Signal Transducers and Activators of Transcription 3 Activation Is Involved in Nuclear Accumulation of β-Catenin in Colorectal Cancer

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Abstract

Nuclear accumulation of β-catenin is a key event for the development of colorectal cancer. Little is known, however, about the mechanisms underlying translocation of β-catenin from the cytoplasm or the membrane to the nucleus. The present study examined whether signal transducers and activators of transcription 3 (STAT3) activation is involved in the nuclear accumulation of β-catenin in colorectal cancer cells. Of the 90 primary colorectal cancer tissues, 40 (44.4%) were positive for nuclear staining of p-STAT3 and 63 (70.0%) were positive for nuclear staining of β-catenin. The nuclear staining of both p-STAT3 and β-catenin were observed predominantly in the periphery of the cancer tissues. Importantly, of the 40 tumors with p-STAT3 nuclear staining, 37 (92.5%) were also positive for nuclear β-catenin staining and there was a significant correlation between p-STAT3 and β-catenin nuclear staining (P < 0.01). Coexpression of nuclear p-STAT3 and β-catenin was associated with lower patient survival (P < 0.01). In an in vitro study using a human colon cancer cell line, SW480, inhibition of STAT3 by dominant negative STAT3 or the Janus kinase inhibitor, AG490, induced translocation of β-catenin from the nucleus to the cytoplasm or membrane. Luciferase assays revealed that STAT3 inhibition resulted in significant suppression of β-catenin/T-cell factor transcription in association with significant inhibition of cell proliferation (P < 0.05). These findings suggest that in colorectal cancer, STAT3 activation is involved in the nuclear accumulation of β-catenin, resulting in poor patient survival. (Cancer Res 2006; 66(6): 2913-7)

Introduction

Loss-of-function mutations in the adenomatosis polyposis coli (APC) gene are the initial genetic alteration in most colorectal cancers, which leads to subsequent nuclear accumulation of β-catenin (1). In the nucleus, β-catenin acts as a transcriptional activator and is involved in colorectal carcinogenesis. Recently, Brabietz et al. (2) reported that although strong nuclear staining of β-catenin was observed at the invasive front, no nuclear β-catenin expression was found in the central areas of primary colorectal cancers and postulated that specific signals from the cancer microenvironment regulate intracellular β-catenin distribution in cancer cells. Indeed, stromal cells, the extracellular matrix, and cytokines within the tumors have a strong influence on the cancer phenotype (3). In various human cancers, signal transducers and activators of transcription 3 (STAT3) translocates to the nucleus and contributes to carcinogenesis by both preventing apoptosis and enhancing cell proliferation (4–7). Recent studies suggest that STAT3 mediates the extracellular signals from surrounding microenvironment, such as stimulation by cytokines, to target genes of the cancer cells (8). Therefore, in this study, we intended to examine whether STAT3 activation is associated with the nuclear accumulation of β-catenin in 90 primary colorectal cancer tissues. Moreover, we also tested the effects of STAT3 inactivation on nuclear accumulation of β-catenin in the SW480 colon cancer cell line.

Materials and Methods

Tissue samples and immunohistochemistry. Ninety surgical samples of primary colorectal cancer were obtained with informed consents at Kyoto University Hospital. This study was approved by the Board of Medical Research of Kyoto University Hospital. The patients consisted of 57 males and 33 females ranging in age from 19 to 82 years (mean 66.4 years). The specimens were immunostained with antiphosphospecific STAT3 (Tyr705, p-STAT3; 1:50, New England Biolabs, Beverly, MA) or anti-β-catenin (1:100, BD Transduction, Lexington, KY) antibodies. Cancer tissues were equally divided into two regions: central and peripheral part. The staining was determined according to the percentage of positively stained nuclei in 200 tumor cells by two independent investigators (M. Kawada and H. Seno), without knowledge of the specific cases, and regarded as positive when over 30% of the tumor cells were stained.

Cell culture and transfections. Human colon cancer cell lines, HT29, LoVo, CaCo2, DLD-1, and SW480 cells, were maintained in DMEM with 10% fetal bovine serum. We also tested the effects of STAT3 inactivation on nuclear accumulation of β-catenin in SW480 cells, whereas the other four had cytoplasmic and/or membranous localization of β-catenin. We also confirmed STAT3 activation in all cell lines by Western blotting. Therefore, we used SW480 cells with or without DN-STAT3 vector (phenylalanine substitution at Tyr705; refs. 6, 7) transfection or a Janus kinase inhibitor, AG490 (Wako, Osaka, Japan) administration. Transient transfection of DN-STAT3 or mock vector was done using FuGENE 6 (Roche, Somerville, NJ). The efficiency of transfection (~60%) was confirmed by transfection of vector with β-galactosidase. Interleukin-6 (IL-6; 100 ng/mL of medium, R&D Systems, Minneapolis, MN) stimulation was done at 37°C for 30 minutes (9).

Immunoﬂuorescence. Cells cultured on chamber slides were fixed in 4% paraformaldehyde, permeabilized, and incubated with anti-β-catenin and FITC-conjugated secondary (1:40; DAKO, Copenhagen, Denmark) antibodies. Immunolabeled cells were counterstained with 4′,6-diamidino-2-phenylindole (DAPI; Sigma, St. Louis, MO) to detect cell nuclei.

Western blotting and immunoprecipitation. Western blotting was done as previously described (7). The membranes were incubated with anti-STAT3, anti-p-STAT3, anti-β-catenin, anti-E-cadherin (BD Transduction), or anti-β-actin (Sigma) antibodies, and incubated with peroxidase-conjugated...
secondary antibodies. For immunoprecipitation, cell lysates were incubated with antiphosphospecific tyrosine (Santa Cruz Biotechnologies, Santa Cruz, CA) or anti-E-cadherin antibodies immobilized on protein A-Sepharose at 4°C overnight.

Dual luciferase assay. SW480 cells in 12-well dishes were transfected with 0.4 μg of TOPFlash or FOPFlash reporter plasmids (Upstate Biotechnology, Charlottesville, VA) with 0.01 μg pRL-TK reporter plasmids (Promega, Madison, WI). Following 24-hour incubation, cells were incubated with or without AG490 for another 48 hours. In another experiment, SW480 cells transfected with luciferase reporter plasmids were cotransfected with 0.4 μg DN-STAT3 plasmid for 24 hours.

Cell proliferation assay. SW480 cells were seeded at a density of 1.0 × 10⁵ cells per 60 mm dish. After 24-hour incubation, cells were incubated with or without DN-STAT3 or 50 μmol/L AG490 for 48 hours. The growth rate was represented as relative values of the cell number at 0 hours.

Statistical analyses. The association between p-STAT3 and β-catenin expression and clinicopathologic factors was analyzed by the χ² test. For survival analysis, the Kaplan-Meier method was used and the statistical significance was analyzed by the log-rank test. The data of relative luciferase activity and growth rate were analyzed by the unpaired two-tailed Student’s t test. P values <0.05 were considered as statistically significant.

Results

Immunohistochemical staining in human colorectal cancer for β-catenin and p-STAT3. Among 90 colorectal cancer tissues, 40 (44.4%) showed positive nuclear staining of p-STAT3 (active form of STAT3), which was essentially observed at the periphery of the cancer tissues, and 63 (70.0%) were positive for nuclear staining of β-catenin (Fig. 1A-C; Table 1). In most of the cancers with nuclear β-catenin staining, the staining was predominantly observed at the periphery of the cancer tissues (Fig. 1A-C). Importantly, of the 40 nuclear p-STAT3-positive cases, 37 (92.5%) were also positive for nuclear staining of β-catenin (Table 1). There was a significant correlation between positive staining of p-STAT3 and that of β-catenin (P < 0.01).

Clinical outcome. Nuclear p-STAT3 was significantly correlated with the lymphatic invasion (P < 0.01), vascular invasion (P < 0.05), and tumor-node-metastasis (TNM) stages (P < 0.01), but not with the tumor stage (Table 2). Nuclear β-catenin was significantly correlated with the tumor stage (P < 0.01), lymphatic invasion (P < 0.05), and TNM stages (P < 0.01), but not with vascular invasion (Table 2). Kaplan-Meier curves revealed that patients with nuclear p-STAT3 had significantly lower disease-specific survival rates (P < 0.01; Fig. 1Da). Increased nuclear β-catenin levels were also associated with a poorer prognosis (P < 0.05; Fig. 1Db). Moreover, the patients with coexpression of nuclear β-catenin and nuclear p-STAT3 had a markedly lower survival rate compared with the other patients groups (P < 0.01; Fig. 1Dc).

Table 1. Relationship between nuclear expression of p-STAT3 and nuclear accumulation of β-catenin in 90 colorectal cancer tissues

<table>
<thead>
<tr>
<th>β-catenin staining</th>
<th>p-STAT3 staining</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Negative</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>Positive</td>
<td>26</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>60 (56.6%)</td>
<td>40 (44.4%)</td>
</tr>
</tbody>
</table>

NOTE: Values are the numbers of patients. (P < 0.01).

Figure 1. A to C, representative examples of colorectal cancer tissues immunostained with anti-p-STAT3 (active form of STAT3) or anti-β-catenin antibodies. A, accumulation of p-STAT3 and β-catenin at the periphery and their absence in the central areas of cancer tissues (>100). B, nuclear accumulation of p-STAT3 and β-catenin was observed at the periphery of the cancer tissue (>400). C, absence of nuclear p-STAT3 and β-catenin expression in the central areas of the cancer tissue (>400). D, Kaplan-Meier curves. a, patients with nuclear p-STAT3 staining had a poorer prognosis than those without nuclear p-STAT3 staining (P < 0.01). b, patients with nuclear β-catenin staining had a poorer prognosis than those without nuclear β-catenin staining (P < 0.05). c, patients with coexpression for nuclear p-STAT3 and β-catenin protein had a poorer prognosis compared with other patients (P < 0.01). Three patients with nuclear p-STAT3 without nuclear β-catenin were excluded from the figure because of the small number. n, number of patients.
STAT3 inactivation decreases nuclear accumulation of β-catenin in SW480 cells. Next, we examined the relationship between STAT3 and β-catenin in the colon cancer cell line SW480, which shows nuclear accumulation of β-catenin (Fig. 2A, a).

Following DN-STAT3 transfection, β-catenin was translocated from the nucleus to the cytoplasm and/or the membrane (Fig. 2A, b). Moreover, nuclear accumulation of β-catenin was lost by AG490, a Janus kinase inhibitor, in a time-dependent (24, 48, and 72 hours) and dose-dependent (25, 50, 100 μmol/L) manner (representative data with 50 μmol/L AG490 after 48 hours is depicted in Fig. 2A, c). Decrease of p-STAT3 by DN-STAT3 transfection or AG490 administration was confirmed by Western blotting (Fig. 2B). On the other hand, to further activate STAT3, we added a high-dose IL-6 (100 ng/mL) to HT29 or LoVo, in which β-catenin was localized in cytoplasm and/or membrane. However, administration of IL-6 did not drive cytoplasmic β-catenin to the nucleus in these cell lines (data not shown).

DN-STAT3 and AG490 inhibit STAT3 activation but do not change total β-catenin levels in SW480 cells. We then investigated the mechanisms by which STAT3 activation regulates β-catenin localization. We first examined whether β-catenin degradation was enhanced by STAT3 inhibition. Inhibition of STAT3 by DN-STAT3 or 50 μmol/L AG490, however, did not alter the total amount of cellular β-catenin (Fig. 2B). We also examined the possibility that STAT3 shuttles β-catenin from the cytoplasm to the nucleus. However, immunoprecipitation study did not reveal any significant bands containing both β-catenin and p-STAT3 (data not shown). Thus, another mechanism seems to be involved in the nuclear accumulation of β-catenin by STAT3 activation.

DN-STAT3 and AG490 do not alter the interaction between β-catenin and E-cadherin in SW480 cells. The amount of cellular β-catenin is also regulated by membrane E-cadherin (2). Therefore, we next examined the effects of STAT3 on the interaction between

### Table 2. Correlations between nuclear p-STAT3 or nuclear β-catenin and clinicopathologic variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>p-STAT3 positive</th>
<th>β-catenin positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;0&lt;/sub&gt; T&lt;sub&gt;1&lt;/sub&gt;, T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>5/18 (27%)</td>
<td>6/18 (33%)</td>
</tr>
<tr>
<td>T&lt;sub&gt;0&lt;/sub&gt; T&lt;sub&gt;4&lt;/sub&gt;</td>
<td>35/72 (49%)</td>
<td>57/72* (79%)</td>
</tr>
<tr>
<td><strong>Lymphatic invasion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>34/58* (59%)</td>
<td>45/58* (78%)</td>
</tr>
<tr>
<td>Negative</td>
<td>6/32 (19%)</td>
<td>18/32 (56%)</td>
</tr>
<tr>
<td><strong>Vascular invasion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>25/44* (57%)</td>
<td>33/44 (75%)</td>
</tr>
<tr>
<td>Negative</td>
<td>15/46 (33%)</td>
<td>30/46 (65%)</td>
</tr>
<tr>
<td><strong>TNM stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 and 2</td>
<td>13/45 (29%)</td>
<td>25/45 (56%)</td>
</tr>
<tr>
<td>3 and 4</td>
<td>18/45* (40%)</td>
<td>38/45* (84%)</td>
</tr>
</tbody>
</table>

NOTE: Values are number of p-STAT3- or β-catenin-positive patients/total number of patients. Values in parentheses show percentages of p-STAT3- or β-catenin-positive cases.

*P < 0.01.

†P < 0.05.
β-catenin and E-cadherin. SW-480 cell lysates after incubation with or without DN-STAT3 or 50 μmol/L AG490 were immunoprecipitated by anti-E-cadherin antibody. Western blotting using anti-E-cadherin or anti-β-catenin antibodies revealed that DN-STAT3 or AG490 did not affect the total amount of E-cadherin and β-catenin coimmunoprecipitates (Fig. 2C). These results indicate that the loss of nuclear accumulation of β-catenin by STAT3 inactivation is not due to changes in the amount of β-catenin bound to E-cadherin.

β-catenin/T-cell factor transcription is inhibited by DN-STAT3 and AG490 in SW-480 cells. To more directly examine the effect of STAT3 activation on WNT signaling, we did β-catenin/T-cell factor (TCF) transcriptional (TOP-FLASH) or FOP-FLASH control assays in SW-480 cells. Expression of the TOP-FLASH reporter was decreased by 56% with DN-STAT3 and 67% with AG490 (P < 0.05), although expression of the FOP-FLASH reporter was unchanged (Fig. 3A). Thus, DN-STAT3 and AG490 significantly inhibit β-catenin/TCF transcription.

DN-STAT3 and AG490 inhibit proliferation of SW-480 cells. We then investigated whether inhibition of STAT3 signaling affects proliferation of SW-480 cells. DN-STAT3 inhibited proliferation of SW-480 cells by 53.3% at 48 hours after the transfection (P < 0.05), and 50 μmol/L AG490 also inhibited cell proliferation by 44.0% at 48 hours (P < 0.05; Fig. 3B). DN-STAT3 and AG490 had no effects on cell viability as measured by trypan blue staining. Thus, STAT3 signaling promotes proliferation of SW-480 cells.

Discussion

In this study, we found that 70% (63 of 90) of colorectal cancer tissues showed nuclear staining of β-catenin and, moreover, that among the 40 colorectal cancer tissues with nuclear p-STAT3 staining, 92.5% (37 of 40) were also positive for nuclear β-catenin staining, demonstrating significant association between STAT3 activation and nuclear accumulation of β-catenin in colorectal cancer cells, essentially at the periphery of advanced cancer tissues. The extracellular environment surrounding cancer cells has important roles in regulating cancer cell behavior (3, 10), and stromal factors affect β-catenin localization in epithelial cells (2, 11, 12). Moreover, STAT3 mediates signals from the extracellular environment to the nucleus (13, 14). Taken together, it is tempting to speculate that STAT3 transmits extracellular signals from the environment of the periphery of cancer tissues, and accelerates nuclear accumulation of β-catenin in colorectal cancer cells. However, it may be noted in our study that 43% (26 of 60) of colorectal cancer tissues with nuclear β-catenin did not show nuclear p-STAT3. In this regard, most colorectal cancers are known to have loss-of-function mutations in the APC gene. Thus, activation of WNT signaling pathway alone may have certain levels of capability to drive β-catenin into the nucleus regardless of STAT3 activation.

We also showed that nuclear p-STAT3 as well as nuclear β-catenin staining was associated with significantly lower patient survival rates. Moreover, patients with simultaneous nuclear expression of p-STAT3 and β-catenin had lower survival than those with nuclear β-catenin alone. Although a previous study showed that nuclear accumulation of β-catenin in colorectal cancer tissues correlates with patient prognosis (15), this is the first report demonstrating synergistic effect of nuclear accumulation of p-STAT3 and β-catenin on poorer survival of the patients. This synergy may be derived from cell cycle-promoting and/or antiapoptotic actions of STAT3, which are independent of WNT signaling pathway (4, 5).

The results of our clinical studies prompted us to further elucidate the functional relationship between STAT3 and β-catenin in vitro. Interestingly, nuclear accumulation of β-catenin was decreased by STAT3 inhibition in colorectal cancer cell line SW-480. Furthermore, we observed that inhibition of STAT3 with a resulting loss of β-catenin in the nucleus reduced β-catenin/TCF transcription. In addition, STAT3 inactivation inhibited cell proliferation.
These in vitro data again suggest that STAT3 activation is involved in nuclear accumulation of β-catenin in colon cancer cells. We also tried to examine whether forced activation of STAT3 by IL-6 administration accumulates β-catenin to the nucleus. However, high-dose IL-6 administration could not change β-catenin localization in HT29 and LoVo cells, in which β-catenin was localized in the cytoplasm and/or the membrane. The unresponsiveness of HT29 and LoVo cells to IL-6 may be due to constitutive activation of STAT3 in these cells. Alternatively, it should be noted that 70% (63 of 90) of colorectal cancer tissues showed nuclear β-catenin, whereas only 20% (1 of 5) of cancer cell lines examined showed nuclear β-catenin although all the cancer cell lines had constitutively active STAT3 and mutation of APC gene. Thus, there may exist some unknown mechanisms that inhibit nuclear accumulation of β-catenin in spite of constitutively active STAT3 in these cells.

How does STAT3 promote nuclear accumulation of β-catenin? β-catenin is mainly degraded by a GSK3β-dependent mechanism. However, because SW-480 cells lack full-length APC protein (2), conventional GSK3β-dependent degradation of β-catenin did not occur in our study. In this study, we revealed that STAT3 inhibition did not alter the total amount of β-catenin, demonstrating that STAT3 inactivation does not involve degradation of β-catenin. We also assessed mRNA and/or phosphoprotein levels of Akt, GSK3β, and BCL-2, which affect the stability of β-catenin (16, 17), but none of the phosphoprotein levels were changed by STAT3 inhibition in SW-480 cells (data not shown). Thus, it is more likely that STAT3 inactivation induces translocation of β-catenin from the nucleus to the cytoplasm in SW-480 cells. In this respect, we next examined the interaction between β-catenin and E-cadherin (2). However, STAT3 inactivation did not influence either the total amount of E-cadherin or the interaction between E-cadherin and β-catenin. Therefore, E-cadherin does not seem to be involved in STAT3-induced translocation of β-catenin to the nucleus. In addition, p-STAT3 and β-catenin did not coimmunoprecipitate, ruling out the possibility that activated STAT3 directly shuttles β-catenin from the cytoplasm and/or membrane to the nucleus. Other molecules, APC and lymphoid enhancer binding factor (LEF)-1, shuttle β-catenin between the cytoplasm and nucleus (18, 19). However, APC gene is mutated in SW-480 cells, and immunofluorescence did not detect any changes in the intracellular localization of LEF-1 (data not shown). Accordingly, it is also unlikely that STAT3 regulates intracellular β-catenin localization via APC- or LEF-1-dependent mechanisms. Further study is required to clarify the mechanisms by which STAT3 regulates β-catenin localization.

The present study showed a strong association between STAT3 activation and nuclear accumulation of β-catenin in both human colorectal cancer tissues and a colon cancer cell line. The fact that nuclear accumulation of both p-STAT3 and β-catenin were observed predominantly at the peripheral edges of the cancer tissues suggests an important role of the microenvironment of the peripheral cancer tissues in regulating cancer cell behavior. Our findings suggest a novel interaction between WNT and Janus-activated kinase/STAT signaling pathways in the pathophysiology of colorectal cancers.

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