Our group is focused on understanding the factors regulating cell viability in cancer. Since inhibition of cell death mechanisms is a common event in tumour development, this poses problems for many forms of chemotherapy that utilise cell death pathways, leading to drug resistance.

We are investigating known cell viability and integrity regulators in several processes including apoptosis and autophagy, as well as searching for novel proteins and pathways that control cell homeostasis, tumour growth and chemoresistance. We envisage knowledge gained from our studies will be translated and lead to improvement of existing clinical regimens or new targets for therapeutic intervention.

**Autophagy in cancer**

For several decades, the preservation of genomic integrity has been considered the central mechanism that protects us from cancer. While maintaining genomic fidelity is undoubtedly critically important, it must be remembered that a mutation in DNA usually only has an effect if it causes a mutation or dysregulation of an RNA or protein. As a result, because cancer can originate from a single erroneous cell, the preservation of RNA and protein integrity are also extremely important in protecting us against cancer.

There are two main systems for the removal and degradation of damaged or misfolded proteins: the ubiquitin–proteasome system and the lysosome. The lysosome degrades the bulk of the cell’s mass and is responsible for the degradation of all cellular constituents, including organelles.

There are several ways in which cargoes are delivered to the lysosome for degradation, but perhaps the best recognised of these is a group of processes termed autophagy (literally, self-eating). There are three main types of autophagy: macroautophagy, microautophagy and chaperone-mediated autophagy.

Macroautophagy is the most extensively studied and the main focus of research in our lab.

The process of macroautophagy begins with the formation of a double-membrane structure that encapsulates cargo destined for degradation as it grows to form a ball-like organelle called an autophagosome. Fusion events can then occur with endosomes and multivesicular bodies, but ultimately fusion occurs with a lysosome to form a new organelle termed an autolysosome within which degradation occurs by lysosomal hydrolases (Figure 1).

Macroautophagy can be stimulated by a variety of internal and external cues and both maintains cellular integrity and helps the cell adapt to numerous forms of stress, including starvation, hypoxia and oxidative damage. As a result, macroautophagy has a fundamental role in cancer. However, the role played by macroautophagy appears to be specific to cell type, context and tumour stage. It is widely considered, however, that in normal cells and in the early stages of tumour development, macroautophagy is tumour suppressive, whereas in fully developed cancers, macroautophagy is tumour promoting. This has made autophagy an attractive target for cancer therapy.

In order to target macroautophagy for cancer therapy, it is imperative that we understand when the process is contributing to the maintenance of cancer rather than acting in tumour suppression, and answering this question has been a major goal of our lab in recent years.

The role of autophagy in melanoma

In our previous work we showed that the role of macroautophagy in pancreatic cancer was determined by the tumour suppressor protein p53, with macroautophagy being oncogenic in the presence of p53 and tumour suppressive in the absence of p53 (Rosenfeldt et al. Nature, 2013; 504: 296–300). We have been exploring to see if similar ‘switch proteins’ like p53 exist in other tumour types and we have recently focused on melanoma, a highly malignant form of skin cancer.

To find this switch we utilised a previously described mouse model of melanoma that is driven by an oncogenic mutation in B-Raf, the signature mutation driving a significant percentage of human melanomas. These mice were crossed to animals containing genetically designed alleles for an essential autophagy gene (Atg7) and the tumour suppressor p53, which can be deleted by a recombinase that is designed to be expressed in all cell types. We have observed that loss of autophagy in the absence of p53 results in acceleration of the disease. In contrast, in animals where melanoma is driven by mutant B-Raf and loss of one allele of p53, the disease is attenuated.

These studies revealed that in melanoma driven solely by mutant B-Raf, autophagy plays a tumour suppressive role, as its deletion results in acceleration of the disease. In contrast, in animals where melanoma is driven by mutant B-Raf and loss of one allele of p53, the loss of autophagy has no impact on disease progression. We speculate that these findings may relate to the roles of autophagy and p53 in senescence, which is known to be a barrier to melanoma development. In the absence of either autophagy or p53, the establishment/maintenance of senescence will be impaired, meaning that loss of macroautophagy will have no further effect in the context of p53 deficiency.

Whatever the reason, these studies once again indicate that specific and definable molecular events can alter the role of macroautophagy in cancer, in a way that determines that the potential for targeting this pathway for cancer therapy.

Searching for biomarkers for the detection of the precancerous lesions associated with pancreatic ductal adenocarcinoma

During our studies on the impact of p53 status in determining the role of autophagy, in pancreatic cancer development, we observed that loss of autophagy in the pancreas of animals expressing mutant K-Ras resulted in a huge increase in the number of pancreatic intraepithelial neoplasia (PanINs), which are considered the precursor lesions leading to pancreatic ductal adenocarcinoma (Figure 2). As the earlier cancer is detected, the better the prognosis, and because pancreatic cancer is usually detected at an advanced stage, we considered that our mouse model with exacerbated PanIN formation could be utilised to identify a biomarker, which could be used to identify the presence of these precancerous lesions. This would then enable the identification of individuals who should be subject to enhanced screening for pancreatic cancer development.

As biopsy of the pancreas is an invasive procedure, its application is not feasible as a screening approach for a broad sector of the population. As a result, we decided to use our mouse model to hopefully identify a liquid biopsy biomarker in either blood or urine. Samples from animals with enhanced numbers of PanINs will be analysed by mass spectrometry (to identify potential protein and metabolic biomarkers) and by RNAseq (to identify potential RNA biomarkers). Biomarkers identified with this approach will then be triaged for detection in mice with a small population. As a result, we decided to use our mouse model to hopefully identify a liquid biopsy biomarker in either blood or urine. Samples from animals with enhanced numbers of PanINs will be analysed by mass spectrometry (to identify potential protein and metabolic biomarkers) and by RNAseq (to identify potential RNA biomarkers). Biomarkers identified with this approach will then be triaged for detection in mice with a small population.