

サイトカインシグナル阻害分子 SOCS の生体標的細胞内への導入による難病治療

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Development of a novel therapy for intractable diseases by targeted intracellular delivery of cytokine signal inhibitor (SOCS) in vivo

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1. Iwahori K, Serada S, Fujimoto M, Nomura S, Osaki T, Lee CM, Mizuguchi H, Takahashi T, Ripley B, Okumura M, Kawase I, Kishimoto T, Naka T. (2010)

Overexpression of SOCS3 exhibits preclinical antitumor activity against malignant pleural mesothelioma.

Int J Cancer, 2010 Oct 14. [Epub ahead of print]

Malignant pleural mesothelioma (MPM) is an aggressive tumor with poor prognosis for which an effective therapy remains to be established. Our study investigated the therapeutic potential of the suppressor of cytokine signaling 3 (SOCS3), an endogenous inhibitor of intracellular signaling pathways, for treatment of MPM. We infected MPM cells (H226, EHME-1, MESO-1 and MESO-4) with an adenovirus-expressing SOCS3 (AdSOCS3) to examine the effect of SOCS3 overexpression on MPM cells. SOCS3 overexpression reduced MPM proliferation and induced apoptosis and partial G0/G1 arrest. SOCS3 also inhibited the proliferation of MPM cells via multiple signaling pathways including Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3), extracellular signal-regulated kinase (ERK), focal adhesion kinase (FAK) and p53 pathways. Notably, AdSOCS3 treatment inhibited tumor growth in an MPM pleural xenograft model. These findings demonstrate that overexpression of SOCS3 has a potent antitumor effect against MPM both in vitro and in vivo and indicate the potential for clinical use of SOCS3 for MPM treatment.

2. Watanabe D, Ezoe S, Fujimoto M, Kimura A, Saito Y, Nagai H, Tachibana I, Matsumura I, Tanaka T, Kanegane H, Miyawaki T, Emi M, Kanakura Y, Kawase I, Naka T, Kishimoto T. (2004)

Suppressor of cytokine signalling-1 gene silencing in acute myeloid leukaemia and human haematopoietic cell lines.

Br J Haematol, 126: 726-735.

The aim of this study was to investigate whether the suppressor of cytokine signalling (SOCS)-1 can act as a tumour suppressor when functioning as a negative regulator of the Janus family tyrosine kinases (JAKs), which have been reported to play important roles in leukaemogenesis. For this purpose, we carried out molecular analysis of the SOCS-1 gene in human acute myeloid leukaemia (AML) and human haematopoietic cell lines. Sequencing alterations in the coding region were found in two of 90 primary AML samples and one of 17 cell lines. Hypermethylation of the SOCS-1 gene was also observed in 72% of primary cases and 52% of cell lines and aberrant methylation strongly correlated with reduced expression. Transfection of SOCS-1 into Jurkat cells harbouring the mutation and methylation suppressed cell growth at a low serum concentration. These findings indicate that SOCS-1 is frequently silenced in haematopoietic malignancies, mainly as a result of hypermethylation, and suggest that SOCS-1 may be able to function as a tumour suppressor.

3. Komazaki T, Nagai H, Emi M, Terada Y, Yabe A, Jin E, Kawanami O, Konishi N, Moriyama Y, Naka T, Kishimoto T. (2004)

Hypermethylation-associated inactivation of the SOCS-1 gene, a JAK/STAT inhibitor, in human pancreatic cancers.

Jpn J Clin Oncol, 34: 191-194.

BACKGROUND: SOCS-1, a JAK-binding protein (SSI-1/SOCS-1/JAB), regulates the JAK/STAT signal transduction pathway that relays signals from various cytokines in the extracellular matrix into the cell. Inactivation of the SOCS-1 gene by methylation has been previously described in hepatocellular carcinomas and multiple myeloma. The purpose of the present work was to analyze the expression of the SOCS-1 gene and identify inactivation of this gene by methylation in pancreatic cancers.

METHODS: 20 samples were analyzed. We identified the expression of SOCS-1 gene using RT-PCR and the mechanism of inactivation in this gene by methylation assay.

RESULTS: We documented marked suppression of SOCS-1 mRNA and reduction of SOCS-1 protein in 7 of 14 primary pancreatic cancers examined; moreover, CpG-rich regions upstream of the SOCS-1 gene were hypermethylated in 8 of the 14 tumors.

CONCLUSIONS: The results suggested that this gene is silenced in a substantial portion of pancreatic cancers through mechanisms that cause methylation in the promoter region.

4. Nagai H, Naka T, Terada Y, Komazaki T, Yabe A, Jin E, Kawanami O, Kishimoto T, Konishi N, Nakamura M, Kobayashi Y, Emi M. (2003)

Hypermethylation associated with inactivation of the SOCS-1 gene, a JAK/STAT inhibitor, in human hepatoblastomas.

J Hum Genet, 48: 65-69.

We recently demonstrated inactivation in hepatocellular carcinomas (HCCs) of the gene encoding SOCS1/JAB1/SSI-1, a JAK-binding protein that regulates the JAK/STAT signal-transduction pathway. In a follow-up immunochemical investigation of expression of SOCS-1 in hepatoblastomas (HBLs), the protein was markedly reduced in half of the HBL tumors we examined. CpG-rich regions upstream of the SOCS-1 gene were hypermethylated in 7 of the 15 HBL cases. The results suggest that hypermethylation may play an important role in silencing the SOCS-1 gene, not only in adult HCCs, but also in liver tumors arising in childhood.

5. Naka T, Narazaki M, Hirata M, Matsumoto T, Minamoto S, Aono A, Nishimoto N, Kajita T, Taga T, Yoshizaki K, Akira S, Kishimoto T. (1997)

Structure and function of a new STAT-induced STAT inhibitor.

Nature, 387: 924-929.

The signalling pathway that comprises JAK kinases and STAT proteins (for signal transducer and activator of transcription) is important for relaying signals from various cytokines outside the cell to the inside. The feedback mechanism responsible for switching off the cytokine signal has not been elucidated. We now report the cloning and characterization of an inhibitor of STAT activation which we name SSI-1 (for STAT-induced STAT inhibitor-1). We found that SSI-1 messenger RNA was induced by the cytokines interleukins 4 and 6 (IL-4, IL-6), leukaemia-inhibitory factor (LIF), and granulocyte colony-stimulating factor (G-CSF). Stimulation by IL-6 or LIF of murine myeloid leukaemia cells (M1 cells) induced SSI-1 mRNA expression which was blocked by transfection of a dominant-negative mutant of Stat3, indicating that the SSI-1 gene is a target of Stat3. Forced overexpression of SSI-1 complementary DNA interfered with IL-6- and LIF-mediated apoptosis and macrophage differentiation of M1 cells, as well as IL-6 induced tyrosine-phosphorylation of a receptor glycoprotein component, gp130, and of Stat3. When SSI-1 is overexpressed in COS7 cells, it can associate with the kinases Jak2 and Tyk2. These findings indicate that SSI-1 is responsible for negative-feedback regulation of the JAK-STAT pathway induced by cytokine stimulation.