Role of RHOA Signaling in Breast cancer metastasis

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Breast cancer refers to malignant tumours arising in breast tissues. In India, the cancer incidence has doubled in the last 26 years and breast cancer is the most common among them [1]. Metastasis is known to be a major contributor to the aforementioned tumour malignancy. Furthermore, dysregulation of cell signalling, cell cycle progression, and cell proliferation is among the major causes of tumour metastasis. GTPase family of proteins - one of the most studied enzymes which alter cell signalling – have been reported to be correlated with uncontrolled growth of cancer cells [2]. Rho-ROCK family members play a major role in cancer cell invasion and migration by facilitating cytoskeleton reprogramming and actin-myosin contraction. Therefore, to understand the role of RHOA signalling in proliferation, metastatic migration, and anoikis resistance, we proceeded to test different subtypes of breast cancer cells (TNBC, Triple positive, Luminal A, and HER2+). We administered Y27632 dihydrochloride exogenously to inhibit RHOA signalling. However, Y27632 treatment did not significantly affect the proliferation capability of the cancer cell in 2D but the reduction was seen in 3D culture. Further downregulation in $CD44^{+}/24^{-}$ population in MDA-MB-231 support the inhibitory role of Y27632 in proliferation. Intriguingly, the migration potential of the MDA-MB-231 and MCF7 in both 2D (wound healing assay), as well as 3D (spheroid migration assay), was observed to be upregulated upon treatment. In addition to that, the clonogenic potential of MCF7 and ZR75.1 was found to be upregulated when treated with Y27632 however no such effect was seen in MDA-MB-231 and SkBr3. Increased expression of β-catenin, p-ERK, and BCL2 in Y27632-treated cells grown in a non-adherent environment supports that Y27632 induces an anti-apoptotic pathway to increase cell survival. Thus, our results indicate that Y27632 has a context-dependent role in breast cancer and inhibition of the ROCK pathway may represent a novel approach for the treatment of breast cancer tumorigenesis and metastases.

Keywords: Breast cancer cells, metastasis, ROCK signaling, TNBC

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