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The origin and mathematical characterization of cancer stem cells based on computer simulated tumor development in uterine epithelium

We have developed a mathematical model of human endometrial cancer previously (Dai et al PLoS 2011, v6:e16859). The information of peak epithelial tissue size, and the time of proliferation for a single stem cell to form a clone in human uterine epithelium, provides the basis for simulating the normal tissue regeneration process and has allowed us to develop some preliminary criteria, such as the number of stem cells committed every day and the normal life cycle of a committed epithelial cell before senescence. Based upon the mathematical description of the process of normal tissue regeneration involving billions of cells in the uterine epithelium, we have simulated the cancer incidence as a result of quantitative interactions of genetic alterations and environmental factors occurring in the human uterine epithelium, leading to a result consistent with the epidemiological data. The tumors created by computer simulations have allowed us to analyze their entire development process and the etiological dynamics associated with that process in order to understand the origin of a model tumor and its intra-tumor heterogeneity.

Based upon the commonly accepted concept that a malignant tumor is monoclonal in origin and upon analysis of the phylogenetic lineage of individual cells in each of approximately 80 simulated tumors, we developed a simple mathematical characterization of a cancer cell in relation to the parameters established for the description of normal cell development. We found that the cancer ancestor cells (the first cancer cell that eventually forms the entire tumor) have varying degrees of loss of differentiation and, consequently, growth potential. The first cancer cell is typically formed after 17 divisions of effectively normal cells and has a differentiation score of 0.3 versus a score of 4.0 for a terminally differentiated cell. Thus, the cancer ancestor cell under this characterization is very similar in differentiation status to cancer stem cells, completely undifferentiated cells.

Among all simulated tumors we analyzed, all cancer stem cells are created through the de-differentiation process from well-differentiated cells as well as the result of further de-differentiation of cancer cells. The probability of a cancer stem cell resulting from direct transformation from a tissue stem cell is very low, since our simulation has not detected any case of direct transformation among the 80 simulated tumors.

We have found that the conversion between cancer stem cells and cancer cells through differentiation and de-differentiation under hormone influence is dynamic with a varying rate, resulting in dramatically different sizes of cancer stem cell pool in individual tumors. While the difference in cellular differentiation between a typical cancer cell and cancer stem cell is very small, there is a significant difference in their potentials to create a mass themselves, and the most significant difference lies in their capability to establish metastatic lesions in ectopic sites. A cancer stem cell after surviving the metastatic process will have a significantly higher probability to form metastatic lesions.

The modeling of solid tumor formation in normal uterine epithelium has provided some insights into the role of cancer stem cells in the oncogenic process and tumor progression.