IGF2BP1 controls cell death and drug resistance in rhabdomyosarcomas by regulating translation of cIAP1

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Presenter: Min-Hua Hsieh  Date: 2015/11/12, 15:10-16:00
Commentator: Chung-Liang Ho  Location: Room 601, Med College Building

Background:
Rhabdomyosarcomas (RMS) are malignant tumours of muscle. It is most commonly seen in children one to five years old. Currently, a major issues for RMS is chemotherapeutical resistance is still a big problem. Cellular inhibitor of apoptosis 1 (cIAP1) is a critical regulator of the nuclear factor-κB signalling pathway and of caspase-8-mediated cell death to promote cancer cell survival. Insulin-like growth factor 2-binding protein 1 (IGF2BP1) is an oncofetal protein that is normally expressed during embryogenesis; down-regulated in adult, but re-expressed in RMS and other tumors. In their previous research, the authors found IGF2BP1, the potential IRES trans-acting factor (ITAFs), binds to Internal ribosome entry site (IRES) of cIAP1 to regulate cIAP1 expression.

Objective:
To prove IGF2BP1 regulates the protein expression of cIAP1 and controls cell death and drug resistance.

Results:
When knocking down IGF2BP1, the protein level of cIAP1 also decreases. The author used polysome profiling assay to examine the cIAP1 translation, in IGF2BP1 knocked-down cells. Next, the authors used monocistronic reporter and bicistronic reporter assays to examine IRES activity. They found that IRES activity is decreased in cell expressing IGF2BP1 shRNA. Furthermore, authors also found the binding region between IGF2BP1 and cIAP1 IRES through UV crosslinking RNA-binding assay. When RH36 cell line transfected with IGF2BP1 siRNA, and treated with TNF-α, the cells showed apoptosis; while the cells with IGF2BP1 knockdown only and without TNF α treatment, the cells survive. It indicates that IGF2BP1 knockdown drives RMS cell to TNF α-mediated cell death. In cell line and animal experiment, authors found that the SMCs, the drug that can degrade cIAP1, could be used in combination with TNF α as a therapeutic approach to trigger the death of RMS cancer cells.

Conclusion:
IGF2BP1 directly regulates translation of the cIAP1 mRNA. It is an IRES trans-acting factor that regulates cIAP1 IRES-mediated translation, and subsequent influence the cancer cell survival and apoptosis.

Reference: