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Editorial

p53 and MDM2: their Yin-Yang intimacy

Guest Editor
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The philosophy of Yin (阴) and Yang (阳) formed in ancient China describes a subtle, complementary, and sometimes intimate relationship between two opposites. This thousands of years old philosophy is, however, perfectly suited to describe the relationship between p53 and MDM2, whose genes evolved hundreds of millions of years ago. p53 and MDM2 are found in both (some) invertebrate and (all) vertebrate organisms, and mutually live with and almost always depend on each other in most multi-cellular organisms, including humans. The MDM2 protein (also called HDM2 for its human homologue) is a natural 'killer' of the p53 protein, as it prohibits p53 functions by promoting its breakdown and/or inhibiting its activity, whereas p53 acts as a transcriptional factor that can rouse the production of MDM2 at its mRNA level, hence forming a negative feedback axis. When p53 is activated, it can execute its functions as a 'guardian of the genome' by either triggering the expression of genes important for the regulation of cell growth and proliferation, cellular senescence, apoptosis, DNA repair, ferroptosis, cell metabolism, angiogenesis, and autophagy, or sometimes even directly inducing apoptosis. The sum of these p53-regulated events either halts cell growth or leads to cell death, essential for both normal organism development and protection from cancers. Thus, p53, which was discovered by Arnold Levine and David Lane in 1979, can be considered as 'Yin'. By sharp contrast, MDM2 can overcome these p53-dependent functions detrimental to cell growth and proliferation as a physiological negative modifier of p53, allowing cells to live. Hence, MDM2 can be considered as 'Yang', as it plays an almost exactly opposite role to that of p53. Intensive studies of this p53–MDM2 negative feedback axis over the past quarter century have unveiled a beautiful molecular 'tale' about the delicate balance of Yin and Yang.

Since the discovery of MDM2 by Dona George in 1991, its tangled and intimate relationship with p53 as two opposite 'Yin' and 'Yang' players for cell growth and death—initially recognized by the Arnold Levine, Bert Vogelstein, and Moshe Oren laboratories—has been continuously proved at multiple levels of research using various *in vitro* and *in vivo* model systems. However, MDM2 does not work alone to monitor p53 functions, as MDMX (also called MDM4), an MDM2 homologue identified by Aart Jochemsen in 1996, has also been shown to inactivate p53 either by itself or by working with MDM2. Over the past decade, greater progresses have been made to further understand the molecular insights in the tight regulation of the MDM2/MDMX–p53 axis and to more systematically illustrate the crucial role of this axis in animal development and cancer prevention. Every other year, a progress update on the field MDM2/MDMX study is presented in an international conference. The most recent conference, the 8th International MDM2 Workshop co-organized by Hua Lu and Wei Gu, was held at Tulane University School of Medicine in New Orleans in November 2015. At this MDM2 conference, MDM2 and MDMX researchers from all over the world reported a number of exciting and new findings, covering almost all aspects of research on these molecules.

This special issue collects nine well-written review articles to in part summarize the progress on MDM2 and MDMX research as presented at the MDM2 Workshop in New Orleans and also to discuss the latest updates in this field as reported in recent literature. The topics include: the anatomy of MDM2 and MDMX evolution by David Lane and his colleagues; the role of the MDM2/MDMX–p53 axis in animal embryogenesis, homoeostasis, and kidney organogenesis by Guillermina Lozano and her colleagues as well as Samir El-Dahr, Zubaida Saifudeen, and their colleagues; the physiological role of MDM2/MDMX–p53 signalling in mouse development by Yanping Zhang and his colleagues; the HAUSP regulation of the MDM2/MDMX–p53 axis via deubiquitylation by Wei Gu and his colleagues; the role of MDM2 and MDM4 in breast cancer development and prevention by Sue Haupt, Ygal Haupt, and their colleagues; and the regulation of p53 by other p53-responsive inhibitors and

oncoproteins dependently or independently of MDM2 by Hua Lu, Xiang Zhou, and their colleagues. In addition to these interesting topics described in seven review essays, two more reviews also cover newly described p53-independent functions of MDM2 and MDMX, i.e. the role of MDM2 and MDMX in the regulation of DNA repair by Christine Eischen and the role of MDM2 in epigenetic regulation by Ute Moll, Matthias Doubelstein, and their colleagues.

As revealed by their titles, these essays cover a plethora of interesting and important areas. They provide advanced information and raise critical, yet unaddressed, questions about these intensively researched proteins or genes, from evolution to embryogenesis, from biochemistry to genetics, from organogenesis to adult homoeostasis, from stem cell renewal to cancer development, and from epigenetics to genomic instability. By reading these reviews, readers will not only enjoy the mysterious 'tale' of the Yin-Yang relationship between MDM2/MDMX and p53 chapter after chapter in different styles, with different biological widths and molecular depths, and from different research angles, but also learn that without MDM2 or MDMX, embryos could not develop, specific organs could not form correctly, animals could not survive, and certain diseases would occur because of the uncontrolled and aberrantly activated p53, whereas without p53, the 'guardian of the genome', normal cells would be converted to cancerous cells, and animals would not live for long due to aggressive tumorigenesis. It is noted that MDM2 and/or MDMX could impair DNA repair or regulate chromatin activity and stem cell renewal independently of p53 as well. Because of this fine balance of Yin (p53) and Yang (MDM2 or MDMX), the animal kingdom, certainly including humans, could develop normally, live healthily, and survive longer.

Due to space limitations, this issue can only cover the aforementioned topics. We apologize to other colleagues and readers in this field for missing their favourites, such as drug discovery targeting the MDM2/MDMX–p53 axis, other signalling pathways relevant to this essential axis, and the association of malfunctions of this axis with other human diseases. Nevertheless, I am sure that those specific topics can be readily found in other recent review articles elsewhere.

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