Mao Li

Dr. med.

Overexpression of Eukaryotic Initiation Factor 4F: a Therapeutic Target in Cholangiocarcinoma

Fach/Einrichtung: Chirurgie

Doktorvater: Herr Prof. Dr. med. Dr. h.c. Peter Schemmer

Protein synthesis is one of the most critical activities in the living cells. The rate-limiting process in translation is the initiation stage. EIF4F is the key factor in translation initiation regulated by several signaling pathways.

In IF staining for eIF4E, eIF4G and 4EBP1, the mean OD in the tumor group had no significant difference compared to the normal group. The *p* for eIF4E, eIF4G and 4EBP1 at 200× were 0.42, 0.11 and 0.11 respectively, and the *p* for eIF4E, eIF4G and 4EBP1 at 400× were 0.87, 0.09 and 0.38 respectively.

In PLA staining, the eIF4E-eIF4G was significantly upregulated in the CCA cells compared to the normal cholangiocytes, while the eIF4E-4EBP1 decreased dramatically. The *p* for eIF4E-eIF4G and eIF4E-4EBP1 at 200× were <0.001 and <0.001 respectively, and the *p* for eIF4E-eIF4G and eIF4E-4EBP1 at 400× were <0.001 and <0.001, respectively.

After SFN, eIF4E-eIF4G was suppressed significantly as compared to the controls, while eIF4E-4EBP1 rose dramatically with SFN. For eIF4E-eIF4G complex, the *p* for HuCCT1, TFK-1 and EGI-1 at 400× were 0.014, 0.048 and 0.02, respectively. For

eIF4E-4EBP1 complex, the *p* for HuCCT1, TFK-1 and EGI-1 at 400× were 0.011, < 0.001 and 0.003, respectively.

SFN targeted Akt activation by drastically suppressing p-Akt formation, leaving the expression level of Akt unchanged. The decreased p-Akt lifted the restriction on TSCs and p-TSCs, a tumor suppressor inhibited by p-Akt. Hence, the hyperactive TSCs and p-TSCs dramatically reduced the expression of the downstream mTOR and p-mTOR. This regulatory cascade influenced the eIF4F formation by significantly upregulating the expression of unphosphorylated 4EBP1, the active form serving as an inhibitor to eIF4F formation. The expression of inactive form of 4EBP1, p-4EBP1, remained stable. In this study, it is clearly demonstrated that eIF4E-eIF4G complex is significantly higher in CCA samples than in normal bile ducts, while eIF4E-4EBP1 complex was in the opposite trend. After *in vitro* SFN treatment in CCA cell lines, cell death was promoted with eIF4E-4EBP1 complex upregulation and eIF4E-eIF4G complex downregulation. SFN suppressed Akt phosphorylation in Akt/mTOR pathway and activated 4EBP1 to inhibit CCA cell proliferation.