Editorial

p53: updates on mechanisms, biology and therapy (II)

Guest Editors
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In the second volume of this special issue, we focus on the activity and function of the mutant p53 proteins. The elegant work of Nakayama and Oshima (2019) uses mouse models of colorectal cancer to directly demonstrate the role that expression of the R273H protein has in promoting invasion. Using both animal studies and organotypic cultures, they are able to demonstrate that the gain-of-function (GOF) is driven by high-level nuclear expression of the protein and that this high-level expression requires escaping from Mdm2-dependent degradation and environmental influence that are especially seen at the invading front of the tumor. Their studies show that wild-type p53 can inhibit the GOF of the mutant protein providing clear support for the need for loss of the wild-type allele as the tumor progresses. This elegant *in vivo* work shows that the dominant-negative function of mutant p53 proteins has limited penetrance and helps to clarify this controversial area.

In a similar vein, the very exciting new work described by Hua Lu and colleagues (Wang et al., 2019) shows that the GOF of a mutant p53 can result directly from its post-translational modification. The R249S mutant p53 found frequently in hepatocellular carcinoma (HCC) does not show clear GOF in mouse models, yet the overwhelming data for its selective high-level expression in HCC demands an explanation. Strikingly, their latest results show that the protein is phosphorylated at the exact mutant amino acid and it is the phospho-R249S protein that has the effector function established through new molecular interactions that occur as a direct result of this phosphorylation. This subtlety is a stark reminder that each mutant p53 might acquire new properties and these properties may be very context-dependent.

Feng and colleagues (Liu et al., 2019) detail the complex regulation of metabolism by p53, including glucose uptake, lipid and nucleotide synthesis, serine metabolism by suppressing NF-κB, and upregulating the ligase Parkin, which in turn also modulates mitochondrial metabolism. Upregulation of these activities is the hallmark of cancer and it is no surprise that GOF mutants of p53 enable proliferation by activating these pathways. Although several questions remain to be answered, this link opens up new ways of therapeutic intervention including combination therapies that for example stabilize p53 and inhibit NF-κB.

Zhou et al. (2019) elaborate on the complex role of mutant p53 in proliferation, invasion, and metastases, thus catalyzing cancer growth. They also help us understand that mutant p53 can create profound resistance to current cancer therapies by suppressing apoptosis and autophagy and increasing cancer stemness. Their own work identified a mutant p53-mediated pathway engaging c-MYC and other partners that is responsive to HBV infection resulting in HCC, thus identifying a likely candidate for therapeutic intervention.

The subtlety of the regulation and function of the mutant p53 protein require new tools and technologies for their effective study. Tan et al. (2019) provide a comprehensive review of the role that computational methods have played in categorizing and defining structure–function relationships in wild-type p53 and the effects of differing mutations on these functions, how the insights have begun to provide guidance for the development of therapeutic intervention that includes stabilizing p53 against Mdm2/Mdm4, in particular the exciting recent developments of stapled peptides in their own efforts and those of other groups, and the development of small molecules that appear to restore wild-type functionalities to mutant p53.

Sabapathy and Lane (2019), in a complementary chapter, show how structure and function of mutant p53 can also be probed using a large collection of monoclonal antibodies with diagnostic

and therapeutic potential. Both these fields are advancing rapidly and the use of new structural information and minibodies that can target mutant p53 inside living cells suggest that the precise functions of mutant p53 molecules in transformation are within grasp.

Finally, molecules selected to kill mutant p53-expressing cells specifically were discovered first by Wiman and colleagues and here, they discuss in detail the great benefit of a phenotype-based screen (Eriksson et al., 2019). The molecules they identified and developed, and now showing promise in the clinic, turn out to have a dual function, directly targeting mutant p53 to regain wild-type folding patterns and activities and also exploiting the altered redox environment of the mutant p53-transformed cells to generate synergistic cytotoxic effects that amplify and complement those due to the reactivation of p53.

As with the small-molecule activators of p53, the hope is that these exciting findings will find greater clinical utility in the coming years. Certainly, the study of mutant p53 offers many new approaches to cancer treatment and diagnosis.

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