**Targeting senescence in Lymphangioleyomyomatosis through senomorphic-like molecules as a paradigm to counteract senescence in lung tumor microenvironment**

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Lymphangioleiomyomatosis (LAM) is a pulmonary low-grade, destructive, metastasizing rare neoplasm occurring in young women as a sporadic disorder or in association with tuberous sclerosis complex (TSC, LAM/TSC). Distinctive of LAM cells are the metastatic capability, the dysregulated mechanistic Target Of Rapamycin (mTOR) and the active secretion of factors that shape the lung parenchyma to create a LAM-favoring microenvironment without the formation of solid masses. While there is no cure for LAM, the only approved pharmacological treatment is the selective inhibitor of mTOR Complex 1 (mTORC1) rapamycin. mTORC1 triggers senescence and, in particular, induce the Senescent Associated Secretory Phenotype (SASP), through which cells reinforce their senescent phenotype and promote senescence in neighbouring cells, a phenomenon that might induce a tumor-sustaining microenvironment. Using LAM as an intriguing paradigm to study how cells establish a tumor favoring microenvironment prior to cancer cells colonization, the aim of this study is the impairment of LAM destructive feature through molecules that might interfere with SASP. In an *in vitro* model of human pulmonary microenvironment, we demonstrated that primary LAM/TSC cells are senescent depending on mTOR hyperactivation and induce senescence in non-LAM pulmonary lung fibroblasts (PLFs) through their conditioned medium. Senescence inducing correlates with the expression and secretion of Interleukin 8 (IL-8), one of the main SASP factor with an important role in lung cancer progression and metastasis. We demonstrated the possibility to counteract both the autocrine senescence in LAM/TSC cells and the development of paracrine senescence in PLFs by inhibiting the IL-8 receptor CXCR2 with the non-peptide small molecule SB225002. Moreover, this treatment impairs the migratory capability of LAM/TSC cells. Finally, as the expression of SASP genes can be regulated by the histone deacetylase p300, whose activity is enhanced by mTOR, we demonstrated the impairment of senescence induction by LAM/TSC cells in PLFs treated with the p300 inhibitor CCS1477. In conclusion, our results indicate that the modulation of senescence with senomorphic-like molecules targeting mTOR downstream effectors and non-mTOR regulated mechanisms is an intriguing novel pharmacological approach to interfere with the pathological communication in LAM microenvironment, with possible future application in lung cancer therapy.