ABSTRACT

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Training Workplace	Department of Biological and Medical Sciences
Doctoral Degree Program	Pharmacology and Toxicology
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Title of Doctoral Thesis	Modulation of cholesterol and bile acid metabolism via soluble endoglin and pharmacotherapy

Endoglin (Eng, CD105) is a transmembrane glycoprotein and co-receptor of the Transforming growth factor-β (TGFβ) receptor complex. Upregulated expression of Eng has been implicated in endothelial dysfunction, liver impairment, and hepatic fibrosis development. When Eng is cleaved by the matrix metalloproteinase-14 (MMP14), its soluble form termed soluble endoglin (sEng, sCD105) is released into the circulation. Increased plasma levels of sEng have not only been observed in patients with cardiovascular and metabolic diseases associated with hypercholesterolemia (e.g., atherosclerosis) but have also been reported to promote conditions of the metabolic syndrome (e.g., hypertension). However, the direct role of sEng in the modulation of hepatic metabolism and liver functions under physiologic or pathological conditions has not been previously explored. Therefore, this doctoral thesis aimed to test the hypothesis that sEng plays a role in the modulation of cholesterol and bile acids (BA) metabolism and entero-hepatic turnover in healthy liver and hepatic liver disease and that sEng levels in circulation may be modulated by pharmacotherapy.

The results obtained in the thesis showed that healthy mice overexpressing human sEng present increased hepatic accumulation of cholesterol and increased hepatic availability of BA, as well as increased plasma concentration of BA by upregulated ileal reabsorption into enterohepatic circulation, as a consequence of complex changes in the expression of responsible liver and ileal transporters. Moreover, increased sEng levels were observed upon nonalcoholic steatohepatitis (NASH) development, and an additional rise in circulating sEng levels results in increased hepatic accumulation of cholesterol and triglycerides. This suggests the possibility of sEng being not only a biomarker of NASH but also that sEng may have a role in impairing essential mechanisms against cholesterol and triglycerides accumulation.

In conclusion, this thesis contributed to the understanding of sEng's unfavorable role in the modulation of cholesterol and BA homeostasis in the liver. Thus, we may suggest that sEng may be a possible biomarker of liver damage with a direct role in liver impairment and that sEng levels should be taken into account in patients prone to develop hepatic pathologies.