

## Editorial

# Noncoding RNAs: ‘our turn’ to join the p53 network

The p53 tumor suppressor is the guardian of the human genome. Since its discovery in 1979, p53 has been the most studied molecule in the field of cancer. Recently, its role has also been extended to other biological and pathological processes. p53 functions primarily as a transcription factor to regulate target genes that encode proteins crucial for promoting apoptotic cell death, cell cycle arrest, senescence, and so on in response to diverse upstream stressors. Interestingly, some of the p53 targets are noncoding RNAs. Noncoding RNAs can be functional without being translated into proteins and are often independent RNA molecules or noncoding parts of messenger RNAs. The past decade has witnessed burgeoning intensive investigation on the interplay of noncoding RNAs with p53, its regulators, and effectors during the development of cancer and/or other diseases. This issue of *Journal of Molecular Cell Biology* presents five essays to review the rapid progress in this area from five different angles and to offer new insight into the role of noncoding RNAs in the p53 signaling web with updated information.

### lncRNAs in p53 signaling

The review by Dr Mo and colleagues highlights the importance of several long noncoding RNAs (lncRNAs) in p53 regulation. Just like protein-coding genes, lncRNAs associated with the p53 pathway serve as regulators or effectors either to maintain p53 proteins at an optimal level or to execute downstream functions in response to p53 activation. One of the well-studied lncRNAs is MALAT1, a p53 repressor that controls the cell cycle progression. This lncRNA is overexpressed in multiple types of solid tumors and thus could be oncogenic. Of the p53 effector lncRNAs, lincRNA-p21 is an established p53 transactivational target and a key mediator of cellular apoptosis. Interestingly, one of the p53 lncRNA regulators, RoR, acts like Mdm2 that suppresses p53 as a negative feedback regulator because its transcription is regulated by p53. However, unlike MDM2, this RoR–p53 auto-regulatory feedback loop is not straightforward, instead involves a protein called

hnRNP I. hnRNP I is an RNA-binding protein that interacts with the 5' UTR of p53 mRNA, and this interaction leads to the increase of p53 translation. As vividly depicted in the review, RoR, induced upon p53 activation in response to DNA damage, interacts with the phosphorylated hnRNP I to inhibit p53 translation, consequently inactivating the DNA damage–p53 pathway. Overall, the authors emphasize that lncRNAs work in concert, potentially with protein-coding genes, to enhance the flexibility for cells to maintain p53 levels and facilitate p53 signaling.

### miRNAs in p53 signaling

MicroRNAs (miRNAs) are a group of tiny noncoding RNAs that negatively regulate gene expression at the post-transcriptional level. These noncoding RNAs join the p53 network as either upstream regulators or downstream effectors of p53. Four of the reviews touch this topic.

### miRNAs as p53 regulators

On one hand, Dr Oren and colleagues offer a prompt review on latest studies on miRNAs that target Mdm2 and Mdm4 as p53's indirect regulators. Interestingly, both Mdm2 and Mdm4 mRNAs possess exceptionally long 3'UTRs, which are prone to miRNA targeting. More interestingly, both of the mRNAs contain Alu sequences – primate-specific highly abundant retroelements spreading throughout the human genome. In this well-put up essay, the authors not only give a good glimpse at those miRNAs and point out that most of these miRNAs can act as feedback regulators of the p53–MDM2/MDMX circuit, but also emphasize the new role of Alu elements and their impact on miRNAs-mediated gene regulation.

On the other hand, Dr Li and colleagues provide an updated account of miRNAs that suppress p53 expression by directly binding to the p53's 3'UTR. Amazingly, 11 of these miRNAs have been identified thus far, including miR-25, which is highly expressed in multiple types of cancer. Intriguingly, 9 of these 11 miRNAs are upregulated in multiple myeloma, a type of blood cancer with an extremely low p53 mutation

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rate (~3%). This raises the possibility that in the absence of p53 mutation, p53 might be inactivated by overexpression of p53-targeting miRNAs. Elucidation of this alternative mechanism of p53 inactivation could offer useful information for future development of p53-dependent therapeutics through inhibition of p53-targeting miRNAs against a large portion of human cancers without p53 mutation.

#### *miRNAs as p53 effectors*

miRNAs have been shown to play a role in executing downstream effects of p53 as its targets since discovery of miR-34 as the first target of p53 as mentioned below. In this issue, Dr Lu and colleagues offer a comprehensive review on the p53 responsive miRNAs. These p53-responsive miRNAs are involved in not only positive or negative feedback regulation of p53, but also execution of p53's cellular functions. For example, a number of miRNAs that are transcriptionally induced by p53 can implement p53-dependent apoptosis, cell growth arrest, senescence, and so on. Also, miR-605 and miR-145, whose expression is activated by p53, can suppress Mdm2 expression by directly binding to its mRNA, consequently increasing p53 stability and activity. The authors also provide a good picture of how p53-responsive miRNAs fine-tune p53 response to cellular stresses and mediate the crosstalk between p53 and other signaling pathways, such as c-Myc and Wnt. Finally, they discuss the potential or pivotal roles of p53 target miRNAs in other biological processes, such as cell metabolism and stem cell renewal, and other human diseases.

*'tanquam ex ungue leonem'* (we recognize the lion by his claw). In one of the most extensive reviews on a single miRNA (family) ever, Dr Hermeking and colleagues offer an in-depth analysis and detailed description of the latest advances from recent investigations on the members of the miR-34 family, the most prevalent p53-induced miRNAs. The members of this family, miR-34a, b, c, are critical mediators of a broad spectrum of cellular processes, including proliferation, apoptosis, differentiation, stemness, epithelial to mesenchymal transition, migration, invasion, and metastasis. These cellular activities of the miR-34 family render it to play crucially physiological roles in spermatogenesis, stem cell differentiation, neuronal development, aging, and cardiovascular functions. Also, dysregulation of the miR-34 family is highly associated with a variety of diseases, such as cancer, brain disorders, osteoporosis, and cardiovascular complications. Collectively and informatively, the authors also tabulate all validated miR-34 target genes, providing a rich resource for p53 and/or cancer researchers.

As concluded in both reviews, miR-34 and other p53-responsive miRNAs have emerged as important downstream players in implementing or facilitating p53 functions involved in various cellular processes and pathways, as well as in physiological homeostasis and pathological disorders in humans.

#### **The noncoding parts of the *TP53* gene**

Despite extensive studies on mutations of the *TP53* gene in cancer, its 3'UTR has been largely overlooked until recently. This topic is picked up by Dr Li and colleagues who discuss both somatic and germline mutations occurring in the p53 3'UTR in their review. Hundreds of novel somatic mutations have been found in the p53 3'UTR from patients with B-cell lymphoma, and the seed match binding sites of 8 of 11 p53-targeting miRNAs are disrupted by such mutations. In addition, somatic mutation in the p53 3'UTR can be utilized as a prognostic indicator of survival, yet its prognosis power is dependent on the status of coding sequences. For germline mutation, a single nucleotide polymorphism rs78378222 is particularly of interest, as it is highly associated with multiple types of cancers. This germline variant is located in the 3'UTR of p53 mRNA, converting the polyadenylation signal (PAS) from AATAAA to AATACA, which impairs 3'-end processing of this mRNA. Notably, the cancer spectrum of patients with the PAS variant is different from that of Li-Fraumeni Syndrome. The former is at higher risk of basal cell carcinoma of the skin, prostate cancer, brain tumors (glioma and neuroblastoma), colorectal adenoma, and esophageal squamous cell carcinoma, whereas the latter develops predominantly breast cancer, brain tumors, acute leukemia, sarcoma, and adrenal cortical carcinoma. It remains mysterious why germline coding and noncoding mutations of the *TP53* gene give rise to differential tumor phenotypes.

In sum, these five reviews provide readers with updated, comprehensive, and in-depth information about recent progresses toward our better understanding the regulation of p53 and execution of its biological functions by a plethora of noncoding RNAs, as well as expansion of the p53 signaling network to other pathways by these regulatory RNAs, even though by no means these essays could cover all aspects of the continually growing number of newly discovered noncoding RNAs in this considerably complicated network. These essays are especially informative and conducive to readers in the fields of p53, noncoding RNAs, cancer research, and beyond, and hence worth reading.