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 cell viability and integrity regulators in several processes, including apoptosis and autophagy, and are searching for novel proteins and pathways that control cell homeostasis, tumour growth and chemosensitivity. We envisage that knowledge gained from our studies will improve existing clinical regimens or lead to new targets for therapeutic intervention.

Autophagy in cancer

Autophagy, literally ‘self-eating’, is a catabolic process in the cell whereby cellular cargoes are delivered to and degraded in lysosomes, allowing the cell to quickly adapt to stimuli. The cell can utilise autophagy to bring about the selective degradation of cellular components including mitochondria, protein aggregates and intracellular pathogens. In the context of cancer, the role of autophagy becomes complex. The consensus is that autophagy is tumour suppressive in normal cells and as they grow they encapsulate cellular cargoes that are destined for degradation in the lysosome. Upon cargo digestion, the constituent parts of macromolecules are delivered back into the cytoplasm and can then either be recycled in biosynthetic pathways or further catabolised for the production of energy.

Autophagy is controlled by an expansive array of cues that can rapidly alter the rate of autophagy, allowing the cell to quickly adapt to stimuli. A key process in this context is promoting tumour maintenance. As such, autophagy is a significant factor in the preservation of cellular integrity.

The most characterised form of autophagy, and the focus of our work, is macroautophagy, simply referred to as autophagy. The process is characterised by the formation of unique double-membraned vesicles - the autophagosomes. Their formation is orchestrated via a series of evolutionarily-conserved Atg/TophagY-related (ATG) proteins as well as three key autophagy-related proteins (Atg3, 7 and 4) that would otherwise be toxic for the cell. As such, autophagy is a significant factor in the preservation of cellular integrity.

The complex role of autophagy in cancer development

We previously showed that p53 tumour suppressor status determines how and when autophagy ceases to be tumour suppressive and switches to support tumour growth and preservation.

The Macrouliphagy pathway

<table>
<thead>
<tr>
<th>Membrane source (ER)</th>
<th>Phagophore</th>
<th>Autophagosome</th>
<th>Autoryosome</th>
<th>Lysosome</th>
<th>Cargo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation</td>
<td>Elongation</td>
<td>Closure</td>
<td>Fusion</td>
<td>Degradation &amp; Recycling</td>
<td>amino acids &amp; lipids released</td>
</tr>
</tbody>
</table>

Figure 1: The macroautophagy occurs in the cytoplasm of the cell and proceeds through various stages to encapsulate cargoes destined for degradation. Ultimately fusion occurs with a lysosome that provides hydrolyses required for cargo degradation. The breakdown products are then recycled or further catabolised.

For Pten, but this effect was lost in animals that were Pten null in their pancreas.

Switching to a different model of cancer development, a mouse model of melanoma driven by a mutant allele of B-Raf (V600E), we again showed that loss of Atg7 was tumour promoting in animals wild-type for Pten, but that this difference was lost in mice hemizygous for this allele (Figure 2).

Collectively, these studies across multiple cancer models provide compelling evidence that autophagy has a role in tumour suppression.

Autophagy in Hepatocellular Carcinoma progression

This previous work led us to question the underlying mechanisms behind the tumour suppressive/promoting role of autophagy as this knowledge is critical for the safe application of autophagy-directed therapeutics.

Through collaboration with Dr. Tom Bird, we examined the formation of liver tumours in mice expressing the liver specific albumin-Cre and floxed alleles for the essential autophagy genes Atg5 and Atg7. These were combined with Pten floxed alleles, as Pten is known to be involved in the development of hepatocellular carcinoma (HCC) and its status affects how the autophagy pathway impacts tumour development.

During the progression of HCC, the liver can undergo a change called the ductular reaction in which there is an expansion of duct-like structures (Figure 3). Ductular reaction is caused by chronic liver injury and is particularly associated with the transition from fibrosis to cirrhosis, an event which significantly increases the risk of HCC development.

Interestingly, ablation of autophagy in the liver by deletion of either Atg5 or Atg7, and hemizygous Pten deletion resulted in tissue damage and a ductular reaction (Figure 3). Using this experimental system, we performed lineage tracing to show that the ductular reaction arose through the dedifferentiation of hepatocytes. Moreover, we found that the ductular reaction was associated with deregulation of transcription factors YAP and TAZ, where co-deletion of these genes reversed the dedifferentiation and the development of HCC (Figure 3). Together, these findings not only provided insight into the role of autophagy in tumour development, but also constituting a significant step forward in understanding the origins of HCC that was previously controversial.

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