Dicer1 functions as a haploinsufficient tumor suppressor

Madhu S. Kumar,1 Ryan E. Pester,1 Cindy Y. Chen,1 Keara Lane,1 Christine Chin,1 Jun Lu,2 David G. Kirsch,3 Todd R. Golub,4,5,6 and Tyler Jacks1,7,8

1Massachusetts Institute of Technology Koch Institute for Integrative Cancer Research, Cambridge, Massachusetts 02139, USA; 2Department of Genetics, Yale University, New Haven, Connecticut 06520, USA; 3Department of Radiation Oncology, Duke University, Durham, North Carolina, 27708, USA; 4Broad Institute of Massachusetts Institute of Technology and Harvard, Cambridge, Massachusetts 02141, USA; 5Department of Pediatric Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts 02115, USA; 6Howard Hughes Medical Institute, Harvard Medical School, Boston, Massachusetts 02115, USA; 7Howard Hughes Medical Institute, Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA

While the global down-regulation of microRNAs (miRNAs) is a common feature of human tumors, its genetic basis is largely undefined. To explore this question, we analyzed the consequences of conditional Dicer1 mutation [Dicer1 “floxed” or Dicer1fl] on several mouse models of cancer. Here we show Dicer1 functions as a haploinsufficient tumor suppressor gene. Deletion of a single copy of Dicer1 in tumors from Dicer1fl/+ animals led to reduced survival compared with controls. These tumors exhibited impaired miRNA processing but failed to lose the wild-type Dicer1 allele. Moreover, tumors from Dicer1fl/fl animals always maintained one functional Dicer1 allele. Consistent with selection against full loss of Dicer1 expression, enforced Dicer1 deletion caused inhibition of tumorigenesis. Analysis of human cancer genome copy number data reveals frequent deletion of Dicer1. Importantly, however, the gene has not been reported to undergo homozygous deletion, suggesting that Dicer1 is haploinsufficient in human cancer. These findings suggest Dicer1 may be an important haploinsufficient tumor suppressor gene and, furthermore, that other factors controlling miRNA biogenesis may also function in this manner.

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MicroRNAs (miRNAs) are short, noncoding RNAs that function to suppress post-transcriptionally the expression of target mRNAs, predominately via inhibition of translation. Such translational inhibition relies on imperfect base-pairing between the miRNA and the target transcript, with the interaction at nucleotides 2–8 (or the “seed” region) of the miRNA being required for translational repression. Computational prediction of miRNA targets based on seed regions and sequence conservation has revealed a widespread potential for miRNA-mediated transcript regulation, with hundreds of putative mRNA targets for an individual miRNA (Bartel 2004).

In line with their broad-based effects, miRNAs have been proposed to function as oncogenes or tumor suppressor genes based on their inhibition of a variety of tumor-suppressive and oncogenic mRNAs, respectively [Plasterk 2006; Ventura and Jacks 2009]. In particular, three distinct mechanisms have been posited. First, oncogenic miRNAs can undergo gain of function in tumors. This has been most clearly demonstrated for the miR-17–92 cluster, whose amplification in B-cell lymphomas promotes their development, potentially through its control of B-cell differentiation [He et al. 2005; Koralov et al. 2008; Ventura and Jacks 2009]. Furthermore, tumor-suppressive miRNAs could undergo loss of function in tumors. This has been shown for several miRNAs, including the let-7 family, whose expression can limit lung tumorigenesis through inhibition of oncogenes like the Ras family and HMG2 [Esquela-Kerscher et al. 2008; Kumar et al. 2008]. In particular, let-7 family members are in sites of frequent deletion in human tumors, and their processing is inhibited by the oncogenic Lin-28 proteins [Heo et al. 2008; Newman et al. 2008; Viswanathan et al. 2008; Chang et al. 2009]. Finally, oncogenes can acquire mutations to remove miRNA-binding sites in tumors. This has been described for HMG2, whose translocation promotes lipoma development by releasing the transcript from let-7-mediated tumor suppression [Mayr et al. 2007].

We reported a global down-regulation of miRNAs in several types of human and murine cancer [Lu et al. 2005]. From this initial study, it was unclear whether this widespread loss of miRNAs was merely a consequence of tumor development or was functionally related to the disease process. We demonstrated previously that this global loss of miRNAs was functionally relevant to oncogenesis, as impairment of miRNA maturation enhanced transformation in both cancer cells and a K-Ras-driven model of lung cancer [Kumar et al. 2007]. While these studies provide a framework to explain inhibition of miRNA biogenesis in cancer, the genetic basis of impaired miRNA processing in human cancer has been largely undefined. For a subset of miRNAs, widespread silencing occurs at the transcriptional level via the c-Myc oncogene [Chang et al. 2008]. However, it has also been shown that such broad reductions in miRNAs can occur post-transcriptionally, since changes in miRNA levels frequently occur without changes in the levels of the primary miRNA transcript [Thomson et al. 2006]. Recently, it was shown that mutations in the miRNA processing component TARBP2 occur frequently in mismatch repair-deficient colon cancer, and that these mutations promote tumorigenesis by impaired processing of miRNAs [Melo et al. 2009]. While interesting, these limited cases do not resolve the common global reduction
We previously reported results using the Kras\textsuperscript{LSL-G12D} mouse embryonic fibroblasts (MEFs), either heterozygous conditional or mutant for Dicer1 (KD\textsuperscript{fl/fl} and KD\textsuperscript{fl/+, respectively}), were intranasally infected with Ad-Cre, and survival was assessed. Median survival was 194 d for KD\textsuperscript{fl/+} mice, 108 d for KD\textsuperscript{fl/+, and 143 d for KD\textsuperscript{fl/fl} mice. Statistical significance was assessed by the log-rank test.

of miRNAs in human cancers. Moreover, the precise genetics of such changes in tumors is poorly defined, especially as no components of the miRNA processing pathway have been reported to be completely deleted in human tumors. This is not surprising, since it has been shown that germline deletion of miRNA processing components Diicer1 and Dicer8 in mice fails to produce viable progeny [Bernstein et al. 2003; Wang et al. 2007]. Thus, conditional deletion of miRNA processing components provides a powerful means of examining the role of miRNAs in tumorigenesis.

### Results and Discussion

We previously reported results using the Kras\textsuperscript{LSL-G12D} strain, which was either heterozygous or homozygous for a conditional allele of Dicer1 (hereafter referred to as KD\textsuperscript{fl/+} and KD\textsuperscript{fl/+, respectively} [Jackson et al. 2001; Harfe et al. 2005]. After intranasal infection with adenovirus expressing Cre (Ad-Cre), these compound mutant animals developed significantly more lung tumors compared with Kras\textsuperscript{LSL-G12D} mice that were wild type for Dicer1 [Kumar et al. 2007]. Based on the protumorigenic effect of hemizygous mutation of Dicer1 in these tumor models, we went on to assess

**Figure 1.** Dicer1 mutation reduces post-infection survival in a genetically engineered mouse model of K-Ras driven lung cancer. Kras\textsuperscript{LSL-G12D} mice, either wild type or heterozygous or homozygous conditional for Dicer1 (KD\textsuperscript{fl/+}, KD\textsuperscript{fl/+, and KD\textsuperscript{fl/fl}, respectively), were intranasally infected with Ad-Cre, and survival was assessed. Median survival was 194 d for KD\textsuperscript{fl/+} mice, 108 d for KD\textsuperscript{fl/+}, and 143 d for KD\textsuperscript{fl/fl} mice. Statistical significance was assessed by the log-rank test.

We further examined Dicer1 recombination in lung cancer cell lines from KPD\textsuperscript{fl/+} mice. In these cell lines, we again found evidence of Cre-Lox recombination. However, the recombination was incomplete, generating KPD\textsuperscript{fl/+} lung cancer cells (Fig. 2B); this incomplete loss of Dicer1 was also observed in sarcoma cell lines from KPD\textsuperscript{fl/+, mice [Supplemental Fig. 2A]. Thus, it is likely that KD\textsuperscript{fl/+} lung tumors undergo selection against complete Dicer1 recombination during tumor progression. To determine if complete loss of Dicer1 product occurs, Dicer1 protein levels were examined in lung cancer cells and sarcomas either wild type or mutant for Dicer1. Although we observed a general reduction in Dicer1 protein in Dicer1 mutant cancer cell lines, all retained some expression of Dicer1 [Supplemental Fig. 2B]. In addition, resequencing of the Dicer1 ORF in lung cancer and sarcoma cell lines from KPD\textsuperscript{fl/+} and KPD\textsuperscript{fl/+, mice revealed no further mutations of the retained Dicer1 allele [data not shown], suggesting that complete loss of Dicer1 function is not achieved through second site mutation. In sum, these data indicate that only partial loss of Dicer1 occurs in these genetically engineered mouse models during tumorigenesis.

Based on the protumorigenic effect of hemizygous mutation of Dicer1 in these tumor models, we went on to assess
the consequence of partial loss of Dicer1 on global miRNA expression. Comparing miRNA profiles in Dicer1 wild-type and heterozygous mutant lung cancer cells, there was a global decrease in steady-state miRNA levels in KPD+/− cells [Fig. 3A, Supplemental Table 1]. Small RNA Northern blot analysis of miRNAs and glutamine tRNA was performed on lung cancer cell lines wild type or heterozygous for Dicer1 as above.

While the genetic analysis of the Dicer1 locus in our mouse cancer models suggested that Dicer1 was functioning as a haploinsufficient tumor suppression gene, it was still formally possible that Dicer1 mutant tumors eventually underwent complete inactivation of Dicer1 via an alternative mechanism like epigenetic silencing. Thus, we assessed the consequences of complete loss of Dicer1 in the genetically engineered mouse models. First, to promote complete loss of Dicer1 in the lung, we infected KD+/+ and KD+/− mice with a lentivirus expressing Cre [Lenti-Cre]. In contrast to the recombinant adenoviruses, which do not integrate in the genome of the infected cells and are eventually lost, lentiviral integration is expected to allow for stable, longer-term expression of Cre and, more likely, complete recombination at the Dicer1 locus. Infection of mice with Lenti-Cre led to a striking decrease in tumor burden in KD+/+ compared with KD+/− mice [Supplemental Fig. 3A–C]. This result contrasts sharply with previous studies in which KD+/+ and KD+/− mice created a similar tumor burden after Ad-Cre infection. Notably, when we isolated DNA from the tumors that did arise in KD+/− mice and assessed Dicer1 loss, all tumors were once again found to have undergone incomplete recombination, suggesting that there is selection against total Dicer1 loss in lung tumors [Supplemental Fig. 3D].

To further examine the effects of complete Dicer1 loss, we transduced a set of sarcoma cell lines with CreERT2 to permit tamoxifen-dependent Cre activity. Treatment with 4-hydroxytamoxifen (4-OHT) led to efficient deletion of Dicer1 in vitro [Fig. 4A]. To assess the effect of complete Dicer1 loss on tumorigenesis, we transplanted untreated KPD+/− sarcoma cells expressing CreERT2 into immune-competent hosts, and recombination was induced by systemic tamoxifen administration. Compared with control treatments, tamoxifen administration substantially slowed tumor growth in KPD+/− sarcomas [Fig. 4B]. Of note, this system allowed for Cre-mediated deletion of Dicer1, as the tumors that developed in tamoxifen-treated animals had extensive Dicer1 recombination [Fig. 4C]. Importantly, tumor suppression was not merely an effect of tamoxifen- or Cre-mediated toxicity, as tamoxifen treatment of animals injected with KPD+/− sarcoma cells expressing CreERT2 did not impair tumor growth [Supplemental Fig. 4]. Taken together, these studies demonstrate that complete deletion of Dicer1 is deleterious to tumor development, strongly suggesting that Dicer1 is a haploinsufficient tumor suppressor. Of note, in a separate study using these cancer cell lines, A Ravi, MS Kumar, C Chin, T Jacks, and PS Sharp [in prep.] have shown that full loss of Dicer1 function can be tolerated, but that Dicer1-null cells have impaired proliferative capacity.

While these findings indicate that partial loss of Dicer1 promotes tumor development, it was not clear whether a comparable situation occurs in human cancer. To explore this question, we assessed DICER1 copy number data from the Cancer Genome Project at the Sanger Institute [Forbes et al. 2008]. In these data sets, there was frequent loss of one allele of DICER1 [via hemizygous deletion] in several different tumor types [Table 1]; similar results were obtained from analysis of copy number data sets of glioblastomas and ovarian cancers from The Cancer Genome Atlas [TCGA] [data not shown]. Although the deletions of DICER1 seen in human cancer were generally broad (>1 Mb), there were
This study describes cancer cell lines (Merritt et al. 2008). Importantly, while suggesting a broad role for found changes in cancers of a variety of genotypes, analysis of miRNA processing machinery mutations has suppressor in the context of K-Ras-driven cancer, the Stomach 9/21 Large intestine 14/39 Kidney 13/21 Breast 17/45 Dmp1 (Inoue et al. 2001; Muraoka et al. 2002). Moreover, haploinsufficiency of deleted genes in such contexts. begin to explore the functional role of chromosomal complete loss is disadvantageous. As genome-wide studies haploinsufficient tumor suppressors to include components of the miRNA processing machinery. The breadth of tumor suppressor genes that function via haploinsufficiency is only beginning to be appreciated [Santarosa and Ashworth 2004]. In fact, the traditional reliance on complete loss of tumor suppressor genes by heterozygous mutation and subsequent loss of heterozygosity (LOH) is likely to overlook factors whose effects do not require complete loss, such as p27Kip1 and Dmp1 [Inoue et al. 2001; Muraoka et al. 2002]. Moreover, such analyses are certain to ignore genes like Dicer1, for which partial loss is advantageous to tumors while complete loss is disadvantageous. As genome-wide studies begin to explore the functional role of chromosomal deletions in human cancer, it will be important to consider haploinsufficiency of deleted genes in such contexts.

**Materials and methods**

**Mice**

*Kras<sub>LSL-G12D</sub>; *Dicer<sup>fl/fl</sup>* animals were generated as described previously [Kumar et al. [2007]. *Kras<sub>LSL-G12D</sub>; Trp53<sup>fl/fl</sup>* animals were bred never high-level amplifications of the *DICER1* locus in these tumor sets, suggesting these losses were not due to random genome instability. More importantly, homozygous deletion of *DICER1* was never reported, in line with our findings of *Dicer1* functioning as a haploinsufficient tumor suppressor [Hill et al. 2009; Melo et al. 2009].

Our results suggest a major cause for the global loss of miRNAs in human cancer [Lu et al. 2005], via partial loss of function of the miRNA processing machinery in human tumors. Although the frequent *DICER1* single-copy deletion noted in human cancers provides a relevant mechanism of impairing miRNA biogenesis, additional mechanisms may occur. In particular, in light of the frequent mutation of *TARBP2* in mismatch repair-deficient colon cancer [Hill et al. 2009] and heterozygous germline point mutations in *DICER1* in patients with pulmonary blastoma [Melo et al. 2009], it is possible that point mutations of *Dicer1* or other components of the miRNA processing machinery can occur in different types of human cancer. Indeed, this has been described for *DICER1* and *DROSHA* in a small number of ovarian cancer cell lines [Merritt et al. 2008]. Importantly, while this study describes *Dicer1* as a haploinsufficient tumor suppressor in the context of K-Ras-driven cancer, the analysis of miRNA processing machinery mutations has found changes in cancers of a variety of genotypes, suggesting a broad role for *Dicer1* as a tumor suppressor.

Beyond such mutational analyses, these results represent an expansion of the list of haploinsufficient tumor suppressors to include components of the miRNA processing machinery. The breadth of tumor suppressor genes that function via haploinsufficiency is only beginning to be appreciated [Santarosa and Ashworth 2004]. In fact, the traditional reliance on complete loss of tumor suppressor genes by heterozygous mutation and subsequent loss of heterozygosity (LOH) is likely to overlook factors whose effects do not require complete loss, such as p27Kip1 and Dmp1 [Inoue et al. 2001; Muraoka et al. 2002]. Moreover, such analyses are certain to ignore genes like Dicer1, for which partial loss is advantageous to tumors while complete loss is disadvantageous. As genome-wide studies begin to explore the functional role of chromosomal deletions in human cancer, it will be important to consider haploinsufficiency of deleted genes in such contexts.

**Table 1.** *DICER1* is frequently deleted in various human cancers

| Tumor type | Fraction of tumors with DICER1 hemizygous loss |
|------------|-----------------------------------------------|
| Breast     | 17/45                                         |
| Kidney     | 13/21                                         |
| Large intestine | 14/39                                       |
| Liver      | 3/9                                           |
| Lung       | 37/149                                        |
| Ovary      | 6/22                                          |
| Pancreas   | 6/16                                          |
| Stomach    | 9/21                                          |

Our results suggest a major cause for the global loss of miRNAs in human cancer (Lu et al. 2005), via partial loss of function of the miRNA processing machinery in human tumors. Although the frequent *DICER1* single-copy deletion noted in human cancers provides a relevant mechanism of impairing miRNA biogenesis, additional mechanisms may occur. In particular, in light of the frequent mutation of *TARBP2* in mismatch repair-deficient colon cancer (Hill et al. 2009) and heterozygous germline point mutations in *DICER1* in patients with pulmonary blastoma (Melo et al. 2009), it is possible that point mutations of *Dicer1* or other components of the miRNA processing machinery can occur in different types of human cancer. Indeed, this has been described for *DICER1* and *DROSHA* in a small number of ovarian cancer cell lines (Merritt et al. 2008). Importantly, while this study describes *Dicer1* as a haploinsufficient tumor suppressor in the context of K-Ras-driven cancer, the analysis of miRNA processing machinery mutations has found changes in cancers of a variety of genotypes, suggesting a broad role for *Dicer1* as a tumor suppressor.

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