



ROLE OF PAK1 IN THE REGULATION OF COLORECTAL CANCER GROWTH BY GASTRINS

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The p21-activated kinase PAK1 functions as a downstream node for many cellular signalling pathways. Activation of PAK1 leads to cytoskeletal reorganization that subsequently influences growth factor-induced cell migration and cancer metastasis. Alterations in PAK1 expression and activity have been reported in human tumours. In particular an increased level of PAK1 protein was associated with the progression of colorectal cancer (CRC), which is the second most common cause of cancer death in western countries. The peptide hormone gastrin and its precursors are growth factors, which have been shown to stimulate the growth and migration of colorectal cancer cells in vitro and to be involved in CRC development in animal models.

We have discovered that PAK1 is required for the effects of gastrin on cell proliferation, migration and apoptosis in gastric epithelial cells.

In this project we plan to study further the role of PAK1 in the regulation of colorectal cancer by gastrins. Cell growth, migration, and angiogenesis in the presence or absence of gastrins will be investigated in colorectal cancer cells transfected with PAK1 mutants or shRNA constructs. We will also investigate the role of PAK1 and its interaction with gastrin in animal models where colorectal cancer cells will be grown as xenografts in nude mice. Furthermore we will investigate colorectal cancer induction and development in PAK1 knockout mice.

Techniques:

- Cell culture
- Proliferation assays
- Angiogenesis assays
- Cell transfection
- RT-PCR
- Animal models of disease
- Transgenic mice

Publications:

He, H., Pannequin, J., Tantiogco, J.-P., Shulkes A. and BALDWIN, G.S. Glycine-extended gastrin stimulates cell proliferation and migration through a Rho- and ROCK-dependent pathway, not a Rac/Cdc42-dependent pathway. *Am. J. Physiol. Gastrointestinal and Liver Physiology*. 2005; 289: G478-G488.

Hollande, F., Shulkes, A. and Baldwin GS Signalling junctions in the gut epithelium. *Sci STKE* 2005; pe 13

He H, Yim M, Liu KH, Cody S, Shulkes A, Baldwin GS Involvement of G proteins of the Rho family in the regulation of Bcl-2-like protein expression and caspase 3 activation by gastrins *Cell Signal* 2008; 20: 83-93.

He, H., Shulkes, A. and BALDWIN, G.S. (2008) PAK1 interacts with beta-catenin and is required for the regulation of the beta-catenin signalling pathway by gastrins. *Biochim. Biophys. Acta. Molecular Cell Research*. 2008; In press.