CHARLES UNIVERSITY

Faculty of Pharmacy in Hradec Králové

Department of Biological and Medical science

Carotuximab effect on endoglin expression and signaling in liver fibrosis

Diploma thesis

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Abstract

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Title of the thesis: Carotuximab effects on endoglin expression and signaling in liver fibrosis

Objective of the thesis

Endoglin is a 180 kDa transmembrane glycoprotein that acts as a coreceptor for binding to the Transforming growth factor β (TGFβ) superfamily and is found in two forms in the blood: membrane endoglin (Eng) and soluble endoglin (sEng) circulating in the blood. It has been demonstrated that Eng might play an important role in the process of liver fibrosis, inflammation, and endothelial dysfunction. According to different studies, Eng can have prefibrotic or antifibrotic activity. The precise impact of Eng expression and signalling changes, and sEng levels during liver disorders are still unknown. Carotuximab, TRC105 (chimeric IgG1), is a therapeutic monoclonal antibody that binds to Eng and influences its expression, signaling, and sEng levels. In experimental liver fibrosis and inflammation, we hypothesize that **c**arotuximab prevents liver alterations by modulating Eng and sEng.

Methods

The liver damage was induced in three-month-old C57BL/6 male mice by 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) diet while control animals were received a standard chow diet. The TRC105 group was administrated with **c**arotuximab (15 mg/kg) twice a week while control animals were administrated with physiological solution, followed by sacrificing the mice after four weeks with subsequent blood collection and molecular analysis of liver samples. Alanine transaminase (ALT)**,** total bilirubin (TBIL) levels were determined by biochemical analysis and the liver samples were collected for the western blot.

Results

The liver impairment and fibrosis in DDC mice were confirmed by the significant increase in the level of ALT**,** TBIL and increased ratio of liver to the body weight. Although the DDC diet significantly increased sEng levels and MMP-14 expression, there was a significant reduction in the expression of Eng in the liver. However, in all analyses, there was no statistically significant difference between the TRC105-administered group and the DDC diet-only group.

Conclusion

DDC diet results in cleavage of Eng by MMP-14 leading to high levels of sEng. Thus, sEng might be considered a circulating biomarker of liver damage after DDC treatment. However, TRC105 treatment itself does not have significant effect on the Eng expression in liver fibrosis in the DDC diet.