Triptolide from TCM abolishes NF-κB-signaling, EMT and Stem-like Features in a Hypoxic Microenvironment of Pancreatic Cancer

Li Liu 1,2, Alexei V. Salnikov 1,3, Markus W. Büchler 2, Ingrid Herr 1,2

1 Molecular Oncology Surgery, University of Heidelberg and German Cancer Research Center, Heidelberg, Germany
2 Department of General Surgery, University of Heidelberg, Heidelberg, Germany
3 Department of Translational Immunology, German Cancer Research Center and National Center for Tumor Diseases, Heidelberg, Germany

Introduction: Pancreatic cancer is characterized by a pronounced hypoxic tumor-microenvironment and the level of hypoxia is considered as an independent factor of poor prognosis. It has been identified that the induction of cancer stem cells (CSCs) characteristics, migratory properties and epithelial-to-mesenchymal transition (EMT)-like signaling in pancreatic cancer cells upon hypoxia. Hypoxia-induced NF-κB signaling is an important mediator of CSC-like cells by induction of EMT signaling. Triptolide from traditional chinese medicine (TCM) is a potent inhibitor of transcriptional activation of NF-κB. Targeting of NF-κB by specific inhibition of c-Rel or Triptolide could be beneficial for targeted therapy in the hypoxic environment of pancreatic cancer.

Aims: To investigate the effect of hypoxia on pancreatic CSCs and to further elucidate the effect and molecular mechanism of Triptolide anti-cancer action under hypoxic microenvironment.

Methods: MIA PaCa-2, AsPC-1 and BxPc-3 pancreatic carcinoma cell lines were used as representatives of CSMH (CSC-high), and CSC- low cell lines, respectively. The ability of hypoxia and Triptolide to target hypoxia-induced CSCs was evaluated by sphere, colony formation assays, measuring ALDH1 activity in vitro. The effect of Triptolide on the CSC/EMT-related and proteins expression evaluated by Western blot analysis upon hypoxia. To elucidate the mechanism of Triptolide on hypoxia-induced EMT and CSC related features NF-κB signaling were investigated.

Characterization of established human pancreatic cancer cell lines

Hypoxia increases stemness characteristics of pancreatic cancer cells

Hypoxia induces morphological changes, EMT features and migration

CRel siRNA inhibits EMT-related features and migration potential

Triptolide inhibits hypoxia-induced EMT-related protein and NF-κB signaling

Triptolide abolishes hypoxia-induced CSC-like features

Conclusions: Hypoxia environment increased migratory capacities of pancreatic cancer cells with elevated stem cell characteristics and EMT features by induced NFκB activity. In addition, traditional chinese medicine-Triptolide treatment inhibited hypoxia-induced NF-κB activity. Furthermore, Triptolide abolished EMT and CSC-like features. Our data suggested that NF-κB inhibition is in volved in the process of hypoxia and EMT. Above results support that Triptolide from TCM may be a good candidate for the treatment of pancreatic cancer enriched in CSCs.