SOCS-3 induces PCSK9 expression in hepatic HepG2 cell line

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The suppressor of cytokine signaling (SOCS) proteins are negative regulators of the JAK/STAT pathway activated by pro-inflammatory cytokines. SOCS3 is also implicated in hypertriglyceridemia-associated to insulin-resistance (IR). Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) levels are frequently found to be positively correlated to IR and plasma very low-density lipoprotein-triglycerides concentrations. The present study was aimed to investigate the role of SOCS3 on *de novo* lipogenesis, cholesterol biosynthesis and PCSK9 expression in human HepG2 cell line. To resemble a condition of chronic-inflammation (characterized by SOCS3 activation), we first stimulated HepG2 cells with tumor necrosis factor (TNF)-a and then generated a HepG2 cell line overexpressing SOCS3 ($HepG2^{SOCS3}$). TNF-a induced both SOCS3 and PCSK9 expression in HepG2 cells and SOCS3 overexpression determined a complete abrogation of STAT3 phosphorylation. This latter condition was associated to activation of *de novo* lipogenesis (induction of fatty-acid (FA) synthase mRNA by 3.59±0.40 fold; stearoyl-CoA desaturase mRNA by 1.92±0.12 fold; and apolipoproteinB secretion by 3.47±0.09 fold). $HepG2^{SOCS3}$ cells express higher levels of PCSK9 mRNA (3.48±0.35 fold) and protein secretion (2.18±1.13 fold) with no effect on its transcriptional activity. No relevant changes of HMG-CoA reductase, low-density lipoprotein receptor levels and cholesterol biosynthesis were found. Insulin stimulation further induced FA synthase and PCSK9 mRNA levels to a similar extent in control and SOCS3-overexpressing cells, although the overall mRNA levels of PCSK9 and FA synthase were significantly higher in $HepG2^{SOCS3}$ cells. In conclusion, the present study provides evidence for the JAK/STAT dependent expression of PCSK9 in hepatic cell line, suggesting the potential molecular basis of the direct relationship between PCSK9 and triglycerides levels observed in clinical settings.