ANDROGEN RECEPTOR PROMOTES GASTRIC CARCINOGENESIS VIA UPREGULATING THE EXPRESSION OF CELL CYCLE-RELATED KINASE

Background Gastric cancer (GC) is a leading global health problem. In most areas of the world, the incidence rate of GC in males was 1.5- to 3-fold higher than that in females. The androgen receptor (AR) is an independent adverse prognostic factor in patients with GC. However, the mechanism of AR regulating the progression of GC remains unclear. The aim of this study is to determine the effect of AR on the progression of GC and the mechanism behind these effects, which will provide novel ideas for the treatment of GC.

Methods The relative expression of AR were detected by semi-quantitative RT-PCR and real-time quantitative PCR. The functions of AR in GC were determined by colony formation experiment, transwell migration and invasion assay. The clinical data were obtained from the website cBioPortal and XENA database. The potential mechanism of AR in GC was searched by Gene Set Enrichment Analysis (GSEA) and DAVID. Chromatin immunoprecipitation (ChIP) and PCR were performed to explore the function of AR as a transcriptional factor. The xenograft mouse models in nude mice were used to verify the function of CCRK in vivo.

Results The expression of AR was upregulated in 6/8 GC cell lines. Compared to adjacent tissues, it’s expression of GC was higher. Ectopic expression of AR promoted the colony-formation ability, migration and invasion of GC cells. In contrast, the knockdown of AR showed the opposite effects. Remarkably, we found that AR regulated the expression of cell cycle related kinase (CCRK) through transcriptional regulation. The AR-CCRK axis promoted GC development through phosphorylation of GSK3β and β-catenin. Furthermore, TCGA data revealed that high expression of AR or CCRK was related to poor prognosis of GC patients. The prognosis of patients with concurrent high expression of AR and CCRK was significantly worse than that of patients with low expression of both AR and CCRK.

Conclusions The expression of CCRK is increased by AR in GC. Low expression levels of AR and CCRK are related to better prognosis in GC patients, suggesting they are also candidates as prognostic indicators in GC.

Background Hepatic cell cycle-related kinase (CCRK) has been shown to be involved in the progression of various cancers. However, the role of CCRK in hepatocellular carcinoma (HCC) development remains unclear. The aim of this study is to determine the effect of CCRK on the progression of HCC and the mechanism behind these effects, which will provide novel ideas for the treatment of HCC.

Methods We conducted a liver-specific CCRK inducible transgenic (TG) mouse model by a Cre/loxP system. Orthotopic and metastatic mouse models were used to investigate the role of CCRK in promoting tumor growth and metastasis. PMN-MDSC was depleted by anti-Ly6G antibody. Cytokine, chemokine, and immune cells profiling were performed after sacrifice.

Results Induction of CCRK expression by tamoxifen injection could increase CD11b^Gr-1^Ly6G^Ly6C^low polymorphonuclear (PMN)-MDSCs liver accumulation specifically in male mice with upregulated Cxcl1 and Gsf2 expression. Intrahepatic injection of a mouse hepatoma cell line Hep1–6 in male TG mice developed larger tumors compared to control and positively associated with increased PMN-MDSCs levels in liver.