Research

The p53/p73 family of tumor-regulators

Cancer genome sequencing efforts have led to the identification of major alterations that occur in a wide variety of genes. Of these, some – especially those that code for enzymes - have been deemed “druggable” and hence, intensely pursued, albeit being of relevance to a small population. On the other hand, many genetic mutations have not received significant attention from the drug discovery perspective, simply due to the perception that they are “undruggable”. One such gene family is the p53 family of tumor suppressors, which are transcription factors. While p53 is the most mutated gene in cancers, its homologue p73 is often overexpressed in cancers. Studies have demonstrated a critical role for mutant p53 and overexpressed p73 in tumor promotion and resistance to therapy. While these molecules could be potential therapeutic targets of enormous benefit to patients, they have not been subjected to major drug discovery efforts due to the difficulties in targeting transcription factors.

Over the years, we have performed systematic analyses to understand the functions of mutant p53, and have demonstrated that p53 mutants may have both common and differing properties, indicating that any targeting effort should be aimed at generating “specific-mutant-p53”-targteing molecules (rather than pan-mutant p53). In this aspect, we are embarking on a program to identify novel molecules that would target mutant p53 expression without having an effect on the WT allele, using a multitude of novel screening strategies.

p73 is a homologue of p53 and belongs to the same family of tumor suppressors. It exists as 2 major forms: the full-length TAp73 from (similar to p53), and the amino-terminal truncated DNp73 (similar to p47). However, unlike p53, it is hardly mutated, but both forms are often variably over-expressed in many cancers, suggesting that p73 may have other differing roles in regulating tumorigenesis. While absence of TAp73 promotes tumor formation in mice – albeit weakly, highlighting a role in tumor suppression, its role in supporting tumor growth had been controversial. Our work over the years has focused on understanding this property, and we had earlier shown that TAp73 is capable of driving cellular proliferation in specific contexts, through the regulation of AP-1 target genes. Recently, we have demonstrated that TAp73 is capable of inducing the expression of angiogeneic genes, especially in hypoxic conditions that are prevalent in tumors. Thus, TAp73 appears to be utilizing multiple mechanisms to promote cancer cell growth, implying that these tumor-promoting pathways may be targetable for improving therapeutic response. We have therefore embarked on identifying key molecular determinants of the TAp73 pathway through high-throughput whole-genome siRNA screens and proteomics approaches, with the eventual goal of inhibiting them to reduce angiogenesis and proliferation of cancer cells. In addition, given the diametrically opposite roles of TAp73 in both promoting and suppressing tumor formation, we are now poised to address the question on how a transcription factor like TAp73 is able to regulate these seemingly opposite cell fate

outcomes. We have therefore started answering this question of cell fate, using novel screening technology and next-generation animal models to study the spatial and temporal role of TAp73 both within the tumor exclusively, as well as in the stromal compartments.

Mouse models for hepatocellular carcinoma, liver fibrosis and liposarcoma

Another major effort in the laboratory is to develop mouse models that would recapitulate the human cancer conditions as best as possible, using state-of-the-art genetic engineering technology. This will enable the identification of novel biomarkers for early detection, as well as potential molecular targets for timely-intervention. In this regard, we have been working on modeling hepatocellular carcinoma (HCC), and liver fibrosis, and have generated mouse models that recapitulate human HCC, both molecularly and histologically. Moreover, we have established the liver fibrosis model in mice, using carbon-tetrachloride, where the fibrotic symptoms could regress upon withdrawal of treatment. We are now interrogating the critical aspects of the fibrotic process, through the analysis of the functions of several transcription factors that are major regulators of liver development and pathology, through their deletion in multiple cells types of the liver.

Other efforts are also ongoing to establish mouse models for liposarcoma, tumors that arise from fat cells (adipocytes) in soft tissues. Though surgery is the main mode of treatment, the understanding of this disease is limited due it being not a common cancer, and hence, treatment modalities have been restricted. While the process of adipogenesis has been well studied, knowledge of the transformation of an adipocyte to liposarcomas is limiting due to the lack of effective model systems to study the development and progression of this disease. Mdm2, the negative regulator of the tumor suppressor p53, is often amplified in all types of sarcomas. Thus, we are generating mouse models in which selective genetic changes are introduced in the germ-line conditionally to follow the transformation of the adipocytes, which will provide a paradigm for studying the biology of liposarcomas, and could open up new opportunities for treatment.

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