

Hedgehog Signaling Mitigates Chemoradiation Response in Esophageal Carcinomas

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Purpose: Despite aggressive chemotherapy, radiotherapy, surgery, or combination approaches, the survival rate of patients with esophageal cancer remains poor. Chemoradiotherapy (CRT) followed by surgery is the most commonly practiced therapy for localized esophageal cancer. This treatment strategy, however, results in only a 25% complete response rate, while 75% of tumors remain CRT-resistant. An increase in tumor proliferation rates by a CRT-resistant clonogenic population after exposure to chemotherapy and radiation results in tumor repopulation and limits the effectiveness of subsequent treatment fractions. Recent studies have suggested that constitutive activation of the Hedgehog (Hh) pathway in cancers of the digestive tract may contribute to the growth and maintenance of cancer. However, the relationship between Hh signaling and therapeutic response is unknown.

Methods: Immunohistochemical analysis of sonic Hh (Shh) and Gli1 expression were performed on residual tumors from patients who received neoadjuvant CRT followed by surgery. Additionally, the expression and temporal kinetics of Hh signaling and

proliferation biomarkers after CRT were examined in esophageal tumor xenografts. The ability of Shh signaling to induce proliferation in esophageal cell lines was determined. Expression of cell-cycle checkpoint proteins was analyzed in cells in which Hh signaling was activated or inhibited. We further determined the impact of Hh signaling blockade on esophageal tumor response to radiation and chemotherapy.

Results: We show that the Shh signaling pathway is extensively activated in esophageal cancer xenografts and residual tumors after CRT and the temporal kinetics of Hh signaling preceded increases in proliferation biomarker expression and tumor size during tumor regrowth. We further demonstrated that Hh pathway activity influences proliferation rates of esophageal cancer cell lines through upregulation of the G1-cyclin-Rb axis. Additionally, we found that blocking Hh signaling increased radiation cytotoxicity of esophageal cancer cells and enhanced chemotherapy effect in an esophageal cancer xenograft model.

Conclusions: These results suggest that activation of the Hh pathway may promote tumor repopulation after CRT and contribute to chemoradiation resistance in esophageal cancers. Our studies suggest that incorporating targeted inhibition of the Hh signaling pathway into current CRT regimens might improve treatment outcome.