High glucose-ROS conditions enhance the progression in cholangiocarcinoma via upregulation of MAN2A2 and CHD8

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Abstract: Diabetes increases risk of the development and progression of various cancers including cholangiocarcinoma (CCA). However, the molecular mechanism link between high glucose and CCA development remains elusive. In the present study, we showed that a high glucose condition significantly increased reactive oxygen species (ROS) production and ROS itself is critical for high glucose-induced proliferation and migration abilities of CCA cells. Unbiased proteomic analysis, mannosidase alpha class 2a member 2 (MAN2A2) was identified as a key enzyme in the downstream of high glucose-ROS signaling, and it was upregulated at both mRNA and protein levels in a high glucose- and ROS- dependent manner. MAN2A2 knockdown significantly reduced aggressive phenotypes of CCA cells. To understand the molecular mechanisms of how MAN2A2 was increased under the high glucose-ROS signaling axis, we used in silico analyses. Chromodomain helicase DNA-binding protein 8 (CHD8) is an important epigenetic regulator between high glucose-ROS signaling and MAN2A2 transcription. CHD8 was significantly induced by high glucose-ROS signaling and regulated MAN2A2 expression. Importantly, cell proliferation and migration were dramatically reduced by MAN2A2 or CHD8 knockdown. In addition, both MAN2A2 and CHD8 were significantly upregulated in CCA tumor tissues compared with the adjacent normal tissues. These data suggested that high glucose-ROS signaling enhanced CCA progression via upregulation of MAN2A2 mediated by CHD8. MAN2A2 and CHD8 are promising therapeutic target for CCA and diabetic high glucose conditions. Our findings therefore have significant potential to improve treatments of CCA.

Keywords: CHD8, cholangiocarcinoma, high glucose, MAN2A2, reactive oxygen species