferation, Cell cycle, Stemness, Epithelial-Mesenchymal Transition