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Two novel SHP-1 agonists, SC-43 and SC-78, are more potent than regorafenib in suppressing the in vitro stemness of human colorectal cancer cells



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Signal transducer and activator of transcription 3 (STAT3) has been shown to play a critical role in the maintenance of cancer stem cells (CSCs). Hence, the inhibition of STAT3 signaling has been suggested to be a viable therapeutic approach for cancer. Moreover, the efficacy of combinations of chemotherapeutic drugs and napabucasin, a small-molecule STAT3 inhibitor, have been assessed in various clinical trials, including those involving patients with metastatic colorectal cancer (CRC). Two recently developed small-molecule STAT3 inhibitors, SC-43 and SC-78, which can stimulate small heterodimer partner-1 (SHP-1) to inactivate STAT3, were found to have anti-tumor activity. In this study, the inhibitory effects of SC-43, SC-78, and regorafenib (a reference drug) on cell viability, STAT3 phosphorylation, and various stemness properties [e.g., sphere-forming and soft agar colony-forming abilities, CD133+/CD44+ (stem cell-like) subpopulations and the expression of several CSC markers] were examined for both HCT-116 and HT-29 human CRC cells. We found that SC-43 and SC-78 but not regorafenib inhibited constitutively and IL-6-induced STAT3 phosphorylation in HCT-116 and HT-29 cells, respectively. Moreover, SC-43 and SC-78 were more potent than regorafenib in suppressing the stemness properties (except stem cell-like subpopulations) of these cells. As expected, SHP-1 knockdown almost completely abolished the suppressive effects of SC-43 and SC-78 on the sphere formation in both cell lines. Furthermore, SC-43 and SC-78 showed synergistic inhibitory effects with oxaliplatin and/or irinotecan on sphere formation. Overall, our results suggest that SC-43 and SC-78 are potent STAT3 inhibitors that may potentially be used in combination therapy for CRC.

Biography

Yeu Su has completed his PhD from University of Wisconsin-Madison. He is a Professor of the Institute of Biopharmaceutical Sciences of National Yang-Ming University, a premier research university in Taiwan. He has published more than 55 papers in reputed journals and has been serving as an Editorial Board Member of several reputed journals.

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