

## Inhibition of pancreatic cancer stem cell characteristics in human and Kras<sup>G12D</sup> transgenic mice by resveratrol

R.K. Srivastava<sup>1</sup>, S-N. Tang<sup>1</sup>, M. Rodova<sup>1</sup>, D. Nall<sup>2</sup> and S. Shankar<sup>2</sup>

<sup>1</sup>Department of Pharmacology, Toxicology and Therapeutics, and Medicine, The University of Kansas Medical Center, USA

<sup>2</sup>Department of Pathology and Laboratory Medicine, The University of Kansas Medical Center, USA

**Background:** Cancer stem cells (CSCs) can proliferate and self-renew extensively due to their ability to express anti-apoptotic and drug resistant proteins, thus sustaining tumor growth. Therefore, the strategy to eradicate CSCs might have significant clinical implications. The objectives of this study were to examine the molecular mechanisms by which resveratrol inhibits stem cell characteristics of pancreatic CSCs derived from human primary tumors and KrasG12D transgenic mice.

**Methodology/principal findings:** Human pancreatic CSCs (CD133+CD44+CD24+ESA+) are highly tumorigenic and form subcutaneous tumors in NOD/SCID mice. Human pancreatic CSCs expressing high levels of CD133, CD24, CD44, ESA, and aldehyde dehydrogenase also express significantly more Nanog, Oct-4, Notch1, MDR1 and ABCG2 than normal pancreatic tissues and primary pancreatic cancer cells. Similarly, CSCs from KrasG12D mice express significantly high levels of Nanog and Oct-4 than pancreatic tissues from Pdx-Cre mice. Resveratrol inhibits the growth (size and weight) and development (PanIN lesions) of pancreatic cancer in KrasG12D mice. Resveratrol inhibits the self-renewal capacity of pancreatic CSCs derived from human primary tumors and KrasG12D mice. Resveratrol induces apoptosis by activating caspase-3/7 and inhibiting the expression of Bcl-2 and XIAP in human CSCs. Resveratrol inhibits pluripotency maintaining factors (Nanog, Sox-2, c-Myc and Oct-4) and drug resistance gene ABCG2 in CSCs. Inhibition of Nanog by shRNA enhances the inhibitory effects of resveratrol on self-renewal capacity of CSCs. Finally, resveratrol inhibits CSC's migration and invasion and markers of epithelial-mesenchymal transition (Zeb-1, Slug and Snail).

**Conclusions/significance:** These data suggest that resveratrol inhibits pancreatic cancer stem cell characteristics in human and KrasG12D transgenic mice by inhibiting pluripotency maintaining factors and epithelial-mesenchymal transition. In conclusion, resveratrol can be used for the management of pancreatic cancer.