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Biophysics of polyploidal cancer cells in an aging stroma

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Senescence is a potent tumor-suppressive mechanism that irreversibly arrests the growth of damaged cells. However, senescent cells that accumulate in tissues eventually develop a senescence-associated secretory phenotype (SASP) that alters the microenvironment to promote cancer. Paracrine factors in the SASP may also contribute to the formation of rare giant polyploidal cancer cells (GPCCs). A single-cell mechanical approach was used to profile cytoskeletal and nuclear mechanics, morphology, motility, and adhesion for breast cancer cells treated with conditioned media from senescent fibroblasts. Our study showed that a small but significant population of MDA-MB-231 breast cancer cells (less than 5%) treated with conditioned media from senescent LF-1 fibroblasts develop an enlarged morphology, chromosomal instability, and polyploidy, a phenotype associated with GPCCs. Although GPCCs are highly invasive and chemoresistant, little is known about their biophysical properties. First, we developed a method for identifying the small subpopulation of GPCCs in a heterogeneous population of cancer cells based on increased nuclear area and confirmed that GPCCs are more resistant to Paclitaxel than normal size MDA-MB-231 cells (NCCs). We then compared critical biophysical properties of NCCs and GPCCs, including cytoskeletal and nuclear mechanics, cell and nuclear morphology, motility, and adhesion. Cells were stained for cytoskeletal proteins actin, tubulin, and vinculin. Cytoskeletal organization was dramatically altered in GPCCs compared to NCCs. GPCCs displayed more disorganized microtubule structure, dense actin stress fibers, and mature focal adhesions. Intracellular particle tracking microrheology was used to measure cytoskeletal and nuclear mechanics. These studies demonstrated that although GPCCs are thought to be highly invasive cancer cells, they are inherently stiffer than NCCs, both in terms of their cytoskeletal and nuclear mechanics. This was surprising since more invasive cancer cells are often more compliant than less invasive cancer cells. This result may be in part to the ability for GPCCs to behave like activated stromal cells that stiffen in the tumor; we confirmed that GPCCs display similar adhesive behavior as activated stromal cells. To determine how mechanics correlates with cell migration, we used time-lapse nuclear tracking to measure cell motility. The average cell speed was higher for NCCs than for GPCCs; however, GPCCs moved longer distances over time because their motion was more directional. These findings highlight the unusual biophysical behavior of GPCCs. To develop pharmacological tools that target GPCCs, it is imperative to understand their biophysical properties.