Abstract

Esophageal squamous cell carcinoma (ESCC) is one of the most prevalent and aggressive forms of esophageal cancer, with poor survival outcomes largely due to late-stage diagnosis and therapeutic resistance. Current treatment for advanced ESCC commonly involves neoadjuvant chemotherapy using the docetaxel, cisplatin, and 5-fluorouracil (DCF) regimen; however, relapse and chemoresistance remain major clinical challenges. Increasing evidence suggests that distinct cell populations with stem/progenitor features contribute to tumor persistence and regrowth following treatment. Among these, leucine-rich repeat-containing G protein-coupled receptor 6 (Lgr6), a regulator of canonical Wnt signaling, has been associated with stemness, tumor progression, and chemotherapy resistance in several carcinomas, including ESCC. Preliminary study using advanced-stage ESCC mouse organoid models demonstrated that $Lgr6^{+}$-derived cells can survive and proliferate following chemotherapy exposure. However, the behavior of these populations during the early stages of ESCC development remains unclear. In addition, different chemotherapy exposure durations may influence treatment response and the emergence of resistant cell populations differently. Therefore, this study aims to investigate the behavior of $Lgr6^{+}$-derived cells in early-stage ESCC organoid models under short-term, continuous, and withdrawal-based chemotherapy regimens to identify potential therapeutic vulnerabilities associated with chemoresistance and tumor relapse.

Keywords: *ESCC, Lgr6, Chemotherapy, Tumor organoids, DCF regimen*