

Inhibition of SOX9 may be an effective target for increasing radiosensitivity in gastrointestinal cancer

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Radiotherapy (RT) plays an important role in the treatment of gastrointestinal (GI) cancer. When combined with other anti-cancer therapy modalities, RT can increase cytotoxicity and improve treatment efficacy. However, some patients develop radioresistance and show treatment failure. In addition, certain patients experience acute enteritis during abdominal RT for GI cancer or sequelae of chronic radiation enteritis after RT. Therefore, it is important to determine the mechanism of radioresistance as well as RT-induced enteritis. Previous studies have demonstrated that two intestinal stem cells respond differentially to RT; one actively proliferating stem cell (aISC) is more radiosensitive, whereas the other reserve intestinal stem cell (rISC) is relatively radioresistant (1). Furthermore, the transcription factor *Sox9* has been reported to regulate proliferation and participate in the biological function of stemness in small intestinal cells (2,3). A study published in *Gastroenterology* by Roche *et al.* showed that SOX9 is required for the production and maintenance of label-retaining cells (4). In their study, Roche *et al.* showed that SOX9 knockout intestinal epithelium lacked regeneration capacity after RT, whereas SOX9 knockout intestinal crypts underwent apoptosis after RT irrespective of cell cycle arrest and DNA repair (4). These findings indicate that SOX9 plays key roles in mediating stemness and radioresistance in intestinal stem cells (ISCs). Thus, it may be possible to improve efficiency and develop potential strategies involving RT for GI cancer

by controlling the expression of SOX9 in stem cells.

Several studies suggested that a small subpopulation of malignant cells, known as cancer stem-like cells (CSCs) or tumor-initiating cells, possesses properties of stem cell such as self-renewal and differentiation; the self-renewal property is thought to be the origin of tumor growth and development (5). In addition, CSCs exhibits resistance to current anti-cancer therapeutics, leading to tumor metastasis and recurrence after treatment (6). Therefore, targeting of CSCs may be useful in cancer therapeutics. The crucial role played by SOX9 in CSCs has been verified in digestive system cancers, including pancreatic cancer and hepatocellular carcinoma (7-9). In a study of pancreatic cancer, Sun *et al.* found that the nuclear factor- κ B signaling pathway can epigenetically regulate the expression of SOX9 and promote the invasiveness of CSCs (7). Grimont *et al.* also demonstrated that SOX9 upregulated the ERBB signaling pathway to promote the tumorigenesis of pancreatic cancer (8). In addition, SOX9 is necessary for tumor cell initiation and division, self-renewal, and tumorigenicity in CSCs of hepatocellular carcinoma (9). In a xenograft mouse model of lung cancer, Luanpitpong *et al.* showed that SOX9 stabilization regulated by SLUG is important for the expansion and metastasis of CSCs (10). Taken together, continuously increased expression of SOX9 may be associated with the maintenance of certain phenotypes of CSCs and contribute to the propagation of several tumor types. On the

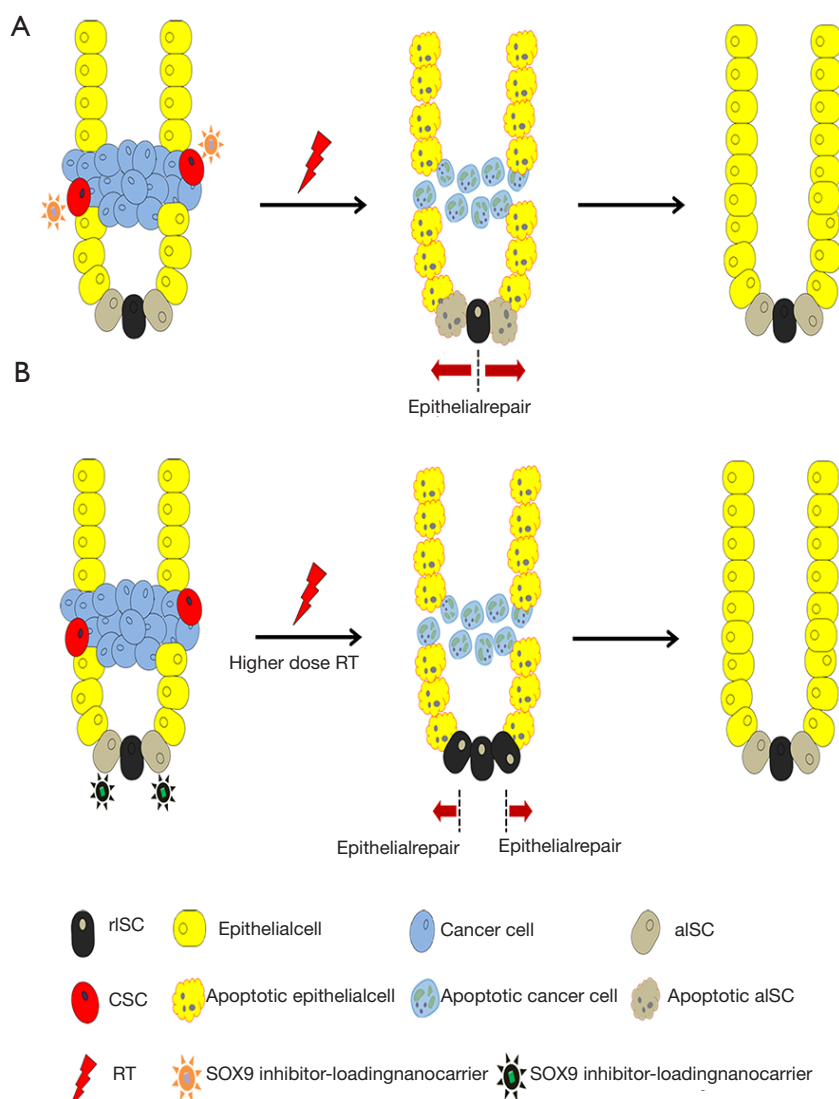


Figure 1 Possible applications of SOX9 in clinical therapeutics of gastrointestinal cancers. (A) The drug-loading nanocarriers should specifically target CSCs and then release SOX9 inhibitor into the CSCs. Inhibition of CSC by SOX9 inhibitors may contribute to eradicating cancer under a normal RT dose. Surviving rISCs, stem cells with high radioresistance, may stimulate tissue repair and regeneration; (B) SOX9 inducer-loading nanocarriers specifically targeting normal stem cells (aISCs and rISCs) may enhance cell radioresistance and simultaneously help active ISCs to convert to an rISC state. In this instance, the RT dose can be increased until CSCs are completely killed. After completing RT treatment, some rISCs will downregulate SOX9 expression and then be converted into an aISC state to rapidly proliferate and divide into new normal tissue. CSCs, cancer stem-like cells; aISCs, actively proliferating stem cells; rISCs, reserve intestinal stem cells.

other hand, SOX9 is a novel cancer stem cell marker and inhibition of SOX9 may be an effective target for eradicating CSCs.

However, the exact role of SOX9 in the mechanism of resistance to cancer therapy remains unclear, particularly for RT. Based on the relationships among SOX9, CSCs,

and resistance, a novel therapeutic strategy related to radioresistance should be developed to eradicate GI cancer. A previous report showed that drug-loaded nanocarriers conjugated with ligands targeted to CSC possess higher target selectivity and effectively release drugs within CSCs (11). Currently, glycans bound to proteins on cell

membrane are regarded as potentially specific CSC markers, which differ from normal stem cells. If SOX9 inhibitors or siRNA can be transported by this specific nanocarrier, we can investigate whether nanocarrier-conjugated SOX9 inhibitors can enhance the RT therapeutic effects in GI cancer, such as pancreatic cancer, hepatocellular carcinoma, and colorectal cancer, using *in vitro* cell lines and *in vivo* xenograft or orthotopic graft models. These approaches will reveal the precise mechanisms of radioresistance involving SOX9 and its regulated signaling in CSCs. In addition to enhanced RT sensitivity, ablation of SOX9 inhibits the extension of CSCs and lessens the invasiveness and metastases of cancer cells. A therapeutic strategy combining SOX9 inhibition and RT should be developed for GI cancer.

Notably, the use of SOX9 inhibitors combined with RT may cause adverse effects, such as enteritis, by reducing aISC-associated intestinal epithelium regeneration. Previous studies demonstrated that RelA, a transcription factor that plays a crucial role in biological processes, and Fgf8 can induce SOX9 expression (12,13). If SOX9 or its inducers can be delivered to normal intestinal tissue specifically and expressed successfully, rISC function can be significantly upregulated to protect against high-dose RT-associated enteritis. If the hypothesis is confirmed, this therapeutic strategy may effectively attenuate RT-induced GI injury and further promote crypt repair and regeneration after the completion of RT. These findings suggest that the importance of determining the applications of diverse clinical therapeutics of SOX9 in GI cancers, such as the use of SOX9 inhibitors in concurrent RT and use of SOX9 inducers after completion of high-dose RT (Figure 1).

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None.

Footnote

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

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