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IGF2 induces CD133 expression in esophageal cancer cells to promote cancer stemness

Wen Wen Xu, Bin Li, Jian Fu Zhao, Jing Ge Yang, Jun Qi Li, Sai Wah Tsao, Qing-Yu He, Annie L.M. Cheung



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Abstract

Failure to eradicate cancer stem cells (CSC) during primary therapy may lead to cancer recurrence. We recently reported that CD133 is a functional biomarker for CSCs in esophageal squamous cell carcinoma (ESCC) but the molecular pathways critical for maintenance of CD133-positive CSCs are largely unknown. Here, we revealed that knockdown of IGF2 or treatment with PI3K/AKT inhibitors markedly inhibited the abilities of CD133-positive ESCC cells to self-renew, resist chemotherapeutic drugs, and form tumors. Further functional analysis identified miR-377 as a downstream regulator of PI3K/AKT signaling, and a mediator of the effects of IGF2 on CD133 expression and CSC properties. We found that the expression levels of IGF2 and CD133 were positively correlated with each other in primary ESCC, and that concurrent elevation of IGF2 and CD133 expression was significantly associated with poor patient survival. Furthermore, *in vivo* experiments demonstrated that IGF2-neutralizing antibody enhanced the sensitivity of tumor xenografts in nude mice to 5-fluorouracil treatment. This study underpins the importance of the IGF2-PI3K/AKT-miR-377-CD133 signaling axis in the maintenance of cancer stemness and in the development of novel therapeutic strategy for treatment of esophageal cancer.

Keywords: cancer stem cells, esophageal cancer, CD133, prognostic biomarker, targeted therapy

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