A novel therapeutic approach for esophageal squamous cell carcinoma: suppressor of cytokine signaling-1 gene therapy

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Although significant improvements have been made in surgical techniques, chemotherapy, and radiotherapy, the prognosis of the patients with esophageal squamous cell carcinoma (ESCC) still remain poor (1-3). Therefore, the identification of new molecules involved in the progression of ESCC is worthwhile, and for this, the elucidation of the underlying signaling pathway is important. Recently, Sugase et al. (4) have suggested a novel promising approach for the treatment of ESCC: overexpression of the suppressor of cytokine signaling-1 (SOCS1).

SOCS1, a member of suppressors of cytokine signaling (SOCS) is located in 16p13 and encodes a 211 amino acid protein. SOCS1 is highly conserved in vertebrate and has been shown to participate in a classical negative feedback loop to inhibit cytokine signal transduction (5). In structure, SOCS1 contains a Src homology 2 (SH2) domains, a nuclear localization sequence (NLS) domain, a SOCS box at C-terminus, and a kinase inhibitory region (KIR) at N-terminus. SOCS1 can be affected by a variety of cytokines and hormones and inhibits signaling by suppression of Janus kinase (JAK) kinase activity through its KIR region by binding to the activation loop of JAK (6). The SOCS box could recruits Elongin B/C, Cullin 2 and Ring-box 2 to form a complex with ubiquitin E3 ligase that raises the degradation of SH2-binding proteins by proteasome (7).

There is a growing evidence indicated that SOCS1 expression displays an antiproliferative effect in a variety of cancer cells. In the present study, Sugase et al. (4) found that SOCS1 overexpression using adenovirus-expressing SOCS1 (AdSOCS1) significantly inhibited the cell proliferation in ten ESCC cell lines and induced apoptosis via multiple signaling pathways including JAK/ signal transducer and activator of transcription (STAT) and focal adhesion kinase (FAK)/p44/42 mitogen-activated protein kinase (p44/42 MAPK). In gastric cancer, Souma et al. (8) also reported that SOCS1 inhibits tumor growth by suppression the JAK/STAT- and MAPK-signaling. In lung cancer, Shimada et al. (9) described that SOCS1 decreases the phosphorylation of FAK tyrosine and promotes the degradation of FAK to inhibit cancer cell progression. In prostate cancer, Neuwirt et al. (10) reported that SOCS1 also exerts a growth-inhibitory function through downregulation of cyclin D1, and cyclin-dependent kinases. Sutherland et al. (11) found that SOCS1 suppressed the growth of ovarian and breast cancer cells. David et al. (12) described that SOCS1 inhibits the invasion and migration of colorectal cancer cells by preventing the epithelial-mesenchymal transition through decreasing transcription factor ZEB1 and increasing E-cadherin, and lower SCOS1 expression in hum
Colon cancer samples are associated with advanced stages. Altogether, these results suggest that SOCS1 plays a tumor suppressor role in human cancers.

Clinically, using primers selected from the CpG islands within exon 1 of SOCS1 gene, Sugase et al. (4) found SOCS1 methylation in four human ESCC tissues, but not in normal esophageal tissue. Hussain et al. (13) in Kashmir reported that compared with the level of SOCS1 expression in normal esophageal tissues, 40 (53%) of 75 of the surgically resected ESCC tissues exhibited decreased SOCS1 expression, which was significantly correlated with advanced stage or high histopathological grade. Among these 75 ESCC samples, aberrant promoter methylation of the SOCS1 gene was found in 34 (45%) tissues, which was also found to be significantly associated with advanced stage. These clinical data indicate that promoter methylation and subsequent transcript downregulation of SOCS1 transcripts play an important role in the multistep carcinogenesis of human ESCC. In ovarian and breast carcinomas, the SOCS1 CpG islands were also found to be hypermethylated in 10 (23%) of 43 patients and 4 (9%) of 43 patients, respectively (11). Except promoter methylation, few references have demonstrated that miRNA-elicited dysregulation of SOCS1 function exerts significant influence on tumor cells. miRNA-19a binds to the 3′-UTR region of SOCS1 to decrease mRNA expression of SOCS1 in lung cancer (14). miR-122 affects the expression of type I interferon (IFN) signal pathway by inhibiting SOCS1 in cervical cancer cells (15). Taken together, a comprehensive understanding of molecular mechanism of SOCS1 regulation in human cancer cells needs to be further investigated.

Using AdSOCS1 or control adenovirus vector (AdLacZ) injected intratumorally in two xenograft models, Sugase et al. (4) investigated the therapeutic effects of SOCS1 in vivo. In the first xenograft model, they used ICR nu/nu mice in which ESCC cell lines, TE14 cells, were subcutaneously implanted. Although cancer cell lines are commonly used in preclinical testing, they often do not reflect the original structural and molecular characteristics such as tumor heterogeneity of human cancers (16). It is better to use more clinically relevant human cancer models to evaluate the treatment efficacy of new target more accurately. Therefore, in second xenograft model, patient-derived xenograft (PDX) model, they used NOD-SCID mice in which human ESCC tissues were subcutaneously implanted. They found that intratumoral injection of AdSOCS1 significantly suppressed tumor growth, compared with that in the control AdLacZ-injected groups in both xenograft mouse models. In particular, this result in PDX mouse model which was implanted with heterogenous human cancer tissue is a first report of SOCS1 gene therapy. In xenograft of non-small cell lung cancer, Shimada et al. (9) showed that overexpression of SOCS1 gene is effective for antitumor therapy. In xenograft of colon cancer, David et al. (12) described that SOCS1 controls metastatic progression. On the other hand, SOCS1 is also important in the regulation of the function of immune cells. For example, previous study showed that SOCS1-silenced dendritic cells can enhance antigen-specific cytotoxic T cell response and antitumor activity (17). Immunization with SOCS1−/− dendritic cells induces hyper type 1 helper T cell (Th1) immune responses and antitumor activities (18). SOCS1-deficient naive CD4+ T cells are predominantly differentiated into Th1 (19). Th1 cells are indirectly responsible for activating tumor-suppressing cytotoxic T lymphocytes by activating the antigen-presenting cells which then present antigen to and activate the cytotoxic T lymphocyte (20). Guenterberg et al. (21) reported that targeting SOCS1 in the T-cell compartment could enhance the antitumor activity of exogenously administered Interferon-alpha in murine melanoma model. In xenograft model used by Sugase et al., the effect of AdSOCS1 on immune cells cannot be evaluated. However, there are immune cells in tumor microenvironment of human cancers which may be influenced by AdSOCS1. Overexpression of SOCS1 proteins in tumor cells is one approach to inhibit tumor growth. Downregulation of SOCS1 proteins in immune cells enhances the antitumor immunity. Due to different roles of SOCS1 in tumor cells and immunocytes, different therapeutic approaches should be considered according to the types of target cells. Further studies are required.

Adenovirus-mediated gene therapy depends upon the ability of the virus to gain entry efficiently into the malignant target cells. Efficient adenovirus infection of target cells relies on the presence of the cell surface coxsackie-adenovirus receptor (CAR), which is the primary receptor for adenoviruses and is important for the attachment of adenovirus to the cell membrane (22). Therefore, the level of CAR on the cell surface is an important factor in the efficacy of adenoviral gene therapy. Although several evidence (22-24) indicates that CAR expression levels are lower in various types of tumors such as ovarian, lung, breast and bladder when compared to their normal counterparts. In the present study, Sugase
et al. reported the CAR expression in 33 of 34 human ESCC specimens, and 74% of specimens showed a stronger expression of CAR than that of normal esophageal tissue. However, Hoshino et al. (23) reported that CAR expression was observed in 40 ESCC specimens examined and the expression in tumor was lower in nine cases compared to that in the corresponding normal epithelium. In other 31 patients, no observable difference was detected between the tumor and normal epithelium expression. Recently, several studies reported that CAR expression is regulated by histone deacetylation, and histone deacetylase inhibitors can increase the protein levels of CAR in ESCC cell lines (23,24). Combination of gene therapy with histone deacetylase inhibitors may be a promising strategy in ESCC to increase gene therapy efficacy.

Over the past decade, based on the discoveries in basic and clinical studies, the functions of SOCS1 in tumor cells as well as immune cells are complex and controversial. These contradictory results may be attributed to the different microenvironments. Further exploring the molecular mechanisms and clinical significances of SOCS1-mediated cancer progression will provide new insights into the therapeutic strategies for cancer treatment in the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References


