PERSPECTIVE

miR than meets the eye

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Retinoblastoma is a rare pediatric cancer that has served as a paradigm to investigate the mechanisms of tumorigenesis. In this issue of *Genes & Development*, Conkrite and colleagues (pp. 1734–1745) found high levels of the *miR-17~92* and *miR-106b~25* microRNAs in primary retinoblastomas and show that overexpression of *miR-17~92* accelerates retinoblastoma development in mice by promoting proliferation, in part by reducing expression of the cell cycle inhibitor p21. These experiments identify the *RB/miR-17~92/p21* axis as a critical regulator of retinoblastoma tumorigenesis and potentially many other cancers.

The *miR-17~92* cluster belongs to a highly conserved family of polycistronic miRNA genes, whose two other members are the *miR-106a~363* cluster and the *miR-106b~25* cluster. Collectively, these three loci encode for 15 miRNAs that can be further grouped into four distinct “seed” families based on sequence similarity (Fig. 1A,B). Gene targeting experiments in mice have shown that *miR-17~92* is essential for mammalian development, and that the three clusters share partially overlapping targets and functions (Ventura et al. 2008). Nevertheless, relatively little is known about the relative contribution of the various miRNAs encoded by the three clusters.

miRNAs and cancer

One of the most exciting new developments of the past two decades has been the identification of microRNAs (miRNAs) and the realization that these small, noncoding RNAs provide an additional layer of complexity in the regulation of gene expression (Bartel 2009). It is estimated that more than one-third of human protein-coding genes are subjected to regulation by miRNAs. Given their widespread effect on gene expression, it is therefore not surprising that miRNAs play key roles in mammalian development and in diseases. In fact, deregulated expression of miRNAs is a common feature of human cancers, and individual miRNAs acting as bona fide oncogenes or tumor suppressors have been described (Ventura and Jacks 2009).

Among the oncogenic miRNAs, the *miR-17~92* cluster, also known as OncomiR-1, is the subject of intense investigation. Recurrent focal amplifications of the *miR-17~92* locus have been reported in a significant fraction of diffuse large B-cell lymphomas (Ota et al. 2004), and overexpression of the six miRNAs encoded by this cluster is observed in a wide variety of solid and liquid tumors (for review, see Olive et al. 2010). Furthermore, experiments in mice have provided conclusive evidence that *miR-17~92* is a bona fide oncogene in lymphoma (He et al. 2005; Mu et al. 2009; Olive et al. 2009), colon cancer (Dews et al. 2006), and medulloblastoma (Uziel et al. 2009).

Retinoblastoma in humans and mice

In this issue of *Genes & Development*, Conkrite et al. (2011) provide compelling evidence implicating *miR-17~92* and *miR-106b~25* in the pathogenesis of retinoblastoma, a cancer of the eye that occurs only in young children. Although retinoblastoma is a rare cancer (approximately one out of 20,000 births), its study has contributed tremendously to our understanding of cancer in general. In fact, the first tumor suppressor gene, *RB*, was identified from retinoblastoma patients, and it is now clear that most human cancers harbor mutations in *RB* itself or in various components of the RB pathway. Importantly, retinoblastoma, whose initiating event is known, provides a simple but powerful system to study cooperating events in tumorigenesis. Thus, studying retinoblastoma development may teach us how most human cancers initiate and progress (for a recent review, see Chinnam and Goodrich 2011).

Retinoblastoma development seems specific to humans. Spontaneous retinoblastomas have never been observed in rodents, and only a handful of cases have been reported in mammals other than humans (Syed et al. 1997; Fugaro et al. 2005; Knottenbelt et al. 2007). Accordingly, targeted deletion of both *Rb* alleles in a variety of mouse retinal cells at different stages of retinal development does not lead to the development of eye tumors, but merely results in ectopic proliferation and increased cell death (Chen et al. 2004; MacPherson et al. 2004; Zhang et al. 2004).

In mammals, RB belongs to a family of structurally and functionally related proteins including RB itself, as well as p107 and p130. The three family members are inhibited by the same Cyclin/cyclin-dependent kinase (CDK) complexes; interact with a number of identical partners, including viral

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Figure 1. (A) Schematic representation of the *miR-17~92* cluster and its two paralogs, *miR-106a~363* and *miR-106b~25*. (B) The 15 miRNAs encoded by these three polycistronic miRNA clusters are shown and grouped based on their “seed” sequence. miRNAs belonging to the same “seed” group are predicted to target largely overlapping sets of genes. (C) Schematic of the many oncogenic activities attributed to *miR-17~92*, with special emphasis on its role as a modulator of cell proliferation. For simplicity, only a subset of interactions is shown. Conkrite et al. (2011) identify the *miR-17~92* miRNA as a novel downstream mediator of RB function. *miR-17~92* expression may be induced by E2F, by members of the MYC family, or due to genomic amplification. In retinoblastoma cells and possibly in other RB mutant cells, *miR-17~92* is thought to promote cancer in part by inhibiting the expression of cell cycle inhibitors, including p21, feeding back onto the RB pathway.

oncoproteins, E2F transcription factors, and chromatin remodeling enzymes; and control cell cycle progression (for review, see Levine 2009; Chinnam and Goodrich 2011). Analysis of mice with combinations of mutations in *Rb* family genes has provided evidence for strong overlapping functions within the RB family. First, *p130*^{-/-}; *p107*^{-/-} mice die just after birth with differentiation defects in bones and abnormalities in chondrocyte proliferation, while deletion of *p107* or *p130* had no developmental consequences in the same genetic background (Cobrinik et al. 1996). In addition, *Rb*^{-/-}; *p107*^{-/-}, *Rb*^{-/-}; *p130*^{-/-}, and *Rb*^{-/-}; *p107*^{-/-}; *p130*^{-/-} embryos die earlier during mouse development than *Rb*^{-/-} embryos, with more pronounced developmental defects, including increased cell death and abnormal proliferation (Lee et al. 1996; Berman et al. 2009; Wirt et al. 2010).

Based on these observations, several groups generated mice with mutations in *Rb* and *p107* or *Rb* and *p130* in the developing retina. These double-knockout mice develop tumors that strongly resemble human retinoblastomas, including in their metastatic potential, thereby providing a novel system in which to study retinoblastoma in vivo and ex vivo (for review, see MacPherson 2008). The tumor suppressor function of p107 and p130 in *Rb* mutant cells has been extended to several other organs and tissues (for recent examples, see Jiang et al. 2010; Schaffer et al. 2010). One caveat of these mouse models of retinoblastoma is that they rely on the inactivation of two genes instead of

just one, as occurs in patients. Nevertheless, the availability of these *Rb/p107* and *Rb/p130* mutant mouse models, coupled with the capacity to compare the mouse tumors with human primary retinoblastomas, has provided powerful means to investigate molecular and cellular events in the genesis of these tumors.

A role for miRNAs in retinoblastoma development

To identify additional events that cooperate with RB loss in retinoblastoma development, Conkrite et al. (2011) performed array comparative genomic hybridization (CGH) on a panel of 21 murine retinoblastomas generated by the concomitant inactivation of *Rb* and *p107*. In two tumors they observed focal amplification of a chromosomal region containing the *miR-17~92* cluster. To extend this finding, they examined a panel of 32 human primary retinoblastomas samples, showing increased *miR-17~92* copy number in two of them. Interestingly, when they looked for *miR-17~92* expression levels in human and murine primary retinoblastomas and retinoblastoma cell lines, Conkrite et al. (2011) found that it correlated well with copy number in murine samples, while in human samples the six miRNAs encoded by this cluster were expressed at very high levels, irrespective of *miR-17~92* copy number. Although this finding needs to be confirmed in a larger set of retinoblastomas, it suggests that in human retinoblastomas, up-regulation of *miR-17~92* is a common event

that is usually achieved via transcriptional or post-transcriptional mechanisms. E2F activity is high in RB mutant cells such as retinoblastoma cells; in addition, the MYC oncogene is activated in a fraction of mouse and human retinoblastomas (Lee et al. 1984; MacPherson et al. 2007). Because *miR-17~92* is a direct transcriptional target of both MYC and E2F1 (O'Donnell et al. 2005; Sylvestre et al. 2007; Woods et al. 2007), the activation of these two oncogenic transcription factors may partially explain the up-regulation of *miR-17~92* levels in retinoblastoma cells.

Correlation is not proof of causation. Hence, Conkrite et al. (2011) used a transgenic approach to determine whether increased expression of *miR-17~92* could play a role in the genesis of retinoblastoma. Overexpression of *miR-17~92* per se did not cause any detectable defect in retinal development, nor was it sufficient to induce tumor formation. However, in the absence of *Rb* and *p107*, it produced a dramatic acceleration of retinoblastoma formation, resulting in highly aggressive bilateral tumors. Unfortunately, *miR-17~92* overexpression in the context of *Rb* loss alone was not sufficient to induce tumors in mice. Thus, while these results clearly implicate *miR-17~92* in the pathogenesis of retinoblastoma, they do not explain why the simultaneous loss of *Rb* and *p107* is required in mice but not in humans.

A particularly interesting aspect of the new data presented by Conkrite et al. (2011) is that they provide new mechanistic insights into the oncogenic activity of *miR-17~92*. Experiments performed in mouse models had previously shown that *miR-17~92* can accelerate tumorigenesis by suppressing apoptosis (Mu et al. 2009; Olive et al. 2009; Mavrikakis et al. 2010), by increasing angiogenesis (Dews et al. 2006), or by suppressing TGF- β signaling (Mestdagh et al. 2010). Conkrite et al. (2011) now show that in retinoblastomas, the main consequence of *miR-17~92* overexpression is an increase in cell proliferation, at least in part via direct inhibition of key cell cycle inhibitors such as p21^{CIP1} and p57^{KIP2}. Furthermore, by performing experiments in retinoblastoma cell lines, they show that this proliferative activity is not due to *miR-19a* and *miR-19b*, but to *miR-17* and *miR-20a*, two other members of the cluster. While the ability of these miRNAs to repress cell cycle inhibitors had been previously reported (Fontana et al. 2008; Ivanovska et al. 2008; Sengupta et al. 2008), Conkrite et al. (2011) demonstrate their functional relevance in vivo.

As is often the case with new findings, the work of Conkrite et al. (2011) raises several interesting questions for future research. For example, it will be important to determine whether endogenous *miR-17~92* is required for retinoblastoma formation. This could have therapeutic implications, as Conkrite et al. (2011) show that genetic inactivation of *miR-17~92* does not interfere with retinal development. Thus, inhibiting these miRNAs in the eyes of young children, at a time when their retinas are still developing, might be a viable strategy to slow or prevent retinoblastoma growth without major side effects.

One of the challenges in the field in the next few years will be to continue to identify key determinants of retinoblastoma development. In particular, one prediction from

the observation that *Rb/p107* and *Rb/p130* mutant mice develop retinoblastoma is that *Rb* deletion might also cooperate with loss of other cell cycle inhibitors such as members of the p16 and p21 families of cell cycle inhibitors. In support of this idea, Conkrite et al. (2011) show that genetic inactivation of p21^{CIP1} in *Rb/p107* mutant retinas leads to increased proliferation at postnatal day 22; it will be interesting to determine whether it also results in accelerated tumorigenesis.

Finally, it will be important to investigate the role of the *miR-17~92* paralogs *miR-106a~363* and *miR-106b~25* in retinoblastoma formation. These two clusters contain miRNAs that are virtually identical to those encoded by *miR-17~92* (Fig. 1A,B) and synergize with *miR-17~92* in modulating embryonic development (Ventura et al. 2008). It is thus plausible that their deregulation may also contribute to retinoblastoma development. Consistent with this hypothesis, Conkrite et al. (2011) detected copy number increase in the region containing *miR-106b~25* in one murine and four human retinoblastomas, although the functional consequences of these alterations were not investigated further.

Regulatory networks downstream from RB in cancer

In the last two decades, a number of positive and negative feedback mechanisms have been identified in cells following loss of RB function. For instance, loss of RB function results in activation of E2F transcription factors and up-regulation of *p107* transcription, which is thought to largely explain why p107 can compensate for loss of RB in many contexts, including in the mouse retina (Burkhart et al. 2010 and references therein). Interestingly, one reason why patients mutant for *RB* develop retinoblastoma even in the presence of a wild-type *p107* gene might be because loss of RB does not up-regulate *p107* in embryonic retinal progenitors (Donovan et al. 2006). Other classical E2F targets whose up-regulation slows cell cycle progression include the cell cycle inhibitors p19^{ARF} (Aslanian et al. 2004) and p21 (Hiyama et al. 1998). In contrast, activation of E2F in RB mutant cells also prevents cell death by increasing the expression of the p53 deacetylase Sirt1 (Chen et al. 2009) and promotes cell cycle progression by increasing the expression of the cell cycle machinery, including E2F1 itself, Cyclin E, and Cyclin A (for review, see Chinnam and Goodrich 2011). Independently of E2F, loss of RB can also lead to decreased levels of the cell cycle inhibitor p27 (Binne et al. 2007). A truly interesting aspect of the new data presented by Conkrite et al. (2011) is that they identify *miR-17~92* as a central node in the regulatory networks centered on RB in the control of the G1/S transition (Fig. 1C). As mentioned above, *miR-17~92* has been shown to be a direct transcriptional target of E2F transcription factors (Sylvestre et al. 2007; Woods et al. 2007), which provides a direct link between the canonical RB pathway and this miRNA.

In conclusion, the new data presented by Conkrite et al. (2011) not only provide novel insights into the pathogenesis of retinoblastoma, but also add to the growing list of human cancers in which the *miR-17~92* cluster plays

a key role. Importantly, these data also show that the mode of action of *miR-17~92* is highly context-specific, with different members of the cluster acting as the key oncogenic determinant in different tumor types. If, as seems highly plausible, a role for *miR-17~92* is confirmed in a broad range of RB mutant tumors, the pharmacologic inhibition of this cluster may have therapeutic potential in a very large group of cancer patients.

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