

TITLE

Autonomous and reciprocal mechanisms of cellular heterogeneity in oral tumors

ABSTRACT

In India, oral cancer accounts for over 30% of all cancers. In terms of incidence rate, it ranks number one among men and third among females. Despite of the improvement in the standard treatment strategies, the 5-years survival rate has remained around 50% since decades. This rate further drops for those patients who are detected with loco-regional metastasis to lymph nodes or extra nodal spread. These distinctive features emphasize the need for carrying out in-depth studies on heterogeneity in oral tumors to understand overall tumor behavior. The 'cancer stem cell model' provides a framework to conduct such studies. We have correlated cellular phenotype of cells with functional properties like cell proliferation, migration and drug resistance. Heterogeneous subpopulations of cells demonstrated stem cell-like properties including long-term proliferation ability, self-renewing capacity and expression of stem cell markers in a subset of cells with high aldehyde dehydrogenase activity. Based on the hierarchical organization driven by 'spontaneous transitioning' of cellular phenotypes, we proposed a novel developmental relationship for generating functionally heterogeneous subpopulations of cells within oral tumors. Adding to the complexity, we further found a nonautonomous mechanism in driving heterogeneity. Stromal fibroblasts established from oral tumor microenvironment were found to be of distinct subtypes, based on the expression of α SMA-stress fibers and unique gene expression pattern. Overall, we demonstrated that cell-autonomous process in mutated cancer/stem cells as well as reciprocal interplay with the niche cells to be responsible for causing heterogeneity in oral cancer.