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Signal transduction in health and disease

The coordination of signal transduction pathways is critical to the maintenance of normal cellular functions. Our laboratory has a range of interests in signalling events in heart disease, stroke and cancer with the aims of defining signalling events and pinpointing new targets for possible therapeutic intervention.

Projects:

(Note that the following four projects will use a range of techniques in cell and molecular biology and biochemistry)

New regulatory roles for c-Jun N-terminal Kinases (JNKs) in the endoplasmic reticulum (ER) stress response

The c-Jun N-terminal kinases (JNKs) are a family of stress-activated protein kinases from the MAPK family that phosphorylate and activate the transcription factor c-Jun as well as a range of other proteins, both nuclear and non-nuclear. Important clues on the roles of JNKs have come from JNK gene knockout studies. Specifically, JNKs have been proposed as therapeutic targets in the treatment of a range of diseases including diabetes, atherosclerosis and neurodegeneration. Thus, approaches directed at inhibiting the activity of JNK have been explored increasingly. In this project, we will examine the actions of JNK in the ER stress response. The lead in this area has come from our identification of the interaction between JNK and the pancreatic ER kinase or PKR-like kinase PERK, a known mediator of the ER stress response.

Contribution of stathmin-mediated microtubule proliferation to cardiac disease

Microtubules are an essential component of the cell cytoskeleton. In the dividing cell, microtubules are involved in chromosome segregation and organelle (ER, Golgi, mitochondria) placement. The function of microtubules in non-dividing, differentiated cardiac muscle cells (myocytes) is less clear. There is evidence that the enhanced proliferation of the microtubule network may contribute to dysfunction of the heart associated with diseases such as cardiac hypertrophy (heart enlargement). However, the proteins that regulate proliferation of the myotube network are unknown.

We have demonstrated microtubule hyperproliferation after stimulation of primary neonatal cardiac myocytes to undergo hypertrophy. This project will involve evaluation by gene knockdown with siRNAs of the contribution of the microtubule-destabilizing protein stathmin to enhanced microtubule array proliferation in hypertrophic cardiac myocytes.

Differential regulation of STAT3 spliceforms by TC45 phosphatase

The Signal Transducer and Activator of Transcription (STAT) 3 isoform of the family of latent transcription factors is essential for embryonic development and is involved in regulating a wide range of cellular processes. STAT3 is overactive in a large number of different cancers and the loss of STAT3 activity in specific cell types has detrimental effects on the immune system (excessive inflammation), mammary gland development and appetite suppression. STAT3 is activated by JAK-mediated phosphorylation of a critical tyrosine residue (Y705); however the phosphatase involved in dephosphorylation of STAT3 is unknown.

In addition, alternative splicing of the STAT3 gene generates two spliceforms, a full-length α (92 kDa) and a shorter truncated β (89 kDa) isoform. Currently, differential regulation and functions of the α and β spliceforms are underappreciated. For example, we have demonstrated that the β spliceform is preferentially phosphorylated in human heart failure. In this project, the dephosphorylation of STAT3 α and STAT3 β by the T-cell protein tyrosine phosphatase 45 (TC45) will be evaluated. TC45-mediated interaction and dephosphorylation of exogenously expressed STAT3 α and STAT3 β will be determined in murine embryonic fibroblasts that lack the STAT3 gene.

Regulation of muscle differentiation by microtubule destabilizing proteins

During development, mono-nucleated immature muscle cells (myoblasts) lose the capacity to divide and fuse into multi-nucleated myotubes in a process called 'myogenesis', central to muscle development. Microtubules are a component of the cell cytoskeleton, which is essential for myogenesis; however the precise function of microtubules is not clear.

In addition, the proteins involved in regulating the microtubule array during myogenesis have not been defined. During the differentiation of myoblasts to myotubes, the expression of the microtubule-destabilizing protein stathmin is down-regulated to almost undetectable levels. In this project, the potential of stathmin downregulation to induce myoblasts to differentiate in proliferating conditions will be evaluated by RNAi-mediated gene knockdown. In addition, the effect on myotube formation of maintaining stathmin expression in differentiating conditions will be investigated.

Recent publications:

9. Arthur PG, Matich GP, Pang WW, Yu DY, Bogoyevitch MA. (2007) 'Necrotic death of neurons following an excitotoxic insult is prevented by a peptide inhibitor of c-jun N-terminal kinase', *J Neurochem*, 102, 65–76.
10. Badrian B, Bogoyevitch MA. (2007) 'Gene expression profiling reveals complex changes following MEK-EE expression in cardiac myocytes', *Int J Biochem Cell Biol*, 39, 349–365.
11. Bogoyevitch MA. (2005) 'Therapeutic promise of JNK ATP-noncompetitive inhibitors', *Trends Mol Med*, 11, 232–239.
12. Ng DC, Zhao TT, Yeap YY, Ngoei KR, Bogoyevitch MA (2010) 'c-Jun N-terminal kinase phosphorylation of stathmin confers protection against cellular stress', *J Biol Chem*, In press.
13. Yeap YY, Ng IH, Badrian B, Nguyen TV, Yip YY, Dhillon AS, Mutsaers SE, Silke J, Bogoyevitch MA, Ng DC. (2010) 'c-Jun N-terminal kinase/c-Jun inhibits fibroblast proliferation by negatively regulating the levels of stathmin/oncoprotein 18', *Biochem J*;430, 345-354.
14. Bogoyevitch MA, Ngoei KR, Zhao TT, Yeap YY, Ng DC (2010) 'c-Jun N-terminal kinase (JNK) signaling: recent advances and challenges', *Biochim Biophys Acta*, 1804, 463-475.