Talk

Modulation of the Tumor Microenvironment in Pancreatic Cancer

Sierra Jiménez, María (1), Díaz Contreras, Irene (1), Rojas González, Anabel* (1)

Centro Andaluz de Biología Molecular y Medicina Regenerativa (CABIMER), Avda. Américo Vespucio 24. Parque científico y Tecnológico Cartuja, 41092, Sevila, España

Tutor académico: Rojas González, Anabel

Keywords: TME; PSC; GATA6

ABSTRACT

Motivation: Pancreatic cancer is one of the most aggressive malignancies, with a five-year survival rate below 5%. Tumor microenvironment (TME) plays a key role in tumor progression, promoting cell proliferation, angiogenesis, and immune system evasion. Pancreatic stellate cells (PCSs) play a major role in this TME. Normally, PSCs are quiescent and store vitamin A in lipid droplets and regulate extracellular matrix (ECM) homeostasis. Upon activation by tumor-derived signals, they lose lipid droplets, gain a myofibroblast-like phenotype, overexpress α-smooth muscle actin (α-SMA) and increase production of ECM (collagens, laminin, etc.). Activated PSCs can facilitate cancer progression by interacting with pancreatic cancer cells and other cells in the TME, which in turn leads to excessive fibrosis, promotes tumor metastasis, induces chemo-radio resistance, and contributes to immunosuppression [1]. The inactivation of PSCs is a promising approach to target pancreatic cancer. Pancreatic and hepatic stellate cells share many features. Previous studies from our lab have shown that the transcription factor GATA4 induces the inactivation of hepatic stellate cells (HSC) [2]. In this work we show that another member of the GATA transcription factor family, GATA6, is a regulator of PSCs phenotype, inducing the reversion towards an inactive state.

Methods: GATA6 was overexpressed in PSCs via adenoviral infection to evaluate its role in reversing activation. Protein expression was assessed by Western blot, and immunocytochemistry analysis were used to analyze α-SMA, laminin and collagen expression. RT-qPCR was performed to quantify gene expression changes, and Oil Red staining was used to evaluate lipid droplet accumulation.

Results: Western blot and immunocytochemistry showed that GATA6 overexpression reduced α-SMA levels, indicating the inactivation of PSC. Immunocytochemistry analyses also confirmed the inactivation by GATA6, displaying a decrease in laminin expression. RT-qPCR and Oil Red staining have not yet provided conclusive data.

Conclusions: These preliminary results suggest that GATA6 may play an important role in the regulation of PSC activation, as the reduction of key activation markers such as α-SMA indicates a potential for GATA6 to revert PSCs phenotype. This could provide new insights into therapeutic strategies for modulating the fibrotic TME and improving treatment responses in pancreatic cancer.

REFERENCES

[1]Jin G, Hong W, Guo Y, Bai Y, Chen B. Molecular Mechanism of Pancreatic Stellate Cells Activation in Chronic Pancreatitis and Pancreatic Cancer. J Cancer. 2020 Jan 14;11(6):1505-1515. doi: 10.7150/jca.38616. PMID: 32047557; PMCID: PMC6995390.

[2]Arroyo N, Villamayor L, Díaz I, Carmona R, Ramos-Rodríguez M, Muñoz-Chápuli R, Pasquali L, Toscano MG, Martín F, Cano DA, Rojas A. GATA4 induces liver fibrosis regression by deactivating hepatic stellate cells. JCI Insight. 2021 Dec 8;6(23):e150059. doi: 10.1172/jci.insight.150059. PMID: 34699385; PMCID: PMC8675192.