Molecular Regulation Laboratory

Prof. Sharad Kumar
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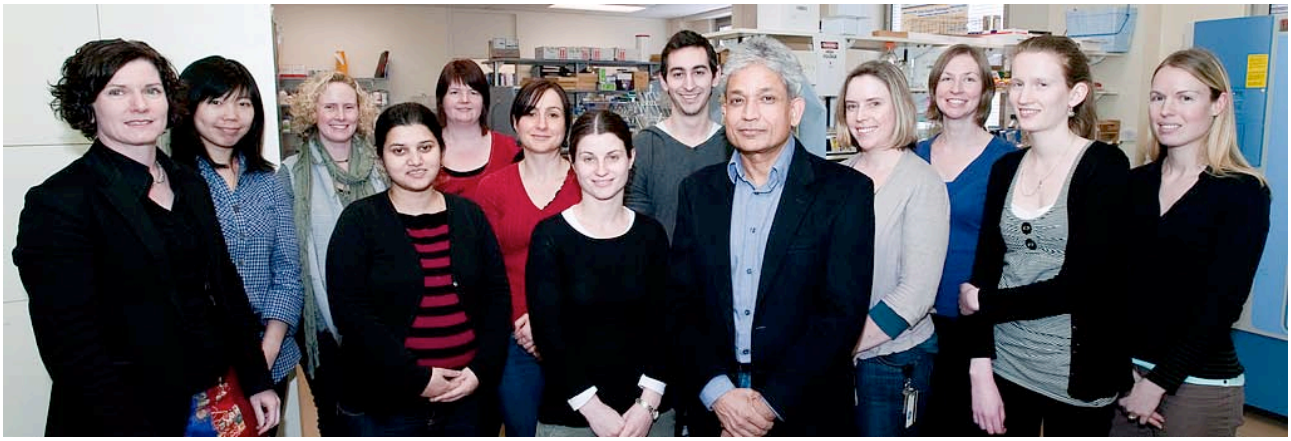

From left to right: Donna Denton, Layla Zhu, Natalie Foot, Sonia Shalini, Natasha Boase, Claire Wilson, Jantina Manning, Joey Puccini, Sharad Kumar, Hazel Dalton, Kathryn Mills, Shannon Nicolson, Loretta Dorstyn.

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Research interests:

The Molecular Regulation Laboratory provides outstanding opportunities for training of graduate students (Honours and PhD). Our broad research focus is on cellular and molecular biology of disease, with an emphasis on cancer biology. One of our major interests is the study of programmed cell death of normal and cancer cells.

Millions of cells in the human body die every minute as part of normal homeostasis by a special process termed apoptosis. Apoptotic cell death plays a fundamental role in cell and tissue homeostasis and too little or too much of it can lead to many human diseases including cancer. Given the essential role of cell death in normal functioning of the human body, deciphering the mechanisms of apoptosis is essential for understanding disease processes and to design effective treatment strategies for diseases which arise due to inappropriate apoptosis. Work in our laboratory has taken advantage of the vinegar fly *Drosophila melanogaster* as a model system to examine regulation of cell death during animal development as the components and pathways found in mammals are conserved in *Drosophila*.

Projects offered for 2012:

(1) Cell death regulation during animal development

We have been utilising *Drosophila* as an *in vivo* model to dissect out the mechanisms of developmentally programmed cell death (PCD). Our ongoing studies have led to several seminal findings, including the discovery of the key canonical pathway of PCD involving the caspase Dronc, and the adaptor Ark. We have also discovered a novel potential regulator of caspase activation from a Dronc-interaction screen. This project will now characterise the role of the novel protein in caspase activation and cell death, and identify other potential regulators of caspase activation using a range of molecular, cellular, biochemical and genetic approaches.

(2) Role of autophagy and growth arrest in cell death

In recent studies we discovered that the Dronc/Ark pathway, while essential for most PCD, is largely dispensable for developmental PCD in specific tissues. This is most obvious in the larval midgut (MG), which undergoes PCD during metamorphosis, and this process is unaffected in *dronc* and *ark* mutants. In preliminary studies we have found that the inhibition of autophagy, a caspase-independent mechanism of PCD, leads to a delay in MG removal indicating a potential role for autophagy in MG PCD. Given that the role of autophagy in cell death is a matter of extensive debate, our discovery that MG PCD can be delayed by genetically blocking autophagy provides a unique model for delineating this controversy. We hypothesise that during development PCD utilises caspase-dependent (most tissues), caspase- and autophagy-dependent (e.g. larval salivary glands), and caspase-independent but autophagy-dependent (e.g. midgut) mechanisms. In this project we will delineate the mechanism of midgut cell death by exploring the contribution of caspases and autophagy. The project also aims to define the role of growth signalling in midgut cell death, to determine how growth signals and death signals may be integrated to regulate autophagy. A range of cellular, molecular and genetic approaches will be utilized in these projects. Given the controversial role of autophagy in human disease a better understanding of the regulation of autophagy is important for future treatments of disease.

Denton D, Shravage B, Simin R, Mills K, Berry DL, Baehrecke EH, Kumar S. (2009) Autophagy, not apoptosis, is essential for midgut cell death in Drosophila. **Curr Biol.** 19:1741-6.

Eligible students will be able to apply for a RAH Research Committee Honours Scholarship.

For more information about our laboratory, please visit our website
http://www.centreforcancerbiology.org.au/kumar.htm