**Suppression of Breast Cancer Cell Malignancy through Bystander Effect of Senescent Secretome of the Blind Mole Rat, Spalax: The Role of Non-Canonical Senescence-Associated Secretory Phenotype (SASP)**

Abstract: The subterranean blind mole rat, Spalax, has evolved intriguing mechanisms to counteract cancer by preserving genome stability and restraining the inflammatory response. Spalax has the unique ability to undergo senescence devoid of the senescence-associated secretory phenotype (SASP), characterized by the absence of key inflammatory mediators. Utilizing the potential paracrine impact of senescent Spalax fibroblasts we hypothesize that conditioned medium (CM) derived from these cells could facilitate the transmission of the senescent phenotype to cancer cells without eliciting an inflammatory reaction, thereby decrease malignant tendencies.

In an effort to unravel this phenomenon, we investigated the impact of Spalax CM on MDA-MB-231 and MCF-7 human breast cancer cells, focusing on proliferation, migration, and secretory profiles. Our findings reveal a complex interplay: Spalax CM induced senescence in cancer cells, as evidenced by increased senescence-associated beta-galactosidase (SA-β-Gal) activity, cellular arrest, and elevated expression of senescence-related p53/p21 genes. Simultaneously, Spalax CM exhibited the remarkable ability to attenuate the secretion of key inflammatory factors within cancer cells, alongside diminishing their migratory potential.

In contrast, when exposed to human fibroblasts CM, MDA-MB-231 cells displayed a slight elevation in SA-β-Gal activity, yet this failed to hinder proliferation, mitigate the inflammatory response, or restrict the migration of cancer cells.

The implications of our discoveries are significant, shedding light on the intriguing possibility of bypassing SASP in tumor cells by utilizing paracrine signals from the senescent microenvironment, or alternatively, by utilizing anti-cancer therapies. This pioneering senotherapeutic approach, which leverages the unique attributes of Spalax's senescent surroundings, paves the way for novel pathways to enhance cancer treatment strategies