Molecular mechanisms driving MYC-mediated cell competition in a colon cancer model

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Cell competition is a mechanism through which weaker cells are recognized by their fitter neighbors and eliminated through apoptosis. It is important to detect and eliminate these cells, to maintain healthy tissues and prevent the development of diseases. However, cells can acquire alterations, such as upregulation of MYC, increasing the relative fitness and inducing the elimination of neighbor wild-type cells. Here, we optimized a cell competition assay to screen for genes involved in this mechanism in winner and loser cells using two colon cancer cell lines expressing different levels of MYC. We observed that LoVo and LS174 engage in cell competition, with LoVo behaving as loser and LS174 behaving as winner, as previously reported. In this scenario, loser cells are eliminated by apoptosis in a caspase-dependent manner, arrest cell cycle at G0/G1 phase and migrate less. On the other hand, winner cells are even less eliminated when in presence of loser cells, increase the number of cells entering S phase and start to migrate more. Also, results from conditioned media and caspase-inhibition experiments suggest that improved survival and increase proliferation of winner cells is based on the presence of a survival factor in culture media, whereas cell elimination of the loser cells is dependent on cell-cell contact with winner cells. In addition, treatment with a chemotherapy agent abolish competition and loser cell elimination suggesting potential therapeutically translation of results. To identify new genes involved in this cell competition scenario we have performed RNA-sequencing of winner and loser cells. We found three genes upregulated in winner cells, *AQP3*, *MYT1* and *NRIP1*, which were functional validated to be required for the elimination of the loser cells. Additionally, members of the PI3K/AKT/mTOR and HER2/EGFR pathways were found to be altered. These data improves our knowledge on cell competition and its role in cancer development.