



RENIN ANGIOTENSIN SYSTEM ROLE IN COLORECTAL CANCER LIVER METASTASES

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Anti-hypertensive agents targeting the renin-angiotensin system (RAS) are commonly used to treat cardiovascular diseases. However, recent studies indicate that patients treated with RAS inhibitors for hypertension have lower rates of certain malignancies or reduced tumour aggressiveness. We have also shown that RAS blockade, with anti-hypertensive agents that block the effects of the key RAS peptide ANG II, can reduce tumour growth in our mouse model of colorectal liver metastases. However, the role of various RAS components is poorly understood and the mechanism by which RAS blockade inhibits tumour growth has yet to be fully elucidated. We have shown that blockade of the RAS impairs tumour

neovascularisation; suggesting an anti-angiogenic effect. Kupffer cells, liver macrophages, may also mediate some of the effects of the RAS in this disease. We are utilizing both our in vivo model of colorectal liver metastases and in vitro systems to investigate the role of the RAS in tumour vascularisation and Kupffer cell function.

Techniques:

Quantitative RT-PCR
Immunohistochemistry
ELISA
Western Blots
Tissue/Cell Culture
Quantitative stereological analyses
Microvascular resin casting
Animal models of disease
Laser Doppler Flowmetry

Projects

1. To determine the role of specific RAS components in the progression of liver metastases by in vivo inhibition/activation of individual components and combination therapies.
2. To identify mechanisms responsible for the tumour-inhibitory effects of anti-hypertensive agents by assessing the effects of RAS on proliferation and growth factor production by endothelial cells, mouse colorectal cancer cells, and Kupffer cells in vitro.
3. To establish the role of Kupffer cells in regulating tumour growth and to define the interactions between the hepatic RAS and Kupffer cell function in vivo and in vitro.

Publications:

Ager, E.I., Neo, J., and Christophi, C. (2008) The renin-angiotensin system and malignancy. *Carcinogenesis*.

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