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Minireview

p53 Enters the MicroRNA World

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Recently, microRNAs, which are regulated by the transcription factor encoded by the tumor suppressor gene *p53*, were identified independently by seven groups. Their studies highlight the microRNAs *miR-34a* and *miR-34b/c* as direct, conserved p53 target genes that presumably mediate induction of apoptosis, cell cycle arrest, and senescence by p53. Since these microRNAs may regulate the levels of hundreds of different proteins, these findings add a new, challenging layer of complexity to the p53 network. The initial evidence suggesting that *miR-34* genes are central mediators of p53 function is summarized here.

Mutations in the p53 pathway are found in nearly all types of cancers (Hollstein et al., 1991; Soussi, 2007). Therefore, the mechanisms by which p53 achieves tumor suppression have been subject to intense research over the past 15 years. The transcription factor encoded by the *p53* tumor suppressor gene is posttranscriptionally activated by DNA-damaging agents/radiation, oxidative stress, or activation of oncogenes (Oren, 2003; Vogelstein et al., 2000; Vousden and Lane, 2007). The critical signals induced by these events are presumably DNA double-strand breaks, which activate ATM kinases that in turn phosphorylate p53. Activated p53 induces cell cycle arrest, which can be transient or permanent (senescence). p53 may promote apoptosis in cases where the damage is too severe. The cellular outcome of p53 activation is largely dependent on the cellular context. Traditionally, the cellular effects of p53 are thought to be mediated by its ability to transactivate genes, which encode effector proteins that regulate cellular processes: examples (and the phenotypic endpoints) are *p21* (G_1 arrest), *14-3-3σ* (G_2 arrest), and *Puma* (apoptosis) (el-Deiry et al., 1993; Hermeking et al., 1997; Yu et al., 2001). However, p53 also has been reported to induce the downregulation of specific proteins: for example, the p53-mediated loss of cyclin-dependent kinases (CDK4) and cyclins (Cyclin E2) may contribute to p53-induced cell cycle arrest (Spurgers et al., 2006). Besides direct repressive effects of p53 on core promoters (Ho and Benchimol, 2003), the induction of microRNAs (miRNAs) represents an attractive mechanism for the downregulation of proteins observed after p53 activation. miRNAs form a class of endogenously expressed, small noncoding RNAs with a recently established key role in the posttranscriptional regulation of gene expression (reviewed in Chen and Rajewsky, 2007; Kloosterman and Plasterk, 2006; Peters and Meister, 2007; Valencia-Sanchez et al., 2006). miRNA-encoding genes are transcribed by RNA polymerases II or III to yield primary transcripts (pri-miRNAs), which are processed by the nuclear RNase III enzyme Drosha to form stem-loop-structured miRNA precursor molecules. These pre-miRNAs are transported to the cytoplasm where the RNase III enzyme Dicer cleaves off the double-stranded (ds) portion of the hairpin and generates a short-lived dsRNA of about 20 to 25 nucleotides in size. The duplex is subsequently unwound, and only one strand gives rise to the mature miRNA, which is incorporated into miRNA-protein complexes (miRNPs). miRNAs guide miRNPs to partially complementary binding sites located in the 3′ untranslated region (UTR) of target mRNAs and inhibit translation or destabilize target mRNAs (Meister and Tuschl, 2004; Pillai et al., 2007). Both processes result in the downregulation of the protein encoded by the respective mRNA. Estimates based on bioinformatics as well as microarray analyses suggest that ~30% of all genes are subject to regulation by multiple miRNAs (Lim et al., 2005).

Roles of miRNAs in Cancer

miRNAs have been implicated in the regulation of proliferation, differentiation, and apoptosis (Kloosterman and Plasterk, 2006). As these processes are altered in cancer cells, numerous studies were undertaken to successfully provide evidence for an involvement of miRNAs in cancer formation. Similar to mRNA-encoding genes, several miRNA-encoding genes have been meanwhile classified as oncogenic or tumor-suppressive genes according to their function in cellular transformation and expression in tumors (for detailed reviews, see Calin and Croce, 2006; Cummins and Velculescu, 2006; Esquela-Kerscher and Slack, 2006; Garzon et al., 2006).

Furthermore, tumor cells seem to undergo a general loss of miRNA expression, and forced reduction of global miRNA expression promotes transformation (Kumar et al., 2007). Interestingly, miRNAs cluster within fragile sites and other genomic regions frequently altered in cancers (Calin et al., 2004, 2007). Besides their causal involvement in tumor formation, miRNAs may be very useful for the classification, diagnosis, prognosis, and therapy of malignancies (Calin and Croce, 2006; Cummins and Velculescu, 2006; Lu et al., 2005).

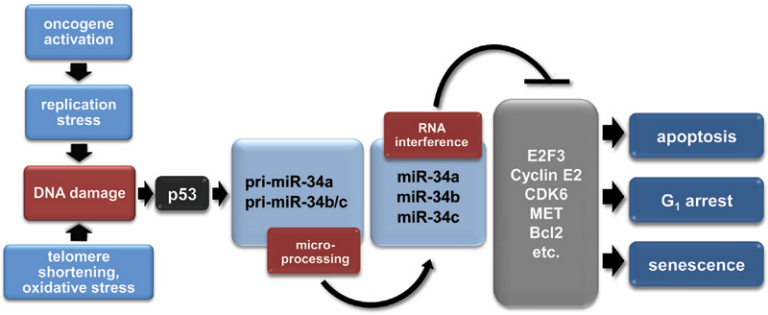

Figure 1. The *miR-34* Family as Mediator of Tumor Suppression by p53

The findings of seven reports are summarized in this model (Bommer et al., 2007; Chang et al., 2007; Corney et al., 2007; He et al., 2007; Raver-Shapira et al., 2007; Tarasov et al., 2007; Tazawa et al., 2007). After the generation of double-strand breaks, p53 is activated via ATM kinases and transactivates target genes through consensus binding sites. The primary transcripts of the induced *miR-34* genes are processed by DROSHA and DICER complexes. The final processed miRNA is incorporated in the RISC complex and mediates inhibition of translation or RNA degradation of the indicated targets and presumably hundreds of other not yet identified targets. So far three cellular outcomes of these events, namely G_1 arrest, apoptosis, and senescence, have been identified.

Connecting p53 and the miRNA World

Recently, reports from several laboratories almost synchronously surfaced, which more or less come to the same conclusion: the members of the *miR-34* family are direct p53 targets, which induce apoptosis, cell cycle arrest, and senescence (Bommer et al., 2007; Chang et al., 2007; Corney et al., 2007; He et al., 2007; Raver-Shapira et al., 2007; Tarasov et al., 2007; Tazawa et al., 2007) (summarized in Figure 1). In mammalians, the *miR-34* family comprises three processed miRNAs that are encoded by two different genes: *miR-34a* is encoded by its own transcript, whereas *miR-34b* and *miR-34c* share a common primary transcript. In mice *miR-34a* is ubiquitously expressed with the highest expression in brain, whereas *miR-34b/c* is mainly expressed in lung tissues (Bommer et al., 2007). These analyses also showed that *miR-34a* is expressed at higher levels than *miR-34b/c*, with the exception of the lung, where *miR-34b/c* is dominantly expressed. Therefore, the two *miR-34* genes presumably have tissue-specific functions.

In five of the seven reports connecting p53 and *miR-34*, the genome-wide analyses of miRNA expression after p53 activation point to *miR-34a* as the most significantly induced miRNA after activation of p53 (Chang et al., 2007; He et al., 2007; Raver-Shapira et al., 2007; Tarasov et al., 2007; Tazawa et al., 2007). To arrive at this conclusion, Moshe Oren's laboratory used microarray analysis to determine the expression levels of 688 miRNAs after activation of a temperature-sensitive p53 mutant in H1299 lung cancer cells (Raver-Shapira et al., 2007). The group led by Joshua Mendell used microarrays to detect 474 different miRNAs and compared their expression after treatment of isogenic HCT116 colorectal cancer cells with DNA-damaging agents in the absence or presence of p53 (Chang et al., 2007). We generated libraries of small RNAs representing p53 "on" and "off" states after activation of a conditional *p53* allele in a human lung cancer cell line (Tarasov et al., 2007). For each library the identity of ~100,000 PCR products was determined by 454 sequencing, which is a combination of emulsion PCR and pyro-sequencing (Margulies et al., 2005). Quantitative analysis of the obtained sequences indicated that 34 miRNAs were significantly induced by p53, whereas 16 miRNAs were repressed. Notably, some of these differentially regulated miRNAs were recently connected to cancer: among the induced miRNAs were *miR-15/16*, which target the oncogene product Bcl2, and *let-7*, which downregulates RAS and HMGA2 (Calin and Croce, 2006; Johnson et al., 2005; Mayr et al., 2007). Among the miRNAs repressed by p53 was *miR-221* (Tarasov et al., 2007), which is known to downregulate the CDK inhibitor p27 (Galardi et al., 2007; le Sage et al., 2007). These regulations could presumably contribute to tumor suppression by p53. As in the other studies, *miR-34a* clearly stood out as the most significantly induced miRNA (Tarasov et al., 2007).

p53 is activated by the deregulated expression of oncogenes, which induce replication stress and thereby DNA damage (Dominguez-Sola et al., 2007; Menssen et al., 2007; and references therein) Therefore, the group led by Greg Hannon compared the expression pattern of miRNAs in mouse embryo fibroblasts derived from *p53*-deficient or wild-type mice expressing the oncogenes *c-MYC*, *RAS*, or *E1A* (He et al., 2007). They initially analyzed the expression of 145 murine, processed miRNAs by quantitative real-time PCR. Arguably, this analysis only covered a fraction of the ~576 currently known murine miRNAs (http://microrna.sanger.ac.uk/) (Griffiths-Jones, 2004). Among the tested miRNAs, *miR-34a* showed the best correlation with p53 status and activity. To a lesser degree the expression of *miR-34b* and *miR-34c* correlated with the presence of p53. The overlap in the differential regulation of miRNAs was relatively small between the independent expression studies, which is presumably due to the different experimental systems. Besides *miR-34a* only a few miRNAs, as *miR-26a* and *miR-182*, were consistently induced after p53 activation and may therefore represent direct p53 targets (Chang et al., 2007; Raver-Shapira et al., 2007; Tarasov et al., 2007).

Eric Fearon's group became interested in *miR-34a* and *miR-34b/c* as potential p53 targets after they found that both genes harbor p53 consensus binding sites, which were found to be occupied by p53 in a genome-wide

ChIP analysis reported previously (Wei et al., 2006), in a distance of 30 kbp from the sequences encoding the mature miRNAs (Bommer et al., 2007). At first sight a p53-binding site in a distance of 30 kbp from a transcription unit would not be considered as a hint for a direct regulation by p53. However, an EST (expressed sequence tag) covered a new, putative first exon of the *miR-34a* gene within 100 bp of the p53-binding site. This first exon of the *miR-34a* primary transcript was experimentally confirmed by RACE (rapid amplification of cDNA ends) and is indeed located 30 kbp upstream of the second exon, which contains the *miR-34a* hairpin (Chang et al., 2007; He et al., 2007; Tarasov et al., 2007). Chromatin immunoprecipitation confirmed that p53 occupies a highly conserved consensus binding site that is located in close proximity to the transcription start site of *miR-34a* (Bommer et al., 2007; He et al., 2007; Raver-Shapira et al., 2007; Tarasov et al., 2007). We characterized two additional p53-binding sites in the unusually large first intron, which correspond to half of the consensus site and are therefore less effective (Tarasov et al., 2007). After treatment with DNA-damaging agents, the expression of *miR-34a* and *miR-34b/c* was also induced in mouse tissues in a p53-dependent manner (Bommer et al., 2007; He et al., 2007; Raver-Shapira et al., 2007). Interestingly, the *miR-34b/c* gene has a similar structure as *miR-34a* with a p53-binding site near the transcription start site. Therefore, the two genes presumably resulted from a gene duplication event. The *miR-34* family is one of only 18 miRNA families that are also conserved in *Drosophila* and *C. elegans* (Ruby et al., 2006). Since the p53 pathway is conserved in these species, the p53-*miR-34* connection may have arisen early in evolution and is therefore presumably of functional importance in a large number of species. In support of this notion, an alignment of the *miR-34* sequences found in different vertebrate and invertebrate species shows very strong sequence conservation (He et al., 2007). However, in invertebrates *miR-34* is represented by one miRNA, as opposed to three isoforms found in vertebrates.

Functions of p53-Induced *miR-34s*

Unexpectedly, the experimental introduction of miR-34s into cells had rather drastic effects on cell proliferation and survival. Ectopic expression of *miR-34a* caused a cell cycle arrest in the G_1 phase (Bommer et al., 2007; He et al., 2007; Tarasov et al., 2007), as did *miR-34b/c* (He et al., 2007). In the study led by Alexander Nikitin, *miR-34b* and *miR-34c* inhibited proliferation and colony formation in soft agar (Corney et al., 2007). Interestingly, introduction of *miR-34a* and *miR-34b/c* into primary human diploid fibroblasts induced cellular senescence (He et al., 2007), a permanent form of cell cycle arrest, which is presumably also relevant for organismal aging (Collado et al., 2007). Interestingly, tumor cells also showed signs of senescence after introduction of ectopic *miR-34a* (Tazawa et al., 2007). Furthermore, expression of *miR-34a* induced apoptosis (Chang et al., 2007; Raver-Shapira et al., 2007; Tarasov et al., 2007; Welch et al., 2007). As cell cycle arrest and apoptosis are common endpoints of p53 activation, *miR-34* genes may be important mediators of tumor suppression by p53. When *miR-34a* was inhibited by introduction of *miR-34a*-specific LNAs (locked nucleotide analogs), the rate of apoptosis induced by DNA damage was reduced (Raver-Shapira et al., 2007). Similarly, *miR-34a*-deficient ES cells showed a slight decrease in spontaneous apoptosis after differentiation (Bommer et al., 2007). Therefore, *miR-34a* may not only be sufficient but also required for mediation of tumor suppression by p53.

An important question then was the following: what are the targets for downregulation by the processed *miR-34* molecules mediating the drastic effects observed after ectopic expression of *miR-34s*? According to algorithms commonly used for miRNA target prediction, there may be hundreds of theoretical target mRNAs for each miRNA. Furthermore, miRNA targets are hard to predict, since they are only partially complementary to the miRNA: only in the seed region of the miRNA a perfect complementarity seems to be required. Another difficulty lies in the feasibility of screening approaches to identify miRNA targets. The use of mRNA profiling seems to be a weak compromise, since miRNAs mainly affect translation and not mRNA abundance. Nonetheless, microarray analyses after ectopic introduction of different members of the *miR-34* family into various cell lines yielded interesting results, as hundreds of putative, downregulated *miR-34* targets were identified (Bommer et al., 2007; Chang et al., 2007; He et al., 2007; Tazawa et al., 2007). As expected, the downregulated mRNAs showed an enrichment of *miR-34a* seed sequences in their 3′UTRs. He et al. found that more than half of the downregulated mRNAs were also repressed after treatment of cells with the DNA damaging agent adriamycin. Therefore, numerous gene repression events that occur after DNA damage may result from induction of *miR-34a* expression by p53. Interestingly, cell cycle-regulatory genes were overrepresented among the repressed genes (Bommer et al., 2007; He et al., 2007). Exemplary protein downregulations were confirmed for CDK4/6, Cyclin E2, E2F5, MET, and Bcl-2 (Bommer et al., 2007; He et al., 2007; Tazawa et al., 2007). Furthermore, the effects on translation of these proteins are presumably direct, since reporters carrying the 3′UTR of the respective genes were inhibited by cotransfection of *miR-34a*. Therefore, the antiapoptotic effect of *miR-34a*-specific LNAs may be a consequence of the elevated expression of the antiapoptotic Bcl-2 protein (Bommer et al., 2007). As expected, introduction of siRNAs specific for the *miR-34a* targets CDK4, Cyclin E2, and MET led to a G_1 arrest, thereby phenocopying the effect of *miR-34* expression (He et al., 2007). The high similarity among the three processed *miR-34* family members suggested that they may have the same targets. Indeed, after separate transfection of *miR-34a*, *miR-34b*, and *miR-34c* the affected mRNAs were almost identical (He et al., 2007).

The induction of *miR-34* genes allows p53 to regulate the expression of a large number of proteins, even after their transcripts have already been synthesized. This type of regulation may be advantageous in situations of cellular stress, as it does not require the translation of additional effector proteins. Furthermore, it facilitates the simultaneous regulation of numerous processes by p53. Interestingly, the mechanism of RNA interference has recently been implicated in other forms of stress response (reviewed in Leung and Sharp, 2007). Furthermore, the targeting of p53-induced mRNAs by *miR-34* may contribute to the fine tuning of the p53 response and prevent an uncontrolled, irreversible response to p53 activation (Cohen et al., 2006).

Inactivation of *miR-34s* in Cancer

As cell cycle arrest, senescence, and apoptosis are tumor-suppressive mechanisms, the inactivation of members of the *miR-34* family, which induce these cellular responses, may be a selective advantage for cancer cells. Besides decreased expression of *miR-34* due to inactivating mutations of *p53*, the *miR-34*-encoding genes themselves may be targets for mutational or epigenetic inactivation in cancer. For example, loss of *miR-34a* expression was observed in neuroblastoma, which may be due to the relatively common deletion of a region on chromosome 1p36, which encompasses *miR-34a* (Welch et al., 2007). Furthermore, expression of *miR-34a* was low or undetectable in 11 of 15 pancreatic cancer cell lines (Chang et al., 2007). The expression level of *miR-34b* was decreased by more than 90% in 6 out of 14 non-small-cell lung cancers (NSCLCs) (Bommer et al., 2007). However, the mechanisms leading to decreased expression of miR-34s require further exploration.

Future Directions

To further substantiate the connection between p53 and the *miR-34* genes, it will be important to define the targets of *miR-34s* in more detail using additional approaches, e.g., proteomic analyses. Furthermore, the relevance of the individual target downregulations mediated by *miR-34s* for tumor suppression by p53 needs to be determined. Knockout approaches combined with mouse models of cancer will presumably allow the organismal function of *miR-34* genes and their relevance for tumor suppression in vivo to be determined. In addition, it will be interesting to determine to what extent p53-induced miRNAs or direct p53-mediated repression account for the downregulation of genes observed after p53 activation.

siRNAs are currently tested and optimized for clinical applications (de Fougerolles et al., 2007). Therefore, it may be possible to restore *miR-34* function for cancer therapeutic purposes in the future. Notably, the administration of *miR-34a*/atelocollagen complexes was shown to suppress tumor growth in mice (Tazawa et al., 2007). Given the tumor-suppressive functions ascribed to the miR-34 family, it will be interesting to determine whether detection of miR-34s has diagnostic or prognostic advantages as previously shown for other miRNAs (Calin and Croce, 2006).

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