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Perspective

PRMT1-SMAD7 Signaling Bridges Stemness and Epithelial-Mesenchymal Transition

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DESCRIPTION

PRMT1 is essential for TGF-induced expression of core *EMT-TF,* including *ZEB1* and *ZEB2,* Snail, and Slug, as a result of the regulation of *TGF/SMAD* signalling. Numerous studies have been conducted on the effects of Epithelial-Mesenchymal Transition (EMT) on cell shape and motility, particularly in the invasion and metastasis of cancer. In more recent times, it has become clearer how EMT and Cancer Stem Cells (CSCs) are related. According to one definition of the CSC, it is a group of cells with characteristics similar to those of stem cells and the capacity to start a tumor's growth and produce a tumor mass. Many cancer types, including breast, lung, pancreatic, and colon carcinomas, have been shown to increase the acquisition of stem-like features when EMT, or a partial EMT, is present. By suppressing the production of miRNAs that impede stemness, EMT-TF *ZEB1* was originally discovered to be necessary for stemness in pancreatic cancer. Slug and Snail, two EMT-TFs, have been demonstrated to support the stemness of mammary epithelial cells and breast tumor-initiating cells in the mammary gland in conjunction with *ZEB1.*

In breast cancer and skin squamous cell carcinomas, *TGF,* a pluripotent cytokine, contributes to the development of cancer stem cells and, thus, the genesis of tumors. We found that *TGF*-induced stem cell formation required *PRMT1* -mediated *SMAD7* methylation, which enhanced EMT-TF expression. In human mammary epithelial cells, the inhibition of *PRMT1* greatly inhibited the expansion of the CD44highCD24low cell population, which is a marker for epithelial stem cells. It was investigated how the protein markers for mammary epithelial stem cells, such as *CD44, KLF4, BMI1, POU5F1* , and *NANOG* , were indicated. The outcome demonstrated that TGF-induced stimulation of the expression of those stemness genes and mammosphere development was severely reduced by *PRMT1* silencing. Our findings showed that *TGF/SMAD* signalling was made possible by *PRMT1*'s methylation of *SMAD7* , which promoted the expression of EMT-TF, the advancement of EMT, and the development of cancer stem cells. These observations also offer more proof between stemness and EMT. Reduced expression of *SMAD7,* a crucial intrinsic negative regulator of the *TGF/SMAD* signalling pathway, increases *TGF*-induced EMT and tumor metastasis. In Hepatocellular Carcinoma (HCC), breast cancer, melanoma, glioblastoma, and renal cancer, lower *SMAD7* expression has been linked to shorter recurrence-free survival and inferior overall survival. AML and melanoma are two cancer forms where elevated *SMAD7* expression has been linked to a worse prognosis. However, some investigations have shown the reverse findings. *SMAD7* was found to play a dual role in Colorectal Cancer (CRC), as it might be linked to either a better or worse prognosis. The bidirectional regulation of cancer by *TGF* may explain the correlation between *SMAD7* expression and cancer prognosis.

Despite the contentious significance of *SMAD7* in cancer prognosis, it is significant that *SMAD7*'s function in maintaining CSCs' stemness is beginning to be understood. According to studies, *SMAD7* expression suppression increases the stemness of CSCs in HCC, breast cancer, Nasopharyngeal Carcinoma (NPC), and glioma. More significantly, it was discovered that *SMAD7* ubiquitination, one of the best known *PTMs* of *SMAD7*, promotes CSC stemness by encouraging its degradation. We showed that *SMAD7* stability was lowered and epithelial stemness was controlled by *PRMT1*-catalyzed methylation. Together, these results show that *SMAD7* plays a role in preserving the stemness of CSCs.

CONCLUSION

It has been discovered that *PRMT1* exhibits abnormal expression in a number of cancer types, including breast, prostate, colon, and leukaemia. It has been shown to play a part in telomere maintenance, DNA repair, apoptosis, and the response to oxidative stress in the development of cancer. According to most reports, higher *PRMT1* expression is linked to a poor prognosis. According to our findings, *PRMT1* promotes EMT throughout the development of tumors in a variety of cancer types. Recently, we discovered that *PRMT1* regulates epicardial differentiation and EMT during heart development by interfering with *p53* stability, further

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demonstrating the crucial functions of *PRMT1* in EMT and stemness. CSC stemness, which is essential for carcinogenesis, therapy resistance, and consequently tumor relapse after treatment, has the potential to be promoted by EMT. We have shown that *TGF/SMAD* signalling and *TGF*-induced EMT depend on *PRMT1*-induced *SMAD7* methylation, which sheds light on the functions of *PRMT1* and the associated *SMAD7* methylation in CSCs-related carcinogenesis, therapy resistance, and therefore tumor relapse after treatment. Our findings suggest that *PRMT1* and *SMAD7* methylation are possible therapeutic targets for the spread and recurrence of tumors.