

Dr. Mark Guthridge

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Qualifications:

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General Overview

Cells in the body are able to accomplish an impressive range of functions within their lifetime. Underlying this diversity in cellular functions are a number of fundamental cellular responses that include cell survival, cell proliferation and cell differentiation. Growth factors are central regulators of each of these cellular responses.

The overall focus of my work lies in understanding the fundamental molecular mechanisms by which growth factors and cytokines regulate specific cell functions and what goes wrong in the regulation of these mechanisms in pathologies such as inflammatory disorders, developmental disorders and cancer.

We have identified a new "switch mechanism" by which growth factors are able to control cell survival, proliferation and differentiation. This mechanism involves site-specific phosphorylation of growth factor receptors, such as the Granulocyte Macrophage Colony Stimulating Factor receptor (GM-CSF receptor), and allows growth factors to tightly control cell function as well as keeping cell numbers in check.

Cancer cells arise because of a loss of regulation between cell survival and proliferation. We have identified signalling components within the cell that are susceptible to "short-circuits" that may lead to deregulation of site-specific phosphorylation and the loss of

control of cell survival and proliferation. We are developing strategies to target these deregulated signalling components in an effort to find the "Achilles' heel" of cancer.

Detailed description of specific research interests:

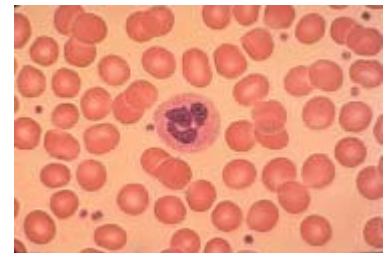
Below are listed three broad areas of ongoing research in my lab. Research opportunities are available for both students and postdoctoral scientists in all three areas.

1. The molecular basis for leukemia

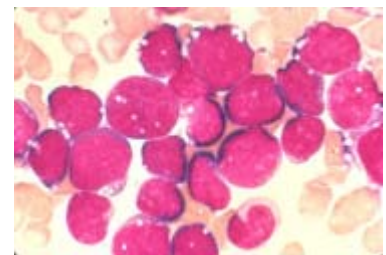
A new mechanism by which cytokine receptor serine phosphorylation regulates cell survival: Its role in normal cell function and the underlying basis for its deregulation in leukaemia.

We have identified a new mechanism by which cytokines and growth factors can regulate cell survival. This mechanism involves the phosphorylation of a specific serine residue in the cell surface receptor for the hemopoietic cytokine Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) and suggests a new paradigm for how growth factors and cytokines regulate cell survival. Importantly, we have shown that control over the receptor serine phosphorylation is lost in some leukaemias and may therefore lead to a loss of control over cell survival. Specifically, we have shown that receptor serine phosphorylation is constitutive in some human leukemias and may lead to uncontrolled cell survival and transformation.

Normal peripheral blood



Leukaemia



Opportunities to study this new signalling mechanism would involve examining the prevalence of constitutive receptor serine phosphorylation in normal (non-transformed) human blood cells compared to human leukaemic cells. These studies would further explore the underlying mechanisms that lead to constitutive receptor serine phosphorylation in leukaemic cells and how deregulation of these processes may lead to cancer. We are also examining a number of approaches to block the constitutive receptor serine phosphorylation in leukaemia and therefore block the deregulated cell survival. The results from such studies may lead to the development of novel strategies for the treatment of a range of cancers such as leukaemia.

2. Growth factors and neurogenesis

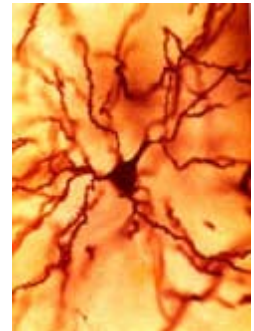
A growth factor receptor "switch" that determines different cellular responses and cell fates during development.

The Fibroblast Growth Factors (FGFs) are a family of growth factors that are critical regulators of embryonic development through their ability to mediate diverse cell functions. The multitude of biological functions attributed to the FGFs and their critical roles in regulating many fundamental biological processes both in health and disease such as development, tissue regeneration and cancer provide a unique opportunity to investigate

the molecular basis for how growth factors regulate specific cell responses. For example, during development, gradients of FGF are established whereby cells in high

concentrations of FGF commit to one cell fate (e.g. differentiation into a neuron) while cells in low concentrations of FGF commit to a different cell fate (e.g. the cells survive but do not differentiate). It is clear that these gradients of growth factors or "morphogens" can establish sharp boundaries in tissues or organs during development. This phenomenon has long been recognized and suggests that a cell can "read" its position in a gradient of growth factor and commit to one or more different cell fates allowing tissue specification. How a cell "reads" its position in a gradient of growth factor and commits to alternative cell fates during development is not known.

Cerebral cortex neuron showing extensive neurite projections



We have identified a new mechanism by which cells may be able to "read" their position in a gradient of growth factor. This mechanism involves a motif in the FGF receptor that specifies different biological outcomes depending on the concentration of growth factor. Using a neurite differentiation assay, we are characterizing the underlying mechanisms that determine neural cell differentiation during development. This assay allows us to establish the molecular basis for how specific signalling events within a cell can lead to different biological responses during development such as neural cell survival, proliferation, differentiation and the extension of neurite processes. These studies have direct implications in our understanding of how growth factors regulate development (e.g. neurogenesis) and how FGF receptor signalling may become corrupted in some pathologies such as Parkinson's or Alzheimer's disease.

3. Growth factors and tumorigenesis

FGF and its role in solid tumour growth

Uncontrolled mitogenic (cell growth promoting) activity and angiogenic (blood vessel growth promoting) activity underlie the growth of solid tumours. The potent mitogenic and angiogenic activities of the FGFs have been shown to support the growth of some solid tumours. For example FGF4 is a potent oncogene (transforming gene) that is able to promote the uncontrolled growth and vascularization of tumours. Blocking the mitogenic or angiogenic activities of the FGFs may prove effective in blocking the growth of some solid tumours. We have identified at least one mechanism by which FGF4 is able to transform cells. This mechanism involves the regulation of a specific intracellular signalling event by the adaptor or scaffold protein, 14-3-3. Ongoing studies in my laboratory will examine the role of 14-3-3 in FGF4-mediated transformation and tumorigenesis. Importantly, we are able to examine the role of 14-3-3 in colonies of FGF4-tumour cells in "real-time" using a newly developed method called Fluorescence Resonance Energy Transfer (FRET). This cutting-edge technology allows the analysis of specific protein-protein interactions in living cells by fluorescence microscopy and offers a unique approach to answering some of the more difficult questions in cell biology. This work will also examine the ability of the FGFs to promote the ability of endothelial cells to form new blood vessels (angiogenesis) and how this is regulated during the growth of solid tumours.

Scientific approaches and methods

New and cutting-edge technologies such as FRET, proteomics and microarray analysis of gene expression are currently applied in my laboratory to gain new insights into fundamental questions regarding how growth factors regulate cell function. The studies outlined above would also employ a wide range of cell biological techniques including cell culture and cell function assays. In addition, they would employ molecular approaches to examine a range of signal transduction pathways within cells or within specific compartments within cells. Molecular biology approaches such as DNA manipulation, cloning and mutagenesis are also widely used.

Recent publications (since 2003)

- P15** Olayioye M.A., **Guthridge M.A.**, Stomski F.C., Lopez A.F., Visvader J.E., Lindeman G.J. (2003) Threonine 391 phosphorylation of the human prolactin receptor mediates a novel interaction with 14-3-3 proteins. *J. Biol. Chem.* 278:32929-35. .
- P16** **Guthridge MA**, Barry EF, Felquer FA, McClure BJ, Stomski FC, Ramshaw H, Lopez AF. (2004) The phosphoserine-585-dependent pathway of the GM-CSF/IL-3/IL-5 receptors mediates hematopoietic cell survival through activation of NF-kappaB and induction of bcl-2. *Blood.* 103(3):820-7.
- P17** Thomas D, **Guthridge MA**, Woodcock J, Lopez A. (2005) 14-3-3 protein signaling in development and growth factor responses. *Curr. Top. Dev. Biol.* 67: 285-303. (invited review)
- P18** **Guthridge MA**, Powell JA, Barry EF, Stomski FC, McClure BJ, Ramshaw H, Felquer FA, Dottore M, Thomas DT, To B, Begley GC, Lopez AF. (2006) Growth factor pleiotropy is controlled by a receptor Tyr/Ser motif that acts as a binary switch. *EMBO J* 25: 479-89.
- P19** **Guthridge MA**, Goodall GJ, Pitson SM. (2006) Meeting Report: Barossa 2005-- Signaling Networks. *Science STKE*, Feb 2006(324):pe9
- P20** **Guthridge MA** and Lopez AF (2007) Phospho-Tyr/phospho-Ser binary switches: A new paradigm for the regulation of PI 3-kinase signalling and growth factor pleiotropy? *Biochemical Society Transactions.* (in press)

These and other publications are available upon request: mark.guthridge@imvs.sa.gov.au

Pubmed search term: guthridge m AND (monash [ad] OR "new york" [ad] OR australia [ad])

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- ➔ National Institutes of Health, USA (National Institute of Allergy and Infectious Diseases, NIAID)(Together with Prof. Angel Lopez and Prof. Michael Berndt).
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- ➔ The Association of International Cancer Research, UK