SULFORAPHANE ENHANCES EFFECTS OF SORAFENIB, QUERCETIN AND CHEMOTHERAPY TOWARDS PANCREATIC CANCER STEM-LIKE CELLS

Vanessa Rausch1,2, Wei Zhou1,2 Sabrina Labsch1,2, Georgios Kalitafsidis1,2, Li Liu1,2, Bernd Baumann1, Jürgen Mattern1,2, Jury Gladkich1,2, Thomas Wirth1, Peter Schemmer2, Markus W. Büchler2, Alexei V. Salnikov1, Ingrid Herr1,2

1Molecular OncoSurgery, University of Heidelberg and German Cancer Research Center, 2Department of General Surgery, University of Heidelberg, Institute of Physiological Chemistry, University of Ulm, Ulm, Germany

Characterization of CSC markers in established pancreatic cancer cell lines

Background: Despite intense efforts to develop treatments against pancreatic cancer, agents that cure this highly resistant and metastasizing disease are not available. Considerable attention has focused on broccoli compound sulforaphane, which is suggested as combination therapy for targeting of pancreatic cancer stem cells. However, there are concerns that anti-oxidative agents such as sulforaphane may interfere with cytotoxic therapy – as suggested e.g. for vitamins.

Material and methods: The effects of sulforaphane upon combination with various standard chemotherapeutics, the dietary agent quercetin and the multi kinase inhibitor sorafenib were evaluated using in vitro and in vivo models of pancreatic tumor cells with stem-like phenotype. CSC-marker expression, ALDH1 activity, self-renewal potential, Notch signaling, migratory activity, apoptosis induction, viability, proliferation, NF-κB-signaling, and angiogenesis were analyzed.

Results: While each therapeutic agent alone diminished the stem-like characteristics, elimination of highly aggressive stem-like cells was not complete. However, combination with sulforaphane led to an additive effect of each single agent. This was due to inhibition of self-renewal activity and sensitization to apoptosis by inhibition of Notch, NF-κB, caspases, clonogenicity, spheroid-forming, migratory activity and downregulation of anti-apoptotic and EMT-related proteins. In vivo, combination treatment was most effective and totally abolished growth of cancer stem-like xenografts. No pronounced side effects were observed in mice. Our data suggest that sulforaphane increases the effectiveness of various cytotoxic drugs, sorafenib and quercetin against cancer stem cells without inducing additional toxicity in mice.

Conclusions: Our data suggest the combination sulforaphane with conventional or novel cancer therapeutics is safe and a promising new concept for targeting of pancreatic cancer stem-like phenotype.