Cholangiocyte Senescence in Primary Sclerosing Cholangitis (PSC)

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Introduction

Primary Sclerosing Cholangitis (PSC) is an incurable etiopathogenetic disease of the cholangiocytes (bile ducts). Cellular senescence (CS) is an important marker for cholangiocytes in patients with PSC. Increased CS is caused by activated phenotypes of stromal fibroblasts.. In vitro, the activity of B-cell lymphoma extra large (Bcl-xL) could be inhibited by the introduction of a molecule called B-cell lymphoma 2 (Bcl-2) homology domain 3 memitic. This caused apoptosis in platelet-derived growth factor (PDGF) activated fibroblasts. This led us to the hypothesis that the absence of Bcl-2 would cause the activated fibroblasts to be dependent on other apoptosis-resistant proteins for survival [1].

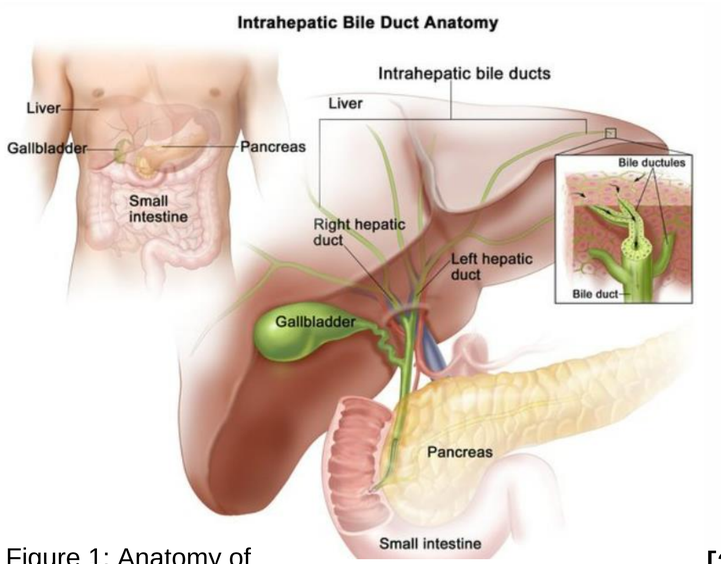

Figure 1: Anatomy of intrahepatic bile ducts [2]

Methods

Naïve fibroblasts were activated by an injection of 50 ng/mL of recombinant human PDGF-BB.

In vitro, the activated fibroblasts were induced to apoptosis by treatment for a duration of 24 hours with the following compounds: 1 μM of navitoclax (target: Bcl-2 and Bcl-xL), 1 μM of A-1195424 (target: Bcl-2), 1 μM of A-1331852, 1 μM of A-1331852 (target: Bcl-xL), and 10 μM of A-1210477 (target: Mcl-1).

In vitro, normal human cholangiocytes (NHCs) were induced to senesce with treatment of 10 J/kg of ionizing radiation, then with the injection of 1 μM of A-1331852 48 hours after treatment.

Coculture and in-situ experiments were done in addition, with different explanatory variables being utilized. These data represent three independent experiments, expressed as the average +/- standard deviation.

A two-tailed t-test assuming unequal variance was used [1].

Results

It was found that senescent cholangiocytes show changes in how Bcl-2 protein is displayed, and are affected by inhibition of the Bcl-xL protein. A Western Blotting experiment showed that in senescent cholangiocytes, Bcl-xL is up-regulated, whereas in non-senescent cholangiocytes, Bcl-2 and Bak remain unchanged [1].

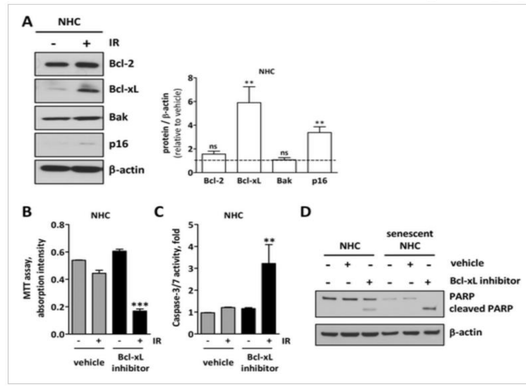

Figure 2: Western Blot showing up-regulation of Bcl-xL in senescent cholangiocytes, and a apoptotic sensitivity to Bcl-xL inhibitor, A-1331852

Conclusion

The Bcl-xL protein is key for the survival of senescent cholangiocytes. Inhibition of this protein with A-1331852 causes a reduction in liver fibrosis, through the mechanism of action triggered by the effect on both activated fibroblasts and senescent cholangiocytes [1].

References

[1] Moncsek, A., Al-Suraih, M. S., Trussoni, C. E., O'Hara, S. P., Splinter, P. L., Zuber, C., … Mertens, J. C. (2017). Targeting senescent cholangiocytes and activated fibroblasts with B-cell lymphoma-extra large inhibitors ameliorates fibrosis in multidrug resistance 2 gene knockout (Mdr2-/- mice). Hepatology, 67(1), 247–259.

[2] Primary sclerosing cholangitis. (n.d.). MedlinePlus.