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Identificación del proyecto

Redirection of T Lymphocytes Against Senescent Cells to Treat Breast Cancer

Descripción del proyecto

Cellular senescence is a terminal cell cycle arrest induced by different stresses, including oncogenes or certain anti-tumor therapies. The effect of cellular senescence on tumor progression remains a contentious issue. While some reports show that it is a tumor defence barrier, others show that senescent cells contribute to tumor progression. This lack of clarity is probably due, at least in part, to the shortage of accurate experimental models. Mechanistically, senescence is caused by high levels of the cyclin-dependent kinases inhibitors p16 or p21, and it is characterised by the secretion of a wealth of inflammatory factors, the Senescence Associated Secretory Phenotype (SASP), which almost invariably includes interleukin-6 (IL-6). In this proposal, we propose to monitor the accumulation of senescent cells and investigate the effect of their elimination (senolysis) at different stages of breast cancer progression, and after different anti-cancer treatments.

To accomplish this goal, we have generated a unique transgenic mouse model (SuSe mice) that allows detection and clearance of cells expressing high levels of p16 and IL-6, and a panel of Senescence-Reporter breast cancer Patient-Derived Tumor Xenografts (Sen-R-PDXs). Preliminary data show that senescence in premalignant lesions is anti-tumorigenic. In contrast, senescent cells in fully-blown carcinomas have a remarkable protumorigenic effect. We plan to expand these observations to additional models and tumor stages.

Further, we will develop a senolytic therapeutic strategy based on the generation of antibodies against specific cell surface factors of breast cancer senescent cells and the development of T-Cells Bispecific Antibodies (TCB). Despite the strengths appreciated by the reviewers, the proposal was rejected last year but resubmission was invited, We have addressed all the concerns expressed on the previous version. In summary, if funded, with this proposal we will determine the therapeutic window of senolysis to treat breast cancers and we will develop novel TCB-based senolytic strategies.

Financiación

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Importe

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