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The Fine Tuning of the Hedgehog and Autophagy Pathways to Combat Cholangiocarcinoma

Yazarlar : Araştırma Görevlisi Nihan Aktaş - Öğrenci Helin Sağır - Araştırma Görevlisi Merve Şansaçar - Yrd.Doç.Dr Mona El Khatib

Kurum : Abdullah Gül Üniversitesi

GİRİŞ - AMAÇ

The American Cancer Society has estimated that cases in liver cancer have increased more than three times since 1980. Cholangiocarcinoma (CCA) is one of the most common liver cancer types with a 5-year survival rates ranging between 15% and 30% for cholangiocarcioma patients [1] . Aberrant signaling pathways could be a main driver in CCA pathogenesis. Hedgehog (Hh) Pathway is one of these pathways, which has role in tissue differentiation and stem cell maintenance [2, 3] . Aberrant activation of this pathway has been observed in several carcinomas including cholangiocarcinoma [3, 4] . Hh pathway is known to crosstalk and regulate autophagy, which is a lysosomal degradation process involved in the regulation of metabolic processes, organelle turnover and cellular homeostasis [5-9] . Based on this crosstalk between Hh pathway and autophagy and aberrant activation of Hh pathway observed in cholangiocarcinoma, we are planning to understand the effects of combination therapy using Hh and autophagy inhibition on cholangiocarcioma progression.

METOD

Accordingly, we performed MTT cell proliferation assay on treated EGI-1 and TFK-1 cholangiocarcinoma cell lines with chloroquine, ammonium chloride, hydroxychloroquine and GANT61 in order to check the effects of autophagy and Hh inhibiton on cholangiocarcinoma proliferation. Using IC50 and IC20 values, we treated TFK-1 cells with chloroquine, hydroxychloroquine and ammonium chloride, EGI-1 cells with chloroquine and checked percentage of apoptotic cells/control. In order to determine autophagy and hedgehog protein expression levels by Western Blotting, we are using primary antibodies against these proteins.

BULGULAR

Proliferation of TFK-1 and EGI-1 cell lines decreased after 24h, 48h and 72h treatment with autophagy inhibitors ammonium chloride, chloroquine, hydroxychlorquine and Hh inhibitor, GANT61. We observed a 30% decrease in the proliferation of TFK-1 cells after hydroxychloroquine, chloroquine and ammonium chloride treatment and a 90% decrease in the proliferation of GANT61 treated TFK-1. Hydroxychloroquine and chloroquine treatment decreased cell proliferation to 10% and we observed 70% and more than 90% dead cells after ammonium chloride and GANT61 treatment, respectively. Percentage of apoptotic cells/control increased after 48h chloroquine, hydroxychloroquine and ammonium chloride treatment. We observed a 1.5X, 2.5X and 3.2X fold-increase in the apoptotic cell percentage compared to control after chloroquine, hydroxychloroquine and ammonium chloride, respectively and almost 420% of apoptotic cells/control in chloroquine treated EGI-1 cells. We are still trying to optimize Western Blotting method to determine autophagy and Hh related protein levels.

SONUC

Considering the crosstalk between Hh and autophagy pathways, we are planning to continue with combination therapy using our obtained data.

ANAHTAR KELİMELER

cholangiocarcinoma, autophagy, Hedgehog pathway, combination therapy