doi: http://dx.doi.org/10.7124/bc.0009BC

mTORC1 pathway in DNA damage response

Yinxing Ma[1], Licia Silveri[1], John LaCava[2], Yegor Vassetzky[1], Svetlana Dokudovskaya[1]

[1] CNRS UMR 8126, Université Paris-Sud, Gustave Roussy, 114, rue Edouard Vaillant, 94805, Villejuif, France; [2] Laboratory of Cellular and Structural Biology, The Rockefeller University, New York, New York, USA.
s.dokud@gmail.com

Living organisms have evolved various mechanisms to control their metabolism and response to various stresses, allowing them to survive and grow in different environments. In eukaryotes, the highly conserved mechanistic target of rapamycin (mTOR) signaling pathway integrates both intracellular and extracellular signals and serves as a central regulator of cellular metabolism, proliferation and survival. A growing body of evidence indicates that mTOR signaling is closely related to another cellular protection mechanism, the DNA damage response (DDR). Many factors important for mTOR pathway are also involved in the DDR. The SEA/GATOR complex is an inhibitor of the mTORC1 pathway. In mammals the GATOR1 complex is composed of the proteins DEPDC5, NPRL2 and NPRL3. We characterized mammalian cells overexpressing the GATOR1 component NPRL2 and found that in the cells with active p53, ectopic expression of NPRL2 induces NOX2-dependent production of reactive oxygen species and DNA damage. Overexpressed NPRL2 accumulates in the nucleus, together with apoptosis-inducing factor (AIF). These events are accompanied by phosphorylation of p53, activation of a DNA-damage response and cell cycle arrest in G1 phase, followed by apoptosis. In the cells negative for active p53, NPRL2 ectopic expression leads to activation of CHK1 or CHK2 kinases and cell cycle arrest in S or G2/M phases. Combined, these results demonstrate a new role for the NPRL2, distinct from its function in mTORC1 regulation.

doi: http://dx.doi.org/10.7124/bc.0009BD

ING3 is required for ATM signaling and DNA repair in response to DNA double strand breaks

Audrey Mouche[1], Jérôme Archambeau[1], Charles Ricordel[1], Laura Chaillot[1, 4], Nicolas Bigot[2, 3], Thierry Guillaudeux[1, 4], Muriel Grenon[6] and Rémy Pedeux[1]*

[1] INSERM U1242, COSS, Université de Rennes 1, CLCC Eugène Marquis, Rennes, France; [2] INSERM U1236, MICMAC, Rennes, France; [3] Present address: Genome Damage and Stability Centre, University of Sussex, Falmer, Brighton BN1 9RQ, UK; [4] UMS Biosit, SFR Biologie-Santé, Rennes; [5] Biochemistry, School of Natural Sciences, National University of Ireland, Galway, Ireland
remy.pedeux@univ-rennes1.fr

ING3 (Inhibitor of Growth 3) is a candidate tumor suppressor gene whose expression is lost in tumors. Aims: We want to identify and characterize new tumor suppresor functions for ING3. Methods: We conduct experiments in yeast and human cells depleted or not for ING3 and exposed to genotoxic agents. Results: - ING3-depleted human cells and yeast cells deleted for its ortholog YNG2 are sensitive to DNA damage suggesting a conserved role in response to such stress. - In human cells, ING3