Methylation of Stat1 Promoter Can Contribute to Squamous Cell Carcinogenesis

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One of the most recently recognized signaling pathways that regulate tumor cell proliferation and survival involves signal transducers and activators of transcription (STAT) proteins. The STAT family of proteins has seven known members: Stat1, 2, 3, 4, 5A, 5B, and 6. Interestingly, it has become evident that different STAT proteins can serve either tumor suppressing or oncogenic roles. Stat1, for example, functions as a tumor suppressor in several capacities (1–5), whereas Stat3 and to a lesser extent, Stat5, play a critical role in malignant progression at multiple levels (6–9).

Although it has been demonstrated that interferon-induced Stat1 activity can cause growth arrest and can induce apoptosis, it is not clear whether a lack of Stat1 in human cancer directly contributes to cancer cell proliferation and survival. If so, what keeps Stat1 from functioning in this manner in tumor cells also remains largely unknown. The article by Xi et al. (10) in this issue of the Journal presents evidence that Stat1 expression in squamous cell carcinoma of the head and neck (SCCHN) is lower than that of normal tissues from individuals without cancer. Restoring Stat1 expression in the tumor cells leads to growth inhibition in vitro and in xenograft tumors, which is accompanied by an increase in p21 expression. Their work further demonstrates that the low expression of Stat1 in SCCHN tumors is associated with Stat1 promoter methylation and that treatment with a methylation inhibitor increases STAT1 and p21 expression and sensitizes SCCHN tumor cells to cisplatin. These findings are novel in several respects.

Many independent studies, which involve mainly mouse tumor models or cell lines, have suggested that Stat1 can function as a tumor suppressor (1–5). How does Stat1 function as a tumor suppressor? Stat1’s ability to mediate host immune defenses against tumors has been elegantly demonstrated in mice (2). Increasing Stat1 activity by interferon treatment also leads to cell growth inhibition, which can be explained by Stat1’s capacity to induce p21waf and caspase expression (1, 5). Moreover, Stat1-deficient cells have defects both in S-phase and G2–M checkpoints in response to DNA damage (11). Also, Stat1- and p53-null mice show more frequent and rapid tumor development than wild-type mice. The basal expression level of the p53 inhibitor Mdm2 is higher in Stat1−/− cells than in wild-type cells, suggesting that Stat1 is a negative regulator of Mdm2 expression (12). The findings by Xi et al. provide direct evidence supporting the
notion that the inhibition of Stat1 expression in human cancer may confer a growth and survival advantage.

This study by Xi et al. also suggests that the roles of STATs in cancer involve not only activation of prooncogenic Stat3 and Stat5 but also lack of function of tumor-suppressing Stat1. In normal cells, STAT proteins transmit cytoplasmic signals from polypeptide cytokines and growth factors that bind receptors with intrinsic or associated tyrosine kinase activity (3,8). Activation of STAT proteins by tyrosine phosphorylation in normal cells is transient and rapid. In sharp contrast to this fact, because tyrosine kinases are among the most frequently activated oncogenic proteins in cancers, Stat3—and to a lesser extent, Stat5—are constitutively activated at very high frequency (50%–90%) in many cancers of diverse origin (6–9). Activation of Stat3 in SCCHN has been extensively characterized, and the need for constitutively activated Stat3 signaling for tumor cell survival and proliferation has been demonstrated (6,9). The present study points to coordinate STAT dysregulation in cancer. In this context, there is compelling evidence that Stat3 activation is much stronger and more prolonged in Stat1-null mouse embryo fibroblasts than in wild-type cells. Conversely, elevated Stat1 activity is observed in cells that lack the Stat3 alleles and in cells with constitutively activated Stat3 that are treated with Stat3 antagonists (13,14). Because Stat1 and Stat3 have opposing biologic effects (15), lack of Stat1 expression and function in tumor cells may enhance the activity of Stat3, thereby promoting malignant progression.

The importance of DNA methylation in tumorigenesis has been demonstrated in cancer cells that harbor global genomic DNA hypomethylation and regional hypermethylation at CpG islands of tumor suppressor genes (16). This CpG promoter hypermethylation can silence expression of the associated gene and thus provide cancer cell with a growth advantage similar to deletions or mutations. For example, aberrant methylation of the retinoblastoma (pRb) gene and the von Hippel Lindau (VHL) gene has been demonstrated in retinoblastoma and renal carcinomas, respectively (17,18). Also, methylation-associated silencing can occur at genes involved in hormonal and cytokine signaling pathways, including hormone receptors and the suppressor of cytokine signaling family of proteins (19). Also, it has been found in several tumors that tumor suppressor genes are inactivated by hypermethylation of genes encoding their regulators (20). However, to date, regulation of Stat1 has been linked mostly to protein tyrosine phosphorylation. The present study by Xi et al. reveals a novel regulatory mechanism for Stat1 in cancer. Their data show that the Stat1 promoter is hypermethylated in SCCHN tissues and cell lines and that demethylation of the Stat1 promoter can sensitize tumor cells to chemotherapeutic agent–induced apoptosis. Although further studies are necessary to identify the regulatory mechanisms involved in methylation of the Stat1 promoter in cancer, the findings of Xi et al. indicate that Stat1 is a tumor suppressor in SCCHN and that demethylation may be a potential therapeutic strategy to restore Stat1’s tumor suppressive functions.

**References**