Is cellular senescence a prerequisite for tumor invasion?

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Epithelial-mesenchymal transition (EMT) and tumor invasion allowing cancer cells to degrade extracellular matrices are crucial events in metastasis dissemination, yet poorly understood. Premature senescence, defined as a stable G1 cell cycle arrest within oxidative stress, the main inducer, is often considered as a mechanism of protection against cancer. Nothing is presently known about how senescence could be linked to tumor invasion and senescence pathways activation has not been reported yet as a prerequisite to cancer invasion. Metastatic and invasive programs are limited by NM23-H1/NME1, the first discovered metastasis suppressor but the mechanisms involved remain unknown. The general goal of this project is to combine experimental and computational approaches to establish and understand the link between senescence and tumor invasion in cancer cells, while highlighting the role of NM23-H1/NME1 in this process. By using human tumoral cell lines endowed with different invasive properties and tumor samples, we show that genetic modulations of NM23-H1 (overexpression/depletion) regulate mitochondrial production of the reactive oxygen species (ROS) and the resulting cellular senescence process. In addition, we have observed that the invasive program of low NM23-H1 cells is significantly reduced in the presence of ROS scavenger. Strikingly, in samples of human colorectal tumors, we observed a senescent phenotype in the tumor budding region i.e a dedifferentiated region with EMT characteristics as compared to the well-differentiated central area. Accordingly, samples of human colorectal cancer of high grade (grade IV) strongly expressed senescence markers as compared to low grade (grade I), associated with a dramatic downregulation of NM23-H1. We constructed a comprehensive signaling network map to systematically represent the knowledge from the scientific literature about these molecular mechanisms and retrieve an explanation for the experimental observations as above and decipher the role of NM23-H1 with respect to senescence and invasion. In particular, we depicted the pathways involved in oxidative stress, senescence, EMT and invasion while focusing on NM23-H1 impact. The map contains around 700 proteins, 1500 reactions, 11 functional modules and it is based on approximately 1400 scientific papers. We performed structural analysis of the network to retrieve models explaining the interplay between oxidative stress, senescence and invasion with respect to the NM23-H1 protein. This work will help to a better understanding of the molecular bases of the invasive program and will permit to design new diagnosis or treatment strategies against metastatic spread. We could indeed give some new answers regarding the possibility to kill senescent cells using senolytic molecules in case of a cancer in order to improve current cancer treatment.