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Epithelial SOX9 drives progression and metastases of gastric adenocarcinoma by promoting immunosuppressive tumour microenvironment

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Objective: Many cancers engage embryonic genes for rapid growth and evading the immune system. SOX9 has been upregulated in many tumors, yet the role of SOX9 in mediating immunosuppressive tumor microenvironment is unclear. Here, we aim to dissect the role of SOX9-mediated cancer stemness attributes and immunosuppressive microenvironment in advanced Gastric Adenocarcinoma (GAC) for novel therapeutic discoveries.

Methods: RNAseq/sc-RNA-seq, patient-derived cells/models and extensive functional studies were used to identify the expression and functions of SOX9 and its target genes in vitro and in vivo. Immune responses were studied in PBMCs or CD45+immune cells co-cultured with tumor cells with SOX9high or knockout and the KP-Luc2 syngeneic models were used for efficacy of combinations.

Results: SOX9 is one of the most upregulated SOX genes in GAC, and highly expressed in primary and metastatic tissues and associated with poor prognosis. Depletion of SOX9 in patient-derived GAC cells significantly decreased cancer stemness attributes, tumor formation, metastases, and consistently increased CD8 T cell responses when cocultured with PBMCs/CD45+ cells from GAC patients. RNA-sequencing identified the leukemia inhibitory factor (LIF) as the top secreted molecule regulated by SOX9 in tumor cells and was enriched in malignant ascites and mediated SOX9-induced M2 macrophage repolarization and inhibited T cell function.

Conclusion: Epithelial SOX9 is critical in suppressing CD8+ T cell responses and modified macrophage function in GAC through the paracrine LIF factor. Co-targeting LIF/LIFR and CSF1R has great potential in targeting SOX9-mediated cancer stemness, T cell immunosuppression, and metastases suggesting the novel combination therapy against advanced GAC.

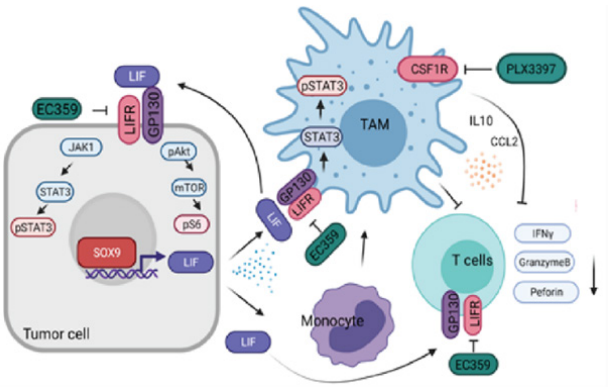

Figure 1: Gastric Adenocarcinoma by promoting immunosuppressive tumor

Recent Publications

1. Ajani JA et al and Song S*. YAP1 mediates gastric adenocarcinoma peritoneal metastases that are attenuated by YAP1 inhibition. Gut. 2021 Jan;70(1):55-66.

2. Song S* et al Targeting cancer stem cells with a pan-BCL-2 inhibitor in preclinical and clinical settings in patients with gastroesophageal carcinoma Gut. 2021 Dec;70(12):2238-2248.

3. Wang R et al and Song S, Ajani JA, Wang L . Single cell lineage diversity of metastatic gastric adenocarcinnoma contributes to the inherent intratumoral heterogeneity and a fundamental prognostic signature. Nat Med. 2021 Jan;27(1):141-151

Biography

Shumei Song is a full Professor in the Department of Gastrointestinal Medical Oncology at the University of MD Anderson Cancer Center. Her research has been focus on gastrointestinal cancers especially on Upper GI malignancy including esophageal and GE Junction and gastric adenocarcinoma for more than 20 years. She has extensive experience in gastrointestinal cancer biology, gene transcription and expression regulation, and molecular approaches to investigations of cellular mechanisms of gastroesophageal cancer progression and metastasis. Her current major research focus is to understand how aberrant stem cell signaling including Hippo/YAP1,TGF-β and Notch signaling play a role in the pathogenesis of esophageal and gastric cancers and to understand how deregulation of these pathways drives tumor progression, therapy resistance and even metastasis through regulation of tumor immunosuppressive microenvironments.

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