

SOCS-3 induces PCSK9 expression in hepatic HepG2 cell line*

Massimiliano Ruscica¹, Chiara Ricci¹, Chiara Macchi¹, Paolo Magni^{1,3}, Alberto Corsini^{1,2}, and Nicola Ferri^{1,2}

¹Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, Milan, ITALY; ²Multimedica IRCCS, Milan ITALY; ³Centro per lo Studio delle Malattie Dismetaboliche e delle Iperlipemie - Enrica Grossi Paoletti, Università degli Studi di Milano, Milan, Italy.

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)- α and then generated a HepG2 cell line overexpressing SOCS3 (HepG2^{SOCS3}). TNF- α 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 \pm 0.40 fold; stearyl-CoA desaturase mRNA by 1.92 \pm 0.12 fold; and apolipoproteinB secretion by 3.47 \pm 0.09 fold). HepG2^{SOCS3} cells express higher levels of PCSK9 mRNA (3.48 \pm 0.35 fold) and protein secretion (2.18 \pm 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.