Stromal Support by Mesenchymal Stem Cells in Breast Cancers.

Cecilia Sanchez*1, Patrice Penfornis*1, Adam Z. Oskowitz1, Aaron G. Boonjindasup1, David Z. Cai1, Brian G. Rowan3, Ameeta Kelekar4, Diane S. Krause5, and Radhika R. Pochampally1,2#

1Gene Therapy Center, 2Department of Pharmacology, 3Department of Structural and Cellular Biology, Tulane University Health Science Center, New Orleans, LA; 4Department of Laboratory Medicine and Pathology and Masonic Cancer Center, University of Minnesota, Minneapolis, MN; 5Department of Laboratory Medicine Yale University School of Medicine, New Haven, CT.

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Running title: MSCs secrete survival factors using autophagy
Abstract

Recent studies have implicated Multipotential Mesenchymal Stem Cells (MSCs) as an aid to breast cancer cell proliferation and metastasis, partly as a result of the MSCs secretome. The stromal support of MSCs in the nutrient deprived tumor core. In this study, we investigated the survival mechanisms used by stressed stromal cells in breast cancers. To address this question we used serum-deprived mesenchymal stem cells (SD-MSCs) and MCF-7 breast cancer cells as model system with a hypothesis that stromal cells in the nutrient deprived core utilize survival mechanisms for both self-survival and supporting cells around them. In this report, we show that SD-MSCs have better stromal support properties. They survive using, autophagy, a lysosomal-mediated process of cytoplasmic degradation to recycle nutrients, and secrete paracrine factors and that support tumor cells following nutrient/serum deprivation. SD-MSCs secreted anti-apoptotic factors as demonstrated in both in vitro cell culture and in chick embryo survival assays. Furthermore, in vitro co-culture assays and in vivo tumor xenografts in immunodeficient mice model showed that SD-MSCs supported MCF-7 breast cancer growth by protection from apoptosis. Western blot and immunochemistry analysis of SD-MSCs demonstrated upregulation and perinuclear relocation of autophagy key regulators such as Beclin-1, ATG10, ATG12, MAP-LC3 and lysosomes. Electron microscopic analysis detected a time-dependent increase in autophagosome formation in SD-MSCs. In addition, proliferation assays showed that SD-MSCs could proliferate in serum free medium and their migration ability increased. Taken together, these data suggest that under nutrient deprived conditions that can occur in solid tumors, stromal cells utilize autophagy for survival and also secrete anti-apoptotic factors that can facilitate solid tumor survival and growth.