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Blockade of autophagy reduces pancreatic cancer stem cell activity and potentiates the tumoricidal effect of gemcitabine

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Cancer stem cells (CSCs) are considered responsible for the recurrence and chemoresistance of cancer. Dysregulated autophagy is highly prevalent in many types of cancer including pancreatic cancer and has been implicated in cytoprotection and tumor promotion. We plan to investigate the role of autophagy in regulating cancer stemness and chemoresistance of pancreatic cancer. In pancreatic cancer tissue microarrays, LC3 expression positively correlated with the expression of CSC markers aldehyde dehydrogenase 1 (ALDH1), CD44 and CD133 in pancreatic cancer tissues. High co-expression of LC3/ALDH1 was associated with both poor overall survival and progression-free survival. In pancreatic cancer cell lines, higher LC3-II expression was observed in the sphere-forming cells than in the bulk cells. Blockade of autophagy by silencing ATG5, ATG7 and BECN1 or the administration of autophagy inhibitor chloroquine markedly reduced the CSC populations, ALDH1 activity, sphere formation and resistance to gemcitabine in vitro and *in vivo.* Furthermore, osteopontin (OPN) was found to stimulate LC3-II, ALDH1, CD44 and CD133 expression in PANC-1 cells, whereas this effect could be prevented by OPN knockdown and autophagy blockade. After treatment with various inhibitors against the major signaling pathways downstream of OPN, only the inhibitor of NF-κB activation, BAY 1170-82, could effectively counteract OPN-induced autophagy and CSC activity. Pancreatic cancer patients manifesting high levels of OPN/LC3/ALDH1 and OPN/CD44/CD133 had poor survival. Induction of autophagy mediated by OPN/NF-κB signaling is required for maintenance of pancreatic CSC activity. In conclusion, combination of gemcitabine with pharmacological autophagy inhibitors is a promising therapeutic strategy for pancreatic cancer.

Biography

Yan-Shen Shan has completed his MD and PhD from National Cheng Kung University. He is the Director division of Trauma and UGI cancer team in National Cheng Kung University Hospital. He has published more than 100 papers in reputed journals and has been serving as an Editorial Board Member of repute.

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