Secreted Cyclophilin A Mediates G1/S Phase Transition of Cholangiocarcinoma Cells via CD147/ERK1/2 Pathway

Sumalee Obchoei, [1,2] Kanlayanee Sawanyawisuth,[1] Chaisiri Wongkham,[1] Watchara Kasinrerk,[3] Qizhi Yao,[2] Changyi Chen,[2] Sopit Wongkham[1]*

[1]*Department of Biochemistry, Liver Fluke and Cholangiocarcinoma Research Center, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*

[2]*Molecular Surgeon Research Center, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, Texas, USA*

[3]*Division of Clinical Immunology, Department of Medical Technology, Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand*

**e-mail: sopit@kku.ac.th*

Introduction: It has previously been shown that cyclophilin A (CypA) is up-regulated in human cholangiocarcinoma (CCA) tissues. Suppression of intracellular CypA (inCypA) significantly reduces cell proliferation *in vitro* and tumor growth in nude mice. In the present study, the effect and potential mechanism of secreted CypA (sCypA) on cell proliferation of CCA cell lines were further investigated.

Methods: CCA cells were treated with sCypA containing conditioned media (CM) or with purified recombinant human CypA (rhCypA). Cell proliferation, cell cycle, ERK1/2 and STAT3 activities were examined by an MTS assay, flow cytometry, and western blotting.

Results: sCypA was detected in CM from MMNK1 (an immortalized human cholangiocyte cell line) and six CCA cell lines. The sCypA levels corresponded to the inCypA levels indicating the intracellular origin of sCypA. Both sCypA-containing CM and rhCypA significantly increased proliferation of CCA cells. CD147 depletion by shRNA-knockdown or neutralizing with a CD147-monoclonal antibody significantly reduced sCypA-, and rhCypA-mediated cell proliferation. Upon rhCypA treatment, ERK1/2 was rapidly phosphorylated; whereas neutralizing CD147 inhibited ERK1/2 phosphorylation. Cell cycle analysis showed a significant increase in S phase and decrease in G1 population in rhCypA-treated cells. The expression levels of cyclin D1 and phosphorylated-retinoblastoma protein in the rhCypA-treated cells were increased compared with those in the un-treated control cells.

Conclusions: CypA is secreted from CCA cells and enhances cell proliferation in an autocrine/paracrine manner, at least via direct binding with CD147, which may activate the ERK1/2 pathway and increase cyclin D1 production and G1 to S transition.

Keywords secreted cyclophilin A; CD147; G1 to S transition; bile duct cancer; ERK1/2; Licartin

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