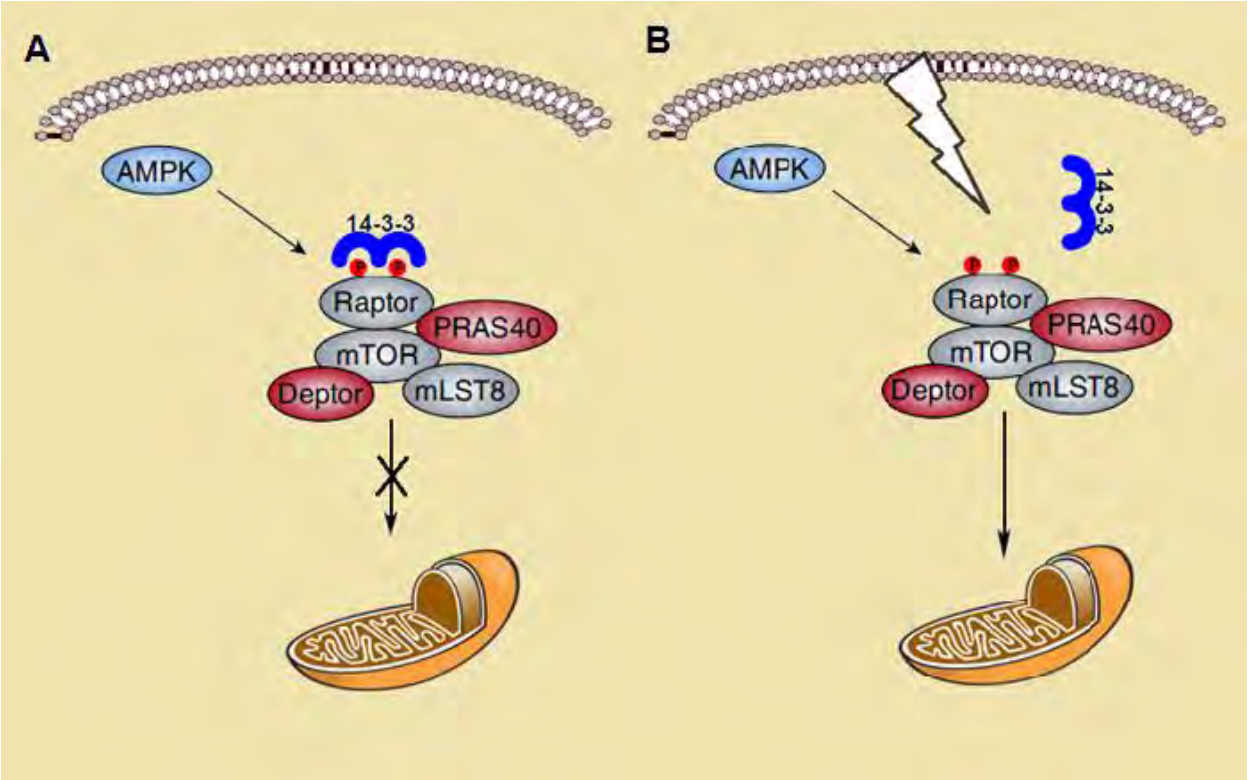
Mechanism underlying mTOR-associated Protection in Low Dose Radiation-induced Adaptive Response

Chung-Ling Lu, Rui Liu, Cuihong Jin and Jian Jian Li

Department of Radiation Oncology, the University of California Davis, Sacramento, California, 95817

Low dose radiation (LDR) can increase the mitochondria function and protect cells from apoptosis. Therefore, by treating normal cells with LDR can increase their radioresistance to the higher dosage of radiation to protect the normal cells from cell death. In the cells one protein that plays this critical role in controlling the cell fate is the mammalian target of rapamycin. Mammalian target of rapamycin (mTOR) is a serine/threonine kinase which controls protein synthesis and cell proliferation. mTOR is not only in the center of many signal transduction pathways but also can controls mitochondrial function by directly intact with its outer membrane. mTOR can activate the anti-apoptotic proteins to increase the mitochondrial membrane potential and, therefore, induce anti-apoptosis (3). When treating the cells with LDR might be able to activate the function of mTOR to induce the anti-apoptotic ability in the mitochondria. mTOR has one partner that is important for it to activate its down-stream substrate, Raptor. Raptor can be phosphorylated by AMPK on Ser 722 and Ser792 (2). When they are phosphorylated 14-3-3 can bind to Raptor and this process can protect the entry of mTOR into organelles. As previous studies showed that LDR can cause dissociation of 14-3-3 from its binding protein it is possible that LDR can cause the dissociation of Raptor and 14-3-3, too (1). When LDR is treated to the cells 14-3-3 will dissociate from Raptor and mTOR can have the ability to transport into the mitochondria to regulate its metabolic function and induce radioresistance against a higher level of radiation. Our study is testing whether LDR treated cells and tissues can induce the dissociation of Raptor and 14-3-3 and then mTOR can transport into mitochondria to regulate the mitochondrial functions. Activation of this mechanism may protect cells from damages of a higher dosage of radiation.



References:

1. Ahmed KM, Fan M, Nantajit D, Cao N, and Li JJ. (2008). Cyclin D1 in low-dose radiation-induced adaptive resistance. *Oncogene* **27:** 6738–6748.
2. Gwinn DM, Shackelford DB, Egan DF, Mihaylova MM, Mery A, Vasquez DS, Turk BE, and Shaw RJ. (2008). AMPK phosphorylation of Raptor mediates a metabolic checkpoint. *Mol cell* **30**:214-226.
3. Ramanathan A, and Schreiber SL. (2009). Direct control of mitochondrial function by mTOR. *PNAS* ***vol. 106, no. 52***, 22229-22232.