TITLE

Tumor cell persistence after stress induces tumor stem cell functions: Implication for drug resistance and tumor recurrence.

ABSTRACT

Recurrence of tumor after chemotherapy or radiotherapy impedes successful cancer treatment. Experimental and clinical studies suggests for a possible selection of drug resistant cells with tumor stem cell like properties after chemotherapy. We have employed experimental cell and animal models to understand the key regulators involved in the cell transitions that reveal that quiescence persister cell population remaining after drug treatment, rarely enters in to cell cycle that subsequently generates distinct and functionally different cell population. Real time imaging of functional features revealed temporally regulated dynamic phenotypic alterations within the emerging population. RNA sequencing of diverse cell population involved in the process allowed us to understand the complex passive and driving molecular events of drug escape and re emergence. Interestingly, the immediate drug escape is even evident in cells treated with extremely higher dose of diverse anticancer agents assisted through an unusual secondary acquisition of cells with increased autophagy and mitophagy, coupled with activation of the redox regulator Nrf-2. This molecular switch prepares a fraction of cells to enter into chronic autophagy followed by Parkin dependant mitophagy /actinophagy that ultimately generates cells with increased heterogeneity. Using stable cancer cells expressing redox sensor allowed us to detect and quantify spontaneous emergence of cells with low intracellular ROS through parkin dependent mitophagy. The identification of unexpected key primary regulators that allow long term survival of persister cell population and secondary regulators that help the persisters to enter in to cell cycle offers new possibilities in preventing drug escape and emergence of drug resistance.