Physical and Metabolic Aspects of Therapy Induced Senescence and Polyploidy in an Evolving Tumor Microenvironment

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Radiation and chemotherapy are highly effective at killing cancer cells but cells that survive treatment often develop therapy-induced senescence (TIS). Since growth is arrested in TIS, this has been considered a positive treatment outcome; however, senescent cells remain metabolically active and develop a senescence associated secretory phenotype (SASP), which can promote cancer progression. In addition, a small number of cancer cells are able to escape this dormant state to contribute to tumor recurrence and resistance. PGCCs are a novel and understudied subpopulation of dormant and multinucleated giant cancer cells that exhibit multiple features of TIS. Although PGCCs share many characteristics with senescent cells, including their large size, arrested cell cycle, and SASP, they also differ from senescent cells, in their ability to escape TIS by undergoing amitotic budding to form new tumors. Increased numbers of large PGCCs are seen in late stage and metastatic cancers; yet, there is a significant gap in our understanding of what allows PGCCs to survive chemotherapy and undergo budding to form chemoresistant and mitotic cancer cells. Through single cell, multicellular, and tissue level studies, we investigated how their cytoskeletal alterations, dysregulated metabolism, and inflammatory SASP contribute to PGCC survival during treatment. Our data suggests that their unique biophysical properties are linked to their dysregulated metabolism and altered cell structure. This presentation will focus on our recent work investigating the role of TIS on cancer and stromal cell interactions in the tumor microenvironment. These studies provide critical information about how aging and TIS affect tumor microenvironments.