Escaping from oncogene induced senescence: Role in cancer

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Oncogene induced senescence (OIS) is activated by the coordinated action of the DNA damage response (DDR) pathway and ARF, alternatively to apoptosis, in early stages of cancer, preventing transformation of incipient cancer cells. Progression to cancer requires antitumor barrier bypass and occurs when critical DDR and ARF pathway components like p53 are impaired, fueling genomic instability. This explains the frequent p53 mutations in cancer and how apoptosis results in "clearance" of incipient cancer cells while escape from OIS, which is a viable state, remains an uncharted territory.

Detection of senescence is of paramount importance, especially *in vivo*, as it plays a bimodal role in cancer and seems to be related to prognosis. Moreover, estimations on the outcome of senotherapeutics that target senescent cells require a reliable senescence biomarker. Until recently, available methods failed to accurately recognize senescent cells *in vivo*. This conundrum was lately addressed by the development of an innovative biotinylated Sudan Black-B (SBB) analogue (SenTraGorTM) and hybrid histochemical/immunohistochemical method, that allows detection of senescent cells in any biological material (including archival one).

As shown for the first time *in vivo*, using the SenTraGorTM methodology, senescence occurs in primary human malignancies and is related to adverse clinical outcome. This might be attributed either to the pro-tumorigenic effect of SASP or to the fact that neoplastic cells "trapped" in senescence exhibit tolerance against classical antitumor strategies and can subsequently escape from senescence. In this context, tumor relapses and a worse clinical outcome may occur rendering their elimination in primary lesions, as a complementary strategy, an attractive perspective.

To examine these issues and to recapitulate the *in vivo* findings *in vitro*, we developed prototypical cellular OIS models. Various manipulations that resulted in aberrant chronic stabilization of the replication licensing factors Cdc6 and/or Cdt1 led to an evolutionary recapitulation of cancer development. Initially, a senescence-like state was observed, characterized by replication stress, DNA-damage and an error-prone DNA repair process that eventually altered the genome. Following, a subpopulation of cells emerged that re-entered the cell cycle. Interestingly, these "escaped" cells exhibited aggressive features and increased chemo-resistance, while epithelial derived ones underwent epithelial to mesenchymal transition.

These findings have uncovered an unprecedented mode of how oncogenes drive cancer development, through escape from senescence, providing also new opportunities for cancer treatment.