



## RAS AND KUPFFER CELLS ROLE IN LIVER REGENERATION AND TUMORIGENESIS

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Partial hepatectomy (PHx) is the standard treatment for patients with colorectal cancer liver metastasis, however is associated with a high recurrence rate. Liver regeneration following hepatectomy correlates with increased tumour recurrence, mainly since the key events of liver regeneration such as cell proliferation, angiogenesis, and extracellular matrix (ECM) remodelling are also involved in tumour growth and metastasis. Evidence suggests that factors related to liver regeneration may play a pivotal role in tumour stimulation and hence recurrence. Angiotensin II (Ang II), a main effector peptide of the Renin Angiotensin System (RAS), has been shown to contribute to tumour metastasis by acting as a novel mitogenic and angiogenic factor via the Ang II type1 receptor (AT1R). Recent

studies have shown that RAS inhibitors can enhance liver regeneration. However, the mechanism remains unclear. Growth factors and cytokines produced by resident liver macrophages, Kupffer cells, also play an important role in regeneration after hepatectomy, although their role in tumour metastasis during liver regeneration remains controversial. Our preliminary results suggest that the number of Kupffer cells dramatically increases with tumour induction immediately after liver resection, suggesting that they may play a role in both establishment and control of the tumour environment. This study investigates the role of RAS in tumorigenesis during liver regeneration in a mouse model of colorectal liver metastases with 70% PHx.

### Techniques:

Histopathology  
Stereology  
RNA extraction  
Real Time RT-PCR  
ELISA  
Immunohistochemistry

### Projects

1. Investigation of RAS components (Ang II, AT1R, ACE, etc) in liver metastases during liver regeneration.
2. The role of Kupffer cells in tumour stimulation during liver regeneration.
3. Examination of the interaction between the hepatic RAS and Kupffer cell function during liver regeneration.

### Publications:

Christophi C, Harun N, Fifis T. Liver Regeneration and Tumor Stimulation-A Review of Cytokine and Angiogenic Factors. Journal of Gastrointestinal surgery. Jan 8. 2008. E pub ahead of print. in press.

Amra Dizdarevic, Nadia Harun, Cathy Malcontenti-Wilson, Arthur Shulkes, Chris Christophi, Graham S Baldwin. Gastrin is not required for liver regeneration. ANZ J Surgery, 1-2, 68-71, Jan 2008.

Neo J H, Malcontenti-Wilson C, Muralidharan V, Christophi C. Effect of ACE inhibitors and Angiotensin II receptor antagonists in a mouse model of colorectal cancer liver metastases. J Gastroenterol Hepatol. 2007 Apr; 22(4):577-84.