Editorial

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

Chang-Han Chen[1,2,3], Shau-Hsuan Li[4]

[1]Institute for Translational Research in Biomedicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; [2]Department of Applied Chemistry, Graduate Institute of Biomedicine and Biomedical Technology, National Chi Nan University, Taiwan; [3]Center for Infectious Disease and Cancer Research, Kaohsiung Medical University, Kaohsiung, Taiwan; [4]Department of Hematology-Oncology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan

Correspondence to: Shau-Hsuan Li, MD. Department of Hematology-Oncology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan. Email: lee.a0928@msa.hinet.net.

Provenance: This is an invited Editorial commissioned by Section Editor Dr. Hongcheng Zhu (Section Editor, Department of Radiation Oncology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

Comment on: Sugase T, Takahashi T, Serada S, *et al.* Suppressor of cytokine signaling-1 gene therapy induces potent antitumor effect in patient-derived esophageal squamous cell carcinoma xenograft mice. Int J Cancer 2017;140:2608-21.

Submitted Apr 30, 2017. Accepted for publication May 06, 2017.
doi: 10.21037/jtd.2017.05.57
View this article at: http://dx.doi.org/10.21037/jtd.2017.05.57

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 is 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 immunocytes 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.

Acknowledgments

None.

Footnote

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

References

1. Li SH, Lu HI, Chang AY, et al. Angiotensin II type I receptor (AT1R) is an Independent prognosticator of esophageal squamous cell carcinoma and promotes cells proliferation via mTOR activation. Oncotarget 2016;7:67150-65.
2. Li SH, Chen CH, Lu HI, et al. Phosphorylated p70S6K expression is an Independent prognosticator for patients with esophageal squamous cell carcinoma. Surgery 2015;157:570-80.
3. Shang QX, Chen LQ, Hu WP, et al. Three-field lymph node dissection in treating the esophageal cancer. J Thorac Dis 2016;8:E1136-49.
4. Sugase T, Takahashi T, Serada S, et al. Suppressor of cytokine signaling-1 gene therapy induces potent antitumor effect in patient-derived esophageal squamous cell carcinoma xenograft mice. Int J Cancer 2017;140:2608-21.
5. Starr R, Willson TA, Viney EM, et al. A family of cytokine-inducible inhibitors of signalling. Nature 1997;387:917-21.
6. Cui X, Shan XH, Qian J, et al. The suppressor of cytokine signaling SOCS1 promotes apoptosis of intestinal epithelial cells via p53 signaling in Crohn's disease. Exp Mol Pathol 2016;101:1-11.
7. Zhang J, Li H, Yu JP, et al. Role of SOCS1 in tumor progression and therapeutic application. Int J Cancer 2012;130:1971-80.
8. Souma Y, Nishida T, Serada S, et al. Antiproliferative effect of SOCS-1 through the suppression of STAT3 and p38 MAPK activation in gastric cancer cells. Int J Cancer 2012;131:1287-96.
9. Shimada K, Serada S, Fujimoto M, et al. Molecular mechanism underlying the antiproliferative effect of suppressor of cytokine signaling-1 in non-small-cell lung cancer cells. Cancer Sci 2013;104:1483-91.
10. Neuwirt H, Puhr M, Santer FR, et al. Suppressor of cytokine signaling (SOCS)-1 is expressed in human prostate cancer and exerts growth-inhibitory function through down-regulation of cyclins and cyclin-dependent kinases. Am J Pathol 2009;174:1921-30.
11. Sutherland KD, Lindeman GJ, Choong DY, et al. Differential hypermethylation of SOCS genes in ovarian and breast carcinomas. Oncogene 2004;23:7726-33.
12. David M, Naudin C, Letourneur M, et al. Suppressor of cytokine signaling 1 modulates invasion and metastatic potential of colorectal cancer cells. Mol Oncol 2014;8:942-55.
13. Hussain S, Singh N, Salam I, et al. Methylation-mediated gene silencing of suppressor of cytokine signaling-1 (SOCS-1) gene in esophageal squamous cell carcinoma patients of Kashmir valley. J Recept Signal Transduct Res 2011;31:147-56.
14. Wang X, Chen Z. MicroRNA-19a functions as an oncogenic microRNA in non-small cell lung cancer by targeting the suppressor of cytokine signaling 1 and mediating STAT3 activation. Int J Mol Med 2015;35:839-46.
15. He J, Ji Y, Li A, et al. MiR-122 directly inhibits human papillomavirus E6 gene and enhances interferon signaling through blocking suppressor of cytokine signaling 1 in SiHa cells. PLoS One 2014;9:e108410.

16. Voskoglou-Nomikos T, Pater JL, Seymour L. Clinical predictive value of the in vitro cell line, human xenograft, and mouse allograft preclinical cancer models. Clin Cancer Res 2003;9:4227-39.
17. Shen L, Evel-Kabler K, Strube R, et al. Silencing of SOCS1 enhances antigen presentation by dendritic cells and antigen-specific anti-tumor immunity. Nat Biotechnol 2004;22:1546-53.
18. Hanada T, Tanaka K, Matsumura Y, et al. Induction of hyper Th1 cell-type immune responses by dendritic cells lacking the suppressor of cytokine signaling-1 gene. J Immunol 2005;174:4325-32.
19. Jiang M, Zhang WW, Liu P, et al. Dysregulation of SOCS-Mediated Negative Feedback of Cytokine Signaling in Carcinogenesis and Its Significance in Cancer Treatment. Front Immunol 2017;8:70.
20. Mailliard RB, Egawa S, Cai Q, et al. Complementary dendritic cell-activating function of CD8+ and CD4+ T cells: helper role of CD8+ T cells in the development of T helper type 1 responses. J Exp Med 2002;195:473-83.
21. Guenterberg KD, Lesinski GB, Mundy-Bosse BL, et al. Enhanced anti-tumor activity of interferon-alpha in SOCS1-deficient mice is mediated by $CD4^+$ and $CD8^+$ T cells. Cancer Immunol Immunother 2011;60:1281-8.
22. Wang Y, Thorne S, Hannock J, et al. A novel assay to assess primary human cancer infectibility by replication-selective oncolytic adenoviruses. Clin Cancer Res 2005;11:351-60.
23. Hoshino I, Matsubara H, Akutsu YA, et al. Role of histone deacetylase inhibitor in adenovirus-mediated p53 gene therapy in esophageal cancer. Anticancer Res 2008;28:665-71.
24. Ma J, Zhao JM, Lu J, et al. Coxsackievirus and adenovirus receptor promotes antitumor activity of oncolytic adenovirus H101 in esophageal cancer. Int J Mol Med 2012;30:1403-9.

Cite this article as: Chen CH, Li SH. A novel therapeutic approach for esophageal squamous cell carcinoma: suppressor of cytokine signaling-1 gene therapy. J Thorac Dis 2017;9(6):1446-1449. doi: 10.21037/jtd.2017.05.57

