Esophageal squamous cell carcinoma

High level expression of lipocalin 2 (LCN2) usually indicates poor prognosis in esophageal squamous cell carcinoma (ESCC) and many other cancers.

A previous study showed LCN2 promotes migration and invasion of ESCC cells through a novel positive feedback loop. However, the key transcription activation protein (KTAP) in the loop had not yet been identified. In this study, Zhao et al., first predicted the most probable KTAPs by bioinformatic analysis. They then assessed the transcription regulatory regions in the human LCN2 gene by fusing deletions of its 5'-flanking region to a dual-luciferase reporter. They found that the region -720/-200 containing transcription factor 7-like 2 (TCF7L2) (-273/-209) and early growth response 1 (EGR1) (-710/-616) binding sites is crucial for LCN2 promoter activity. Chromatin immunoprecipitation (ChIP) experiments demonstrated that TCF7L2 and EGR1 bound directly to their binding sites within the LCN2 promoter as KTAPs. Mechanistically, overexpression of TCF7L2 and EGR1 increased endogenous LCN2 expression via the ERK signaling pathway. Treatment with recombinant human LCN2 protein enhanced activation of the ERK pathway to facilitate endogenous LCN2 expression, as well as increase the expression level of TCF7L2 and EGR1. Treatment with the MEK inhibitor U0126 inhibited the activation by TCF7L2 or EGR1 overexpression. Moreover, overexpression of TCF7L2 or EGR1 accelerated the migration and invasion of ESCC cells. A synergistic effect was observed between TCF7L2 and EGR1 in amplifying the induction of LCN2 and enhancing migration and invasion. Taken together, our study indicates that TCF7L2 and EGR1 are the KTAPs of LCN2, within a positive "LCN2 → MEK/ERK → LCN2" path, to promote the migration and invasion of ESCC cells. Based on their clinicopathological significance, LCN2 and its two expression regulators TCF7L2 and ERG1 might be therapeutic targets for ESCC [1)].

---

investigated whether the incidence of brain metastasis (BM) from primary esophageal and esophagogastric cancer is increasing. A single-institution retrospective review identified 583 patients treated from January 1997 to January 2016 for stages I through IV cancer of the esophagus and esophagogastric junction (follow-up, ≥3 months). Collected data included demographic information, date and staging at primary diagnosis, histologic subtype, treatment regimen for primary lesion, date of BM diagnosis, presence or absence of central nervous system symptoms, presence or absence of extracranial disease, treatment regimen for intracranial lesions, and date of death. The overall cohort included 495 patients (85%) with adenocarcinoma and 82 (14%) with squamous cell carcinoma (492 [84%] were male; median age at diagnosis, 68 years [range: 26-90 years]). BM was identified in 22 patients (3.8%) (median latency after primary diagnosis, 11 months). Among patients with BM, the primary histology was adenocarcinoma in 21 and squamous cell carcinoma in 1 (P = 0.30). BM developed in 12 who were initially treated for locally advanced disease and in 10 stage IV patients who presented with distant metastases. Overall survival (OS) after BM diagnosis was 18% at 1 year (median, 4 months). No difference in OS after BM diagnosis was observed in patients initially treated for localized disease compared to patients who presented with stage IV disease; however, OS was superior for patients who initially had surgical resection compared to patients treated with whole brain radiotherapy or stereotactic radiosurgery alone (1-year OS, 67% vs. 0%; median OS, 13.5 vs. 3 months; P = 0.003). The incidence of BM is low in patients with esophageal cancer. Outcomes were poor overall for patients with BM, but patients who underwent neurosurgical resection had improved survival [2)].

Everson et al. utilized human glioblastoma cell cultures to induce expression of New York-esophageal squamous cell carcinoma (NY-ESO-1) following in vitro treatment with the demethylating agent decitabine. We then investigated the phenotype of lymphocytes specific for NY-ESO-1 using flow cytometry analysis and cytotoxicity against cells treated with decitabine using the xCelligence real-time cytotoxicity assay. Finally, we examined the in vivo application of this immune therapy using an intracranially implanted xenograft model for in situ T cell trafficking, survival, and tissue studies.

The studies showed that treatment of intracranial glioma-bearing mice with decitabine reliably and consistently induced the expression of an immunogenic tumor-rejection antigen, NY-ESO-1, specifically in glioma cells and not in normal brain tissue. The upregulation of NY-ESO-1 by intracranial gliomas was associated with the migration of adoptively transferred NY-ESO-1-specific lymphocytes along white matter tracts to these tumors in the brain. Similarly, NY-ESO-1-specific adoptive T cell therapy demonstrated antitumor activity after decitabine treatment and conferred a highly significant survival benefit to mice bearing established intracranial human glioma xenografts. Transfer of NY-ESO-1-specific T cells systemically was superior to intracranial administration and resulted in significantly extended and long-term survival of animals.

These results reveal an innovative, clinically feasible strategy for the treatment of glioblastoma [3].

1)
Zhao Y, Xia Q, Liu Y, Bai W, Yao Y, Ding J, Lin L, Xu Z, Cai Z, Wang S, Li E, Xu H, Wu B, Xu L, Du Z. TCF7L2 and EGR1 synergistic activation of transcription of LCN2 via an ERK1/2-dependent pathway in esophageal squamous cell carcinoma cells. Cell Signal. 2018 Dec 14. pii: S0898-6568(18)30309-7. doi: 10.1016/j.cellsig.2018.12.007. [Epub ahead of print] PubMed PMID: 30557604.

2)
Welch G, Ross HJ, Patel NP, Jaroszewski DE, Fleischer DE, Rule WG, Paripati HR, Ramirez FC, Ashman JB. Incidence of brain metastasis from esophageal cancer. Dis Esophagus. 2017 Sep 1;30(9):1-6. doi: 10.1093/dote/dox071. PubMed PMID: 28859365.

3)
Everson RG, Antonios JP, Lisiero DN, Soto H, Scharnweber R, Garrett MC, Yong WH, Li N, Li G, Kruse CA, Liau LM, Prins RM. Efficacy of systemic adoptive transfer immunotherapy targeting NY-ESO-1 for glioblastoma. Neuro Oncol. 2016 Mar;18(3):368-78. doi: 10.1093/neuonc/nov153. Epub 2015 Sep 1. PubMed PMID: 26330563; PubMed Central PMCID: PMC4767237.