SOCS-3 induces Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) expression in hepatic HepG2 cell line: a potential link between hypertriglyceridemia and insulin resistance

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Background: Obesity is characterized by low-grade chronic inflammation, elevated circulating cytokines, and hepatic overexpression of suppressor of cytokine signaling (SOCS) proteins, which are negative regulators of the JAK/STAT pathway activated by pro-inflammatory cytokines, including the tumor necrosis factor-alpha (TNF-alpha). SOCS3 is also implicated in hypertriglyceridemia associated to insulin-resistance (IR) (1). Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) levels are frequently found to be positively correlated to IR and plasma very low-density lipoprotein-triglycerides (VLDL-TG) concentrations (2). **AIM**: To investigate, in a condition of IR, the role of SOCS3 on *de novo* lipogenesis, cholesterol biosynthesis and PCSK9 expression in human HepG2 cell line. **Results:** To resemble a condition of chronic-inflammation (characterized by SOCS3 activation), we stimulated HepG2 cells with TNF-alpha and resistin and then generated an HepG2 cell line overexpressing SOCS3 (HepG2^{SOCS3}). TNF-alpha and resistin induced both SOCS3 and PCSK9 expression in HepG2 cells and for TNF-alpha. These effects were inhibited by transfection with siRNA anti-STAT3, suggesting the involvement of the JAK/STAT pathway. In parallel retroviral SOCS3 overexpression determined a complete abrogation of STAT3 phosphorylation. HepG2^{SOCS3} showed higher *de novo* lipogenesis (induction of fatty-acid synthase (FAS) mRNA by 3.59±0.40 fold; stearoyl-CoA desaturase (SCD-1) mRNA by 1.92±0.12 fold; and apolipoproteinB (apoB) secretion by 3.47±0.09 fold). These responses were associated with significant increase of SCD-1 protein, activation of SREBP-1, accumulation of cellular TG, and secretion of apoB. HepG2^{SOCS3} cells express higher levels of PCSK9 mRNA (3.48±0.35 fold) and protein secretion (2.18±1.13 fold) No relevant changes of HMG-CoA reductase, low-density lipoprotein receptor levels and cholesterol biosynthesis were found. In addition, TNF-alpha significantly induced SCD-1, apoB and FAS mRNA levels (2.11±0.43, 1.60±0.33 and 1.39±0.21 fold, respectively). Insulin stimulation further induced FAS, SREBP-1 and PCSK9 mRNA levels to a similar extent in control and SOCS3-overexpressing cells, although the overall mRNA levels of these genes were significantly higher in HepG2^{SOCS3} cells. Akt and IRS-1 phosphorylation in response to insulin was attenuated in HepG2^{SOCS3}, supporting IRS-1 inhibition as the mechanism of abrogated Akt, and STAT3 phosphorylation. **Conclusions:** Our data provide evidence for the JAK/STAT dependent expression of PCSK9 in hepatic cell line, suggesting the potential molecular basis of the direct relationship between PCSK9, triglycerides levels and IR observed in clinical settings.

Reference: (1) Ueki et al., PNAS 2004 Jul 13;101(28):10422-7. (2) Ridker et al., Eur Heart J. 2015 Oct 27

Nothing to Disclose: MR, CR, CM, PM, AC, NF