Hepatocytes are the key target for regenerative therapy for patients with liver disease and are the source of liver cancers (hepatocellular carcinoma, HCC). These cells show immense regenerative capacity, but despite our current understanding of the mechanisms that control liver regeneration, no therapeutic breakthroughs have been achieved to date. It is the aim of my group to understand what makes some hepatocytes regenerate whilst others do not, and to unpick the molecular pathways that underpin the transformation of regenerating hepatocytes into malignant hepatocytes.

Mechanisms controlling hepatocyte proliferation

The Wnt/β-catenin signalling pathway is crucial for establishing and maintaining the zones of the liver in which we believe that the regenerative cells reside. Activation of the Wnt pathway is sufficient to cause hepatocytes to divide and the liver to grow. It also allows hepatocytes with a greater propensity to regenerate than those without its activation. However, when this occurs, anti-proliferative pathways are also activated, preventing ongoing liver growth. We are investigating the nature of these pathways, and how they might be controlled therapeutically. The process of preventing proliferation may result in a state of permanent cell cycle arrest known as senescence. This state leaves many of the functional abilities of the hepatocyte preserved but renders it incapable of participating in regeneration. In severe liver injury we have shown that senescence may occur in response to injury (Fig. 1). We are investigating the pathways by which this process is activated and are currently performing preclinical trials in models of acute severe liver injury to prevent senescence formation and improve regeneration. Our recent work suggests that senescent hepatocytes may affect their surrounding environment in many ways, including immune activation, matrix deposition, and the induction of senescence in other cells. We have started to characterise the phenotype at single-cell level within this environment. We are now studying ways to interfere with such spreading senescence as a means to develop treatment for states of regenerative failure e.g. fulminant liver failure, alcoholic hepatitis and small-for-size syndrome.

Transformation of regenerative hepatocytes into malignancy

Whilst the Wnt/β-catenin pathway plays a role in regeneration, it is also the most frequent site of mutations in liver cancer. The actions of active β-catenin in hepatocytes are different to those in other organs, and typically the mutations which occur in HCC prevent current therapies targeting the pathway from working in this condition. We are investigating how the blockade of proliferation imposed by β-catenin on hepatocytes may be broken during cancer formation and if new therapies targeting β-catenin downstream of its destruction complex might be effective in this condition. We are also working on studying the role β-catenin plays in promoting evasion of tumour detection by the immune system.

We have developed a number of models of HCC, utilising a combination of targeted genetic manipulations in a clonal population of hepatocytes. These genetic targets have been chosen to mimic the genetic changes most frequently occurring in a variety of human HCC subtypes to create models for each subtype of human cancer (Fig. 2). We are then able to track the expansion of the altered hepatocyte clones as they progress rapidly from single cells into large nodules and within months into HCC. These tumours model human disease well, including spread to other organs and response to therapies. Using the advanced facilities within the Institute we are able to track and characterise tumours as they develop using a combination of preclinical imaging and analysis of mRNA transcription, protein expression and secretion. Our aim, with the input of other groups within the Institute, is to map the evolution of the tumours and test therapies aimed at preventing tumour initiation, expansion and metastasis.

Early detection of hepatocellular carcinoma in the UK, 10–20% of the population are potentially at risk of liver disease, and 50,000 adults in the UK estimated to have cirrhosis as a result of a trebling in incidence in the last 30 years. Hand in hand with chronic liver disease, primary liver cancers are becoming more common, having trebled in the last 15 years. Liver disease is reversible, as is the risk of HCC. HCC is potentially curable, providing it is detected at an early stage. However, deaths from liver cancer are likely to continue to increase until we are able to identify people at risk of liver disease and HCC, prevent their disease and provide rescue therapies for those detected with late-stage disease.

Using large patient cohorts we are studying how we can improve the use of serum biomarkers to identify patients who may be at risk of liver cancer. We hope to provide a rationale for inclusion of these biomarkers in routine clinical practice, to facilitate the early treatment and cure of HCC in those at risk. We are collaborating with experts in public health and statistics to gather and analyse additional data collected from across Scotland and have already shown that by the application of novel statistical analysis of dynamic changes in serum biomarkers in individual patients we are able to detect HCC in its early forms. With the integration of additional clinical variable and other biomarkers, we aim to improve the accuracy of this approach and move towards clinical trials.

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