Ying-Jan Wang, J Cancer Sci Ther 2016, 8:10(Suppl)
http://dx.doi.org/10.4172/1948-5956.C1.093

Synergistic antitumor effects of radiation and proteasome inhibitor treatment in pancreatic cancer through the induction of autophagy and the down-regulation of TRAF6

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Ninety percent of human pancreatic cancer is characterized by activating K-RAS mutations. TRAF6 is an oncogene that plays a vital role in K-RAS mediated oncogenesis. We investigated the synergistic effect of combining ionizing radiation (IR) and proteasome inhibitor (MG132). Furthermore, following combined treatment with IR and MG132, we analyzed the expression of TRAF6 and the mechanism of human pancreatic cancer cell death in vitro and in an orthotopic pancreatic cancer mouse model. The combined treatment groups displayed synergistic cell killing effects and induced endoplasmic reticulum stress in human pancreatic cancer cells. The combined treatment groups were characterized by enhanced cytotoxicity, which resulted from increased autophagy induction through the inhibition of TRAF6. Significantly reduced cytotoxicity was observed following MG132 and IR treatment of MIA PaCa-2 cells pre-treated with 3-MA (an autophagy inhibitor). Down-regulation of TRAF6 led to a significant increase in apoptosis and autophagy. In an orthotopic xenograft model of SCID mice, combination MG132 and IR therapy resulted in a significant increase in the tumor growth delay time and a decreased tumor tissue expression of TRAF6. IR combined with a proteasome inhibitor or TRAF6 inhibition could represent a new therapeutic strategy for human pancreatic cancer.

Biography

Ying-Jan Wang has completed his PhD from National Taiwan University and Postdoctoral studies from National Taiwan University, College of Medicine. He is the Director of Department of Environmental and Occupational Health, College of Medicine, National Cheng Kung University. He has published more than 120 papers in reputed journals and has been serving as an Editorial Board Member of PLOS ONE.

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