Editorial

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

Guest Editors
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In July 2017, the 17th International p53 Workshop was held in Singapore. With an attendance of over 300 scientists from all over the world, the meeting was an outstanding success and many new observations about the p53 pathway were discussed for the first time. The enthusiasm to gather these insights into a form that would be available to the whole community led us and the editors of *Journal of Molecular Cell Biology* to design a special issue of the journal composed of articles and commentaries from some of the key contributors to the meeting. As is usual, deadlines have to stretch a little, but in the end, 14 excellent papers have been assembled and many cited papers that have literally been published only in the last few months ensuring a remarkably up to date coverage of the field. We have had to spilt the contributions over two volumes in order to accommodate them within the journal, but there is also a natural split as one area of intense study is the regulation of the wild-type protein, while the other strongly developing area is the growing realization that the point-mutant proteins expressed at high levels in many human cancers are acting as driver oncoproteins. The hope is that the intense study of both areas will lead to new insights into how to prevent, diagnose, and treat cancer.

In the first volume, we include seven papers that focus on the function and regulation of the wild-type protein. In a highly focused study, Fahreus and colleagues (Karakostis et al., 2019) describe how the interaction of p53 mRNA with the Mdm2 protein opens up new processes by which p53 translation is controlled. Emphasizing the role of the RNA itself, they show profound effects of synonymous mutations in the coding region of p53. Such mutations have largely been ignored, but their work is a call to arms for much closer examination of the role of such variants in the regulation of the p53 pathway.

In a very thoughtful review, Bowen and Attardi (2019) demonstrate clearly that the developmental effects of many mutations are mediated by p53 activation. This extraordinary finding, first seen by the zebrafish community (Danilova et al., 2010), has now been greatly extended by studies of mouse models of human genetic diseases and also by direct observations of human patient material. Genetic mutations that affect ribosomal function, DNA repair, and the control of mitosis through the centriole all activate p53, and this activation is critical for the observed developmental phenotypes, as many mutations are rescued by p53 deletion in the mouse. This includes phenotypes associated with advanced aging. Many years ago, Peter Hall named p53 'Guardian of the Babies' (Hall and Lane, 1997) and this idea has now been remarkably vindicated. However, in order to use this knowledge, one would have to contemplate inhibiting p53 during development or, as Bowen and Attardi (2019) correctly suggest, find out specific ways to block the signaling pathway that connects the mutation to the activation of p53 and selectively and temporarily block that signal.

Andreas Strasser and the team's work on the function of p53 as a tumor suppressor triggered a major revolution in the field, as his Puma, Noxa, and p21 triple-knockout mice failed to develop cancer despite clearly attenuated cell cycle and apoptotic responses to DNA damage. In this elegant chapter (Lieschke et al., 2019), they discuss their recent identification of critical DNA repair proteins regulated by p53 playing an essential role in tumor suppressor mechanisms in haemopoietic cancers. They also directly challenge the community to resolve why p53 activation causes apoptosis in some scenarios but cell cycle arrest or senescence in others. This central issue remains unresolved despite its vital importance.

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While the role of p53 as a tumor suppressor is always highlighted, Ito and colleagues (Bae et al., 2019) make a strong case that the RUNX genes have an even more important role, as they act to block the initiation of the cancer cascade rather than progression events. This is certainly true in the colorectal system (Vogelstein et al., 2013), though in other types of cancer, such as serous ovarian cancer, p53 mutations may be an essential early step. Like p53, RUNX is a transcription factor, but Bae et al. (2019) highlight recent compelling data for its direct role in DNA repair. By analogy, they also discuss the recently developed understanding of p53 as also playing a direct role in DNA repair, particularly acting at the interface between transcription and repair and the reinitiating of replicative DNA synthesis after repair events.

One of the other key partners for p53 is the Mdm2 and Mdm4 family of proteins. Haupt et al. (2019) make a strong case for the vital role of Mdm4 in human cancers, especially with the ability of the MDM4 isoforms in repressing p53 transcriptional activity, and discuss their findings whereby MDM4 promotes cancers carrying mutant p53. They highlight recent findings that MDM4 promotes epithelial–mesenchymal transition and lipid metabolism and highlight the need for detailed structural investigations to guide the development of molecules that will specifically target Mdm4 as well as Mdm2.

The area of small molecule regulators of p53 is comprehensively reviewed by Ladds and Lain (2019) who summarize and discuss many small molecule activators of p53 that have been discovered. Examining the developments of nongenotoxic activators of p53 in order to minimize side effects, they focus on molecules that stabilize p53. The authors highlight the potential of synergy between different inhibitors by demonstrating that inhibition of DHODH (resulting in ribonucleotide depletion) and of Mdm2 by nutlin resulted in synergistic tumor cell death.

Finally, in a highly complementary chapter, Cheok Chit Fang and the team (Aning and Cheok, 2019) search the p53 pathway and its downstream effector mechanisms to seek synthetic lethal inhibitors that will kill only cells in which p53 has lost its function. They identify a series of metabolic pathways that indeed provide such opportunities and have in their own work, also summarized here, shown that p53 regulation of lipid metabolism does indeed create such a selective vulnerability to an FDA-approved small molecule.

Overall these chapters provide a remarkable summary of the properties and regulation of the p53 pathway that will be of great interest to the field, especially as we all anticipate approval for the first few p53 activating drugs in the coming years.

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