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Dicer Regulates the Expression of Major Histocompatibility Complex (MHC) Class I Chain-Related Genes A and B

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1. Introduction

RNAi constitutes a key component of the innate immune response to viral infection in both plants and invertebrate animals, and has been postulated to function as the genome or intracellular immune system (Fire A., 2005; Plasterk RH., 2002; Umbach JL. & Cullen BR., 2009). Knockdown of Dicer, the key component of the RNAi pathway, elicits DNA damage and induces the expression of MHC class I chain-related gene A and B (MICA and MICB), two ligands of the NKG2D receptor expressed by natural killer cells and activated $CD8^+$ T cells (Tang KF. et al, 2008b). In this chapter, I discuss the possible molecular mechanisms by which decreased Dicer expression elicits DNA damage and induces the expression of MICA and MICB. MICA and MICB are frequently up-regulated in epithelial tumors of diverse tissue origins (Gasser S. & Raulet DH., 2006). Dicer is down-regulated in most tumor tissues (Merritt WM. et al, 2008; Wu JF. et al, 2011), and DNA damage response is activated in human tumors and precancerous lesions (Bartkova J. et al, 2005, 2006; DiTullio RA Jr. et al, 2002; Gorgoulis VG. et al, 2005). Therefore, the possible roles of Dicer, DNA damage, and MICA and MICB in tumorigenesis are also discussed.

2. RNA interference and the intracellular immune system

Experimental introduction of antisense RNA into cells was once used to interfere with the function of endogenous genes (Izant JG. & Weintraub H., 1984; Nellen W. & Lichtenstein C., 1993). However, Fire and colleagues found in 1991 that plasmid-encoded sense RNA is sufficient to cause interference (Fire A. et al, 1991); Guo and Kemphues reported in 1993 that, in addition to antisense RNA, sense RNA and double-stranded RNA (dsRNA) interfere with the function of endogenous genes (Guo S. & Kemphues KJ., 1995). In 1998, Fire and colleagues found that double-stranded RNA is substantially more effective at producing interference than either strand individually (Fire A. et al, 1998). After injection into adult animals, purified single strands had at most a modest effect, whereas double-stranded mixtures caused potent and specific interference (Fire A. et al, 1998). This phenomenon is now termed RNA interference (RNAi). Historically, RNAi was also known as other names, including posttranscriptional gene silencing (PTGS) and co-suppression in plants (Napoli C. et al, 1990; van der Krol AR. et al, 1990), RNA-mediated

virus resistance in plants (Lindbo JA. & Dougherty WG., 1992), and"quelling" in Neurospora (Cogoni C., 1996) and algae (Wu-Scharf D. et al, 2000). It was postulated that the main functions of the RNAi pathway include antiviral defense, heterochromatic silencing, and transposon regulation (Martienssen RA. et al, 2008; Umbach JL. & Cullen BR., 2009). Therefore, Plasterk and Fire proposed that RNAi is the genome or intracellular immune system (Fire A., 2005; Plasterk RH., 2002).

3. Dicer is the key component of the RNAi pathway

RNAi is characterized by the presence of RNAs of about 22 nucleotides in length that are homologous to the gene being suppressed (Hamilton AJ. & Baulcombe DC., 1999; Hammond SM. et al, 2000; Zamore PD. et al, 2000). These 22-nucleotide sequences, called short interfering RNAs (siRNAs), serve as guide sequences that instruct a multicomponent nuclease, RNA-Induced Silencing Complex (RISC), to destroy the homologous messenger RNAs (Hammond SM. et al, 2000). Dicer, the key component of the RNAi pathway, was identified by Bernstein and colleagues (Bernstein E. et al, 2001). They demonstrated that immunoprecipitated Dicer can generate 22-nucleotide RNAs from dsRNA substrates, and that inhibition of Dicer expression significantly reduces processing of long dsRNA in whole-cell lysates or in Dicer immunoprecipitates (Bernstein E.et al, 2001). In addition to the extrogenous siRNAs, Dicer is also responsible for the biogenesis of endogenous siRNAs. In Schizosaccharomyces pombe, Dicer processes endogenous dsRNA derived from centromeric repeats. The small RNAs are then associated with Ago1, Chp1, and Tas3 to form the RNA-induced initiation of transcriptional gene silencing (RITS) complex that is required for heterochromatin assembly in fission yeast (Verdel A. et al, 2004). Deletion of Dicer results in the aberrant accumulation of complementary transcripts from centromeric heterochromatic repeats. This is accompanied by transcriptional de-repression of transgenes integrated at the centromere, loss of histone H3 lysine-9 methylation, and impaired centromere function (Volpe TA. et al, 2002). The Drosophila endogenous siRNAs are derived from transposons, heterochromatic sequences, and stem-loop structures containing RNAs. Normal accumulation of these endogenous siRNAs requires the siRNA-generating ribonuclease, Dicer, and the RNA interference effector protein, Ago2; mutations in Dicer causes an increase in these transcripts (Czech B. et al, 2008; Ghildiyal M. et al, 2008; Kawamura Y. et al, 2008; Okamura K. et al, 2008). SiRNAs are target-dependent amplified in some organisms. DsRNA is cut into siRNAs, the double-stranded siRNAs are converted into single-stranded siRNAs by the slicer activity of Ago2, the sense strands are degraded, and the antisense strands anneal to their targets and induce target degradation. Alternatively, the antisense RNAs may serve as primers, inducing dsRNA synthesis by the RNA-dependent RNA polymerase (RdRP); Dicer then cuts the dsRNAs to generate secondary siRNAs (Plasterk RH., 2002). Whether there are endogenous siRNAs in organisms lacking RdRP activity was investigated by means of deep sequencing. Two groups found that endogenous siRNAs derived from pseudogenes, natural antisense transcripts, and transposable elements exist in mouse oocytes (Tam OH. et al, 2008; Watanabe T. et al, 2008).

In addition to producing siRNA, Dicer is also required for the biogenesis of other types of small RNAs. Hutvagner and colleagues presented evidence that in Drosophila, a developmentally regulated microRNA (miRNA) precursor, pre-let-7, is cleaved by an RNA

interference-like mechanism to produce mature let-7 miRNA (Hutvágner G. et al, 2001). In cultured human cells, knockdown of Dicer leads to accumulation of the let-7 precursor. This is the first evidence that the RNA interference and miRNA pathways intersect (Hutvágner G. et al, 2001). In addition to the biogenesis of siRNAs and miRNAs, Dicer is also required for the degradation of unstable RNAs containing AU-rich elements (AREs) in 3-prime untranslated regions (UTRs) (Jing Q. et al, 2005). Morever, Dicer also functions in fragmenting chromosomal DNA during apoptosis. Nakagawa and colleagues reported that inactivation of the Caenorhabditis elegans Dicer gene compromises apoptosis and blocks apoptotic chromosome fragmentation (Nakagawa A. et al, 2010). Dicer is cleaved by the Ced3 caspase to generate a C-terminal fragment with deoxyribonuclease activity, which produces 3-prime hydroxyl DNA breaks on chromosomes and promotes apoptosis (Nakagawa A. et al, 2010).

4. Dicer is essential for heterochromatin formation

Depletion of Dicer disrupts heterochromatin formation in Schizosaccharomyces pombe, Arabidopsis thaliana, Caenorhabditis elegans, Tetrahymena thermophila, and Drosophila melanogaster (Grewal SI., 2010; Lejeune E. & Allshire RC., 2011; Martienssen RA. et al, 2008; Riddle NC. & Elgin SC., 2008). However, whether Dicer is involved in heterochromatin formation in mammalian cells is still controversial. Kanellopoulou and colleagues reported that knockout of Dicer in mouse ES cells disrupts centromeric heterochromatin formation, with reduced histone H3K9 di-methylation and tri-methylation, reduced DNA methylation, and increased levels of centromeric repeat RNAs. The decondensation of heterochromatin is accompanied by markedly reduced levels of the 25-30 nt centromeric small dsRNAs, suggesting that Dicer-dependant small RNAs are required for the formation of centromeric heterochromatin (Kanellopoulou C. et al, 2005). Two groups found that the retinoblastoma-like 2 protein (Rbl2) is the target of miR-290 family miRNAs, and that Rbl2 can inhibit the expression of DNA methyltransferases (Dnmts), including Dnmt1, Dnmt3a and Dnmt3b (Benetti R. et al, 2008; Sinkkonen L. et al, 2008). Dicer deficiency in mice leads to decreased DNA methylation. DNA-methylation defects correlate with decreased expression of Dnmts and miR-290 family miRNAs, and can be reversed by transfection with miR-290 family miRNAs. These results indicate that the DNA hypomethylation in Dicer knockout cells is the consequence of low levels of miR-290 family miRNAs (Benetti R. et al, 2008; Sinkkonen L. et al, 2008). However, Benetti and colleagues found that Dicer is not required for histone tri-methylation. They observed that Dicer-null cells have a normal density of H3K9me3 and H4K20me3 marks and of HP1-binding at pericentric repeats, and that these heterochromatic histone marks are significantly increased at telomeric chromatin in Dicer-null cells compared to wild-type controls. They also found that the active chromatin mark, AcH3K9, is decreased at Dicer-null telomeres compared to wild-type telomeres, and that the density of this mark was not significantly decreased at pericentric chromatin. These results suggest that Dicer knockout cells have a higher degree of chromatin compaction and silencing at telomeric chromatin (Benetti R. et al, 2008). Hannon's group reported that although loss of Dicer affects the abundance of transcripts from centromeres in mouse ES cells, the histone modification status at pericentric repeats and methylation of centromeric DNA are not affected in Dicer knockout ES cells (Murchison EP. et al, 2005). Cobb and colleagues reported that the maintenance of constitutive and facultative heterochromatin seemed to be unperturbed in Dicer knockout thymocytes (Cobb BS. et al, 2005).

5. Decreased Dicer expression elicits DNA damage

The timing of DNA replication is tightly regulated and correlates with chromatin state. Highly condensed heterochromatin replicates late in S phase, while less condensed euchromatin tends to replicate early (Donaldson AD., 2005). Although the replication times of many single copy loci, including a 5 Mb contiguous region surrounding the Rex1 gene, are unchanged in Dicer mutant ES cells, the temporal control of satellite DNA replication is sensitive to loss of Dicer (Jørgensen HF. et al, 2007). Misregulation of the timing of DNA replication may cause stalled and collapsed replication forks, which in turn elicit a DNA damage response (Sancar A. et al, 2004). Loss of Dicer in Drosophila cells not only results in decondensation of heterochromatin but also leads to accumulation of extrachromosomal circular (ecc) repeated DNAs. Ligase IV, an essential regulator of nonhomologous end-joining and perhaps other DNA damage-repair machinery, participates in eccDNA formation (Peng JC. & Karpen GH., 2007). This suggests that, while heterochromatin decondensation increases the access of DNA repair and recombination proteins to repeated DNA, activation of DNA damage response may also contribute to the formation of eccDNA in Dicer mutant cells. RNAi is postulated to function as the genome's immune system, defending against molecular parasites such as transposons and viruses, and loss of Dicer may activate transposition (Fire A., 2005; Plasterk RH., 2002). Transposition generates double strand DNA breaks and elicits a DNA damage response (Gasior SL. et al, 2006). Chromatin structure is essential for maintaining genome integrity (Peng JC. & Karpen GH., 2008). For example, Drosophila cells that lack the Su(var)3-9 H3K9 methyltransferase have significantly elevated frequencies of spontaneous DNA damage in heterochromatin. Accumulated DNA damage in these mutants correlates with chromosomal defects, such as translocations and loss of heterozygosity. Based on the observation that S-phase in Su(var)3-9 mutants is significantly shorter than that in wild type cells, the authors proposed that accumulation of DNA damage in Su(var)3-9 mutants is the consequence of defective DNA replication (Peng JC. & Karpen GH., 2009). The regions of repetitive DNA may be incompletely replicated or defective in chromatin reassembly because of a shortened S phase. Alternatively, repeated DNA in heterochromatin may undergo faster replication, resulting in more replication errors. However, the demonstration that DNA damage is detected in G1, S, and G2 stages in Su(var)3-9 mutants suggests that defective DNA replication is not the only cause of the increased DNA damage. HP1β, whose localization requires H3K9me, is needed for efficient DNA damage detection in mammalian cells (Ayoub et al, 2008). Therefore, another explanation for the increased frequencies of DNA damage in Su(var)3-9 mutant cells may be that proper DNA damage detection and subsequent DNA repair response are impaired (Peng JC. & Karpen GH., 2009). We also demonstrated that 5-Aza-2'-deoxycytidine (5-aza-dC), a DNA methyltransferase inhibitor, induces DNA damage in human cells (Tang KF. et al, 2008a).

To test whether loss of Dicer can induce DNA damage, we knocked down Dicer in HEK293T cells and human hepatoma HepG2 cells and measured markers for DNA damage. Immunostaining assays for the phosphorylated form of histone H2AX (γ-H2AX), a widely used marker for double-strand DNA breaks (Foster ER. & Downs JA., 2005), and for the replication protein A 70 (RPA70), a protein that becomes phosphorylated and forms intranuclear foci upon exposure of cells to DNA damage (Zou Y. et al, 2006), revealed that a much higher percentage of Dicer knockdown cells display intense γ-H2AX foci and RPA foci compared to control cells (Tang KF. et al, 2008b). Using a comet assay to directly assess DNA

damage, we confirmed that knockdown of Dicer resulted in accumulation of DNA breaks (Tang KF. et al, 2008b). Consistent with our results, Peng and Karpen reported a significant increase in spontaneous DNA damage in heterochromatic DNAs of Dicer mutant Drosophila cells (Peng JC. & Karpen GH., 2009). Mudhasani and colleagues reported that loss of Dicer activates a DNA damage checkpoint, up-regulates p19(Arf)-p53 signaling, and induces senescence in primary cells (Mudhasani R. et al, 2008).

In Figure 1, I summarize the possible mechanisms on how loss of Dicer leads to DNA damage. First, loss of Dicer reduces the level of endogenous siRNAs, resulting in heterochromatin decondensation. Heterochromatin decondensation may induce DNA damage via the following mechanisms: (i) loss of H3K9 methylation compromises DNA damage detection and subsequent DNA repair response, leading to DNA damage accumulation; (ii) disruption of DNA replication timing induces DNA damage; and (iii) mobilization of transposon and retrotransposon creates DNA double-strand breaks. Second, loss of Dicer stabilizes dsRNA derived from transposons and retrotransposons, causing a high level of transposition and generating DNA double-strand breaks. Third, loss of Dicer compromises miRNA biogenesis. Some miRNAs, such as the miR290 family, can suppress the expression of DNA methyltransferases or histone modifiers; loss of such miRNAs may cause heterochromatin decondensation, which in turn results in DNA damage. Loss of miRNAs that target to components of the DNA damage repair pathway may cause insufficient DNA damage repair, leading to DNA damage accumulation. These molecular events may act synergically or additively in Dicer mutant cells to induce DNA damage.

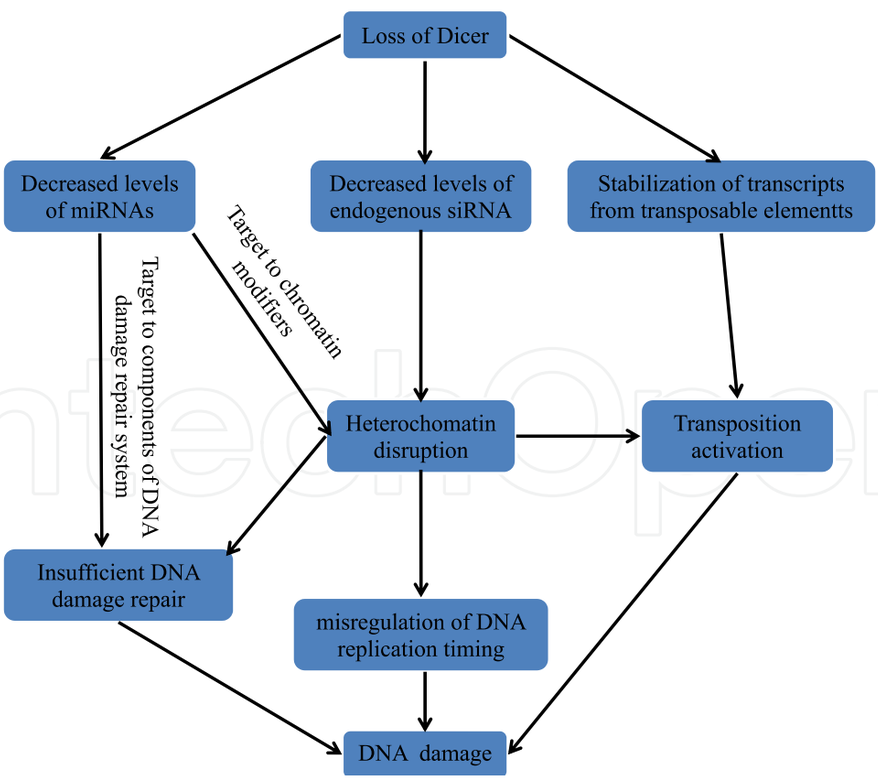


Fig. 1. Molecular mechanisms of DNA damage arising from decreased Dicer expression.

6. DNA damage response induces the expression of ligands for the NKG2D receptor

Natural killer (NK) cells, components of the innate immune system, can kill certain transformed or virus-infected cells lacking MHC class I, yet spare the cells expressing MHC class I. The ability to attack cells missing 'self' markers predicted the existence of both inhibitory and activating receptors on NK cells (Lanier LL., 2008). Unlike T and B cells, which possess a single antigen receptor that dominates cellular development and activation, NK cells do not possess one dominant receptor, but instead have a vast array of receptors to initiate effector functions. None of the receptors alone, with the exception of CD16, is able to elicit cytolytic activity or cytokine secretion (Lanier LL., 2008). The NKG2D receptor complex is one of the activating NK receptors. It is a hexamer, with one NKG2D homodimer associated with two DAP10 homodimers. A single gene encodes NKG2D, which is a C-type lectin-like superfamily member, and a type II transmembrane-anchored glycoprotein expressed as a disulfide-bonded homodimer on the surface of NK cells, γδ T cells, and $CD8^+$ T cells (Lanier LL., 2008). Engagement of NKG2D by its ligands leads either to the direct activation of killing and cytokine secretion by NK cells or to a costimulation of cytotoxic T-lymphocyte cytotoxicity (Lanier LL., 2008; Stern-Ginossar N. & Mandelboim O., 2009). In humans, NKG2D ligands are divided into two families: the MHC class I polypeptide-related chain (MIC) protein family, which contains MICA and MICB; and the cytomegalovirus UL16-binding proteins (ULBP) family, which consists of five members (ULBP1, ULBP2, ULBP3, ULBP4, and REAT1G) (Stern-Ginossar N. & Mandelboim O., 2009).

Gasser and colleagues found that NKG2D ligands are up-regulated in non-tumor cell lines by genotoxic stress and stalled DNA replication, conditions known to activate a major DNA damage checkpoint pathway (Gasser S. et al, 2005). The DNA damage checkpoints employ damage sensor proteins, such as ATM, ATR, the Rad17-RFC complex, and the 9-1-1 complex, to detect DNA damage and to initiate signal transduction cascades that employ Chk1 and Chk2 Ser/Thr kinases and Cdc25 phosphatases. The signal transducers activate p53 and inactivate cyclin-dependent kinases to inhibit cell cycle progression from G1 to S (the G1/S checkpoint), DNA replication (the intra-S checkpoint), or G2 to mitosis (the G2/M checkpoint) (Sancar A. et al, 2004). The up-regulation of NKG2D ligand induced by genotoxic stress was prevented by pharmacological or genetic inhibition of ATR, ATM, or Chk1, indicating that up-regulation of NKG2D ligands is a consequence of DNA damage response (Gasser S. et al, 2005). Induction of DNA damage leads to p53 activation. The role of p53 in the up-regulation of NKG2D ligands was addressed by Textor and colleagues. They found that induction of wild-type p53, but not mutant p53, strongly up-regulated mRNA and cell surface expression of ULBP1 and ULBP2, and that the intronic p53 responsive elements in these two novel p53 target genes are responsible for the up-regulation of ULBP1 and ULBP2 (Textor S. et al, 2011). The biological and medical implications of these findings have been addressed by several groups. Soriani and colleagues demonstrated that treatment with low doses of therapeutic agents such as doxorubicin, melphalan, and bortezomib commonly used in the management of patients with multiple myeloma leads to up-regulation of NKG2D ligands, and that the drug-induced expression of NKG2D ligands was abolished after treatment with the ATM and ATR pharmacologic inhibitors (Soriani A. et al, 2009). We showed that treatment with 5-Aza-2'-deoxycytidine (5-aza-dC), a DNA methyltransferase inhibitor, induces DNA

damage-dependant up-regulation of NKG2D ligands (Tang KF. et al, 2008a). Cerboni and colleagues demonstrated that in response to superantigen, alloantigen, or a specific antigenic peptide, the expression of NKG2D ligands on the surface of T lymphocytes is induced, and that the induction of NKG2D ligand expression is the consequence of DNA damage (Cerboni C. et al, 2007). In addition, they demonstrated that activated T cells became susceptible to autologous NK lysis via NKG2D/NKG2DLs interaction and granule exocytosis, suggesting that NK lysis of T lymphocytes via NKG2D may be one of the mechanisms limiting T-cell responses (Cerboni C. et al, 2007). HIV up-regulates cell-surface expression of NKG2D ligands, including ULBP1, ULBP2, and ULBP3, but not MICA or MICB, in infected cells both in vitro and in vivo. HIV-1-induced up-regulation of NKG2D ligands contributes to HIV-1-induced $CD4^+$ T-lymphocyte depletion. Recently, two groups demonstrated that the HIV-1 Vpr protein activates the DNA damage response, which specifically induces surface expression of ULBP1 and ULBP2 (Richard J. et al, 2010; Ward J. et al, 2009).

7. Decreased Dicer expression elicits up-regulation of MICA and MICB

The DNA damage pathway regulates expression of innate immune system ligands for the NKG2D receptor. Human NKG2D ligands are up-regulated by genotoxic stress and stalled DNA replication. Dicer knockdown elicits DNA damage in human cells. These observations prompted us to test whether NKG2D ligands were up-regulated in Dicer knockdown cells. Quantitative RT-PCR and flow cytometry revealed markedly increased levels of MICA and MICB mRNAs and proteins in Dicer knockdown cells compared with mock-transfected or control siRNA-transfected cells. In contrast, inhibiting the expression of Dicer did not significantly alter the levels of ULBP1, ULBP2, and ULBP3 mRNAs. Up-regulation of MICA and MICB by Dicer knockdown is prevented by pharmacologic or genetic inhibition of DNA damage pathway components, including ATM, ATR, or Chk1. This finding suggests that up-regulation of MICA and MICB is the result of DNA damage response activated by Dicer knockdown. Dicer knockdown cells also exhibited greater sensitivity to lysis by NKL, a cell line derived from an aggressive form of human natural killer cell leukemia. Lysis was partially inhibited by anti-NKG2D antibody, which indicated that up-regulated NKG2D ligands make the cells more susceptible to lysis by NK cells. This result suggests that Dicer-deficient cells may be cleared by NK or other immune cells (Tang KF. et al, 2008b).

Although we have shown that up-regulation of MICA and MICB in Dicer knockdown cells is the result of DNA damage response activation, further studies are necessary to determine whether other mechanisms are also involved in the regulation of MICA and MICB in Dicer knockdown cells. Stern-Ginossar and colleagues reported that one of the human cytomegalovirus encoded miRNAs, hcmv-miR-UL112, specifically down-regulates MICB expression during viral infection, leading to decreased binding of NKG2D and reduced killing by NK cells (Stern-Ginossar N. et al, 2007). The hcmv-miR-UL112 binding site in the MICB 3′-untranslated region is conserved among different MICB alleles and a similar site exists in the MICA 3′-untranslated region, suggesting that these sites are targeted by cellular microRNAs (Stern-Ginossar N. et al, 2007). To test this hypothesis, Stern-Ginossar and colleagues expressed MICB with or without its 3′-UTR in primary human foreskin fibroblast (HFF) cells. MICB expression was much higher when it was expressed without its 3′-UTR. Fusion of the 3′-UTR of MICA to green fluorescent protein (GFP) also inhibited GFP

expression. These results indicated that the 3′-UTRs of MICA and MICB inhibit expression of the corresponding proteins. Knockdown of Drosha, an enzyme essential for miRNA biogenesis (Lee Y. et al, 2003), relieved the inhibitory effects, suggesting that cellular microRNAs do indeed regulate MICA and MICB expression. Further studies demonstrated that miR-20a, miR-93, miR106b, miR-372, miR-373, and miR-520d are involved in the regulation of MICA and MICB expression (Stern-Ginossar N. et al, 2008). Yadav and colleagues reported that miR-520b acted on both the MICA 3′-UTR and the promoter region, causing a decrease in the levels of the MICA transcript and protein. However, an antisense oligonucleotide inhibitor of miR-520b increased the expression of a reporter construct containing the MICA 3′-UTR (Yadav D. et al, 2009). Dicer is the key enzyme involved in miRNA biogenesis, and knockdown of Dicer reduces levels of miRNAs. Therefore, it is conceivable that reduced levels of miRNAs may contribute to the up-regulation of MICA and MICB in Dicer knockdown cells.

Interferon-alpha promotes expression of MICA in tumor cells (Zhang C. et al, 2008). Some siRNAs are found to activate protein kinase R (PKR) and induce global up-regulation of interferon-stimulated genes (Marques JT. & Williams BR., 2005; Sledz CA. et al, 2003). Because dsRNAs are natural substrates of Dicer, knockdown of Dicer may stabilize endogenous dsRNAs. Elevated levels of endogenous dsRNAs may activate the interferon pathway. Therefore, it seems possible that up-regulation of MICA and MICB is the consequence of nonspecific activation of the interferon pathway in Dicer knockdown cells. Our results indicated that the phosphorylation status of PKR and the expression of interferon-stimulated genes are not changed in Dicer knockdown cells compared to control cells (Tang KF. et al, 2008b). However, we cannot exclude the possibility that complete depletion of Dicer may yield levels of endogenous dsRNAs high enough to activate the interferon pathway, and eventually up-regulate the expression of MICA and MICB.

The expression of MICA and MICB is tightly correlated with cell proliferation status. Highly confluent HCT116 cells grown to quiescence contain small amounts of MICA and MICB mRNAs and display low MIC surface protein expression. In rapidly proliferating cells, MICA and MICB mRNAs and surface proteins are strongly induced (Venkataraman GM. et al, 2007). Knockout of Dicer in hepatocytes leads to increased cell proliferation (Sekine S. et al, 2009), and Dicer knockdown lung adenocarcinoma (LKR13) cells grow faster than control cells (Kumar MS. et al, 2007). Therefore, it is possible that up-regulation of MICA and MICB is the consequence of increased cell proliferation induced by down-regulation of Dicer.

Further studies are necessary to elucidate why loss of Dicer leads to up-regulation of MICA and MICB. Some possible mechanisms, summarized in Figure 2, are as follows: (i) decreased Dicer expression elicits DNA damage , which in turn induces up-regulation of MICA and MICB; (ii) loss of Dicer impairs biogenesis of miRNAs, some miRNAs, such as miR-20a, miR-93, miR106b, miR-372, miR-373, miR-520 and miR-520d, can repress the expression of MICA and MICB transcriptionally and posttranscriptionally; (iii) loss of Dicer may result in increased cell proliferation, and increased proliferation induces the transcription of MICA and MICB; and (iv) loss of Dicer stabilizes endogenous dsRNAs, and increased levels of the dsRNAs activate the interferon pathway, which in turn induces the expression of MICA and MICB.

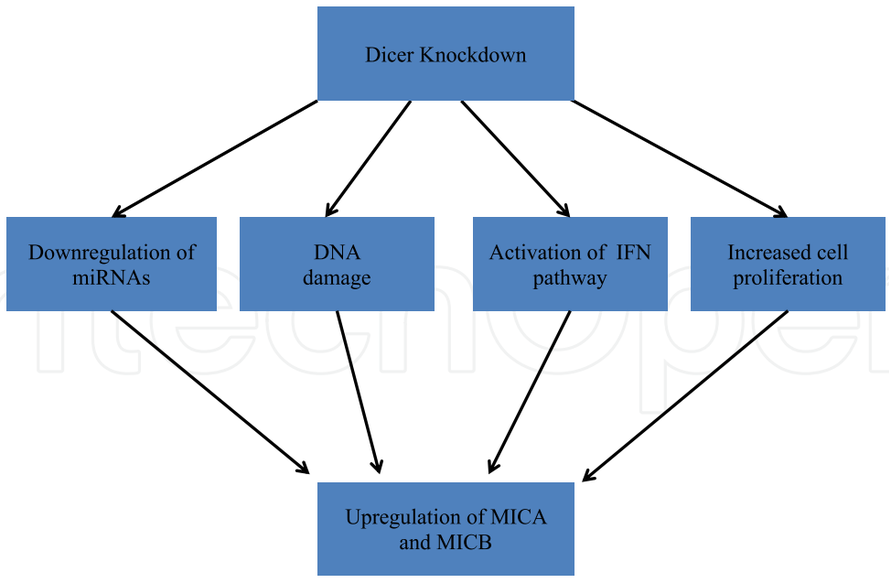


Fig. 2. Molecular mechanisms linking decreased Dicer expression to increased MICA and MICB expression

8. Dicer, DNA damage, and tumorigenesis

Compared with normal tissue, miRNAs are generally down-regulated in tumor tissue (Lu J. et al, 2005). Levels of Dicer mRNA and protein are decreased in 60% of ovarian-cancer specimens. Low Dicer expression is significantly associated with advanced tumor stage and poor prediagnosis (Merritt WM. et al, 2008). We found that compared to the adjacent non-cancerous liver tissues, Dicer mRNA and protein are reduced in hepatocellular carcinoma tissues in 34 of 36 patients (Wu JF. et al, 2011). Signs of a DNA damage response, including histone H2AX and Chk2 phosphorylation, p53 accumulation, focal staining of p53 binding protein 1, are widely found in clinical specimens from different stages of human tumors and precancerous lesions, but not in normal tissues (Bartkova J. et al, 2005, 2006; DiTullio RA Jr. et al, 2002; Gorgoulis VG. et al, 2005). Decreased Dicer expression elicits DNA damage (Mudhasani R. et al, 2008; Peng JC. & Karpen GH., 2009; Tang KF. et al, 2008b). Therefore, the following questions are intriguing: Is there an association between DNA damage and Dicer down-regulation in cancer tissues? If the answer is yes, what is the causal relationship between DNA damage and Dicer down-regulation in the process of carcinogenesis? What is the role of Dicer in carcinogenesis?

Kumar and colleagues found that loss of Dicer promotes tumorigenesis (Kumar MS. et al, 2007). They showed that Dicer knockdown cancer cells had a more pronounced transformed phenotype. In animals, Dicer knockdown cells formed tumors with accelerated growth; the tumors were also more invasive than control tumors. Furthermore, conditional deletion of Dicer enhanced tumor development in a K-Ras–induced mouse model of lung cancer (Kumar MS. et al, 2007). Sekine and colleagues disrupted Dicer in hepatocytes using a conditional knockout mouse model and found that Dicer elimination induces hepatocyte proliferation and overwhelming apoptosis. Unexpectedly, they found that two-thirds of the mutant mice spontaneously developed hepatocellular carcinomas (HCCs) at 1 year of age. The fact that the majority of Dicer deficient hepatocytes undergo apoptosis and that only a

minor subset of Dicer-deficient hepatocytes gives rise to HCCs suggests the requirement of a "second hit" that promotes hepatocarcinogenesis in Dicer-deficient hepatocytes (Sekine S. et al, 2009). Based on these observations, I propose a simple model to explain how Dicer knockout leads to hepatocarinogenesis (Figure 3). Dicer depletion induces DNA damage via the mechanisms described in Figure 1, and DNA damage response leads to cell apoptosis or senescence. DNA damage may also result in DNA mutation such that cells containing oncogenic mutations may escape from apoptosis and senescence, eventually forming cancer.

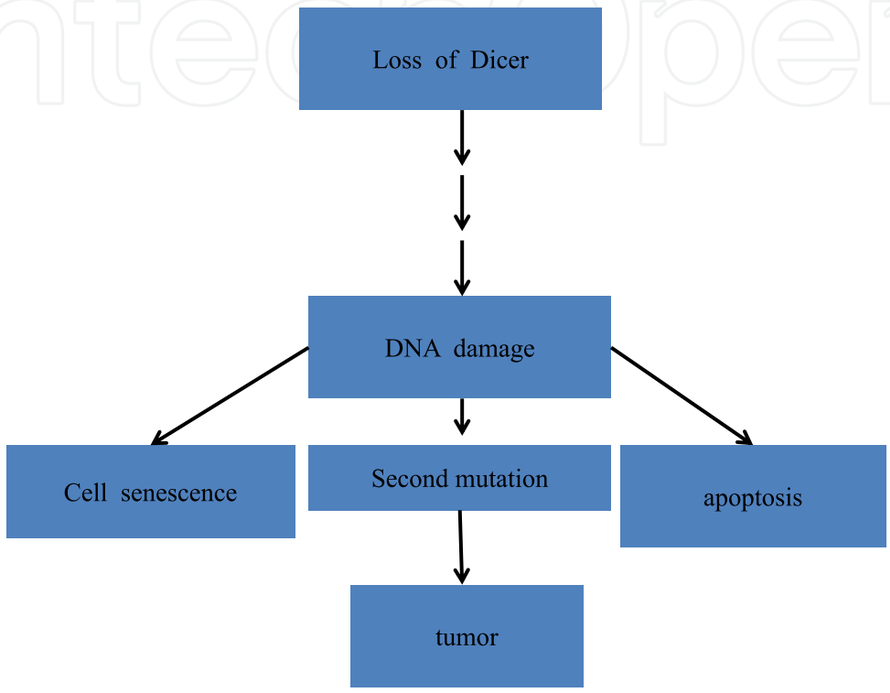


Fig. 3. Molecular mechanisms of Dicer knockout-induced tumorigenesis

Oncogene activation leads to augmented numbers of active DNA replicons and to alterations in DNA replication fork progression. These alterations activate DNA damage response, and eventually cell senescence or apoptosis. Genetic analyses indicate that early in tumorigenesis (before genomic instability and malignant conversion), human cells activate an ATR/ATM-regulated DNA damage response network that delays or prevents cancer. Mutations compromising this DNA damage response network might allow cell proliferation, survival, increased genomic instability and tumor progression (Bartkova J. et al, 2005, 2006; Di Micco R. et al, 2006).

Comparison of the mechanisms of oncogene-induced carcinogenesis (Figure 4) and Dicer depletion induced carcinogenesis suggests that Dicer is a tumor suppressor gene. However, Kumar and colleagues demonstrated that Dicer functions as a haploinsufficient tumor suppressor gene (Kumar MS. et al, 2009). Deletion of a single copy of Dicer in tumors from Dicerfl/+ animals reduced survival compared with controls. Moreover, tumors from Dicerfl/fl animals always maintained one functional Dicer allele; forced deletion of Dicer inhibited tumorigenesis. Analysis of human cancer genome copy number data reveals frequent deletion of Dicer. However, the gene has not been reported to undergo homozygous deletion (Kumar MS. et al, 2009).

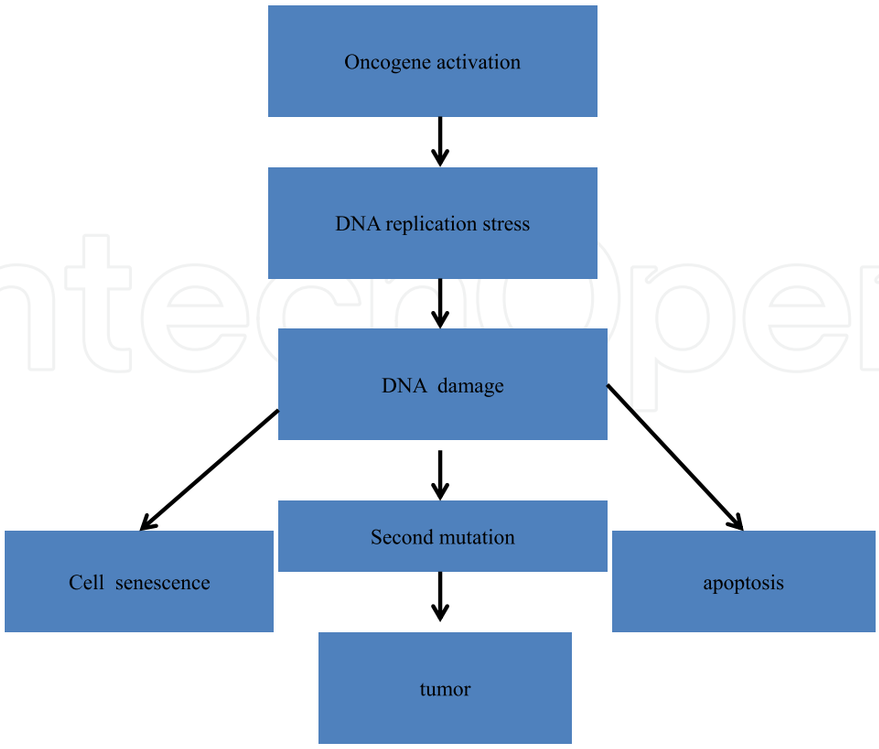


Fig. 4. Molecular mechanisms of oncogene-induced tumorigenesis

9. MIC molecules, DNA damage and tumorigenesis

Although evolved in parallel with the human MHC class I genes, MIC molecules (MICA and MICB) are quite different from MHC class I molecules. The characteristics of MIC molecules include the lack of association with beta-2-microglobulin, stable expression without conventional class I peptide ligands, and the absence of a CD8 binding site. The MIC genes are highly polymorphic. Around 60 alleles of MICA and 25 alleles of MICB have so far been identified (Bahram S. et al, 1994; Eagle RA. & Trowsdale J., 2007;). T cells with variable region V-delta-1 gamma/delta T-cell receptors are distributed throughout the human intestinal epithelium and may function as sentinels that respond to self-antigens. MIC molecules are expressed on the surface of the intestinal epithelium cells, and are recognized by intestinal epithelial T cells expressing diverse V-delta-1 gamma/delta TCRs. These data suggest that MIC molecules may regulate the protective responses by the V-delta-1 gamma/delta T cells in the epithelium of the intestinal tract (Groh V. et al, 1998). Cytomegalovirus (CMV) infection induces MIC expression and a concurrent down-regulation of MHC class I molecules on fibroblasts and endothelial cells (Groh V. et al, 2001). Functional analysis of T-cell cytotoxicity against CMV-infected fibroblasts showed that early after infection when MIC expression was low, antibodies to MHC class I, but not to MIC or NKG2D, could block T cell-mediated cytolysis (Groh V. et al, 2001). As MIC expression increased, antibody masking of MIC or NKG2D reduced target-cell lysis; anti-MHC class I antibodies further reduced cytolysis. This study suggests that MIC molecules are involved in the immune clearance of virus-infected cells (Groh V. et al, 2001). MICA binds NKG2D on gamma/delta T cells, $CD8^+$ alpha/beta T

cells, and natural killer cells. Engagement of NKG2D activates cytolytic responses of gamma/delta T cells and NK cells against transfectants and epithelial tumor cells expressing MICA (Bauer S. et al, 1999). These results indicate that MICA and MICB play important roles in anti-viral and anti-tumor immune response.

DNA damage response is activated in clinical specimens from different stages of human tumors and precancerous lesions, but not in normal tissues (Bartkova J. et al, 2005, 2006; DiTullio RA Jr. et al, 2002; Gorgoulis VG. et al, 2005). Activation of the DNA damage response results in cell cycle arrest, senescence, and apoptosis. It was proposed that tumor progression requires the appearance of mutations that misregulate the DNA damage response pathway, such as p53 mutations, which allay the cell cycle block and allow tumor outgrowth (Gasser S. & Raulet DH., 2006; Halazonetis TD., 2004). DNA damage induces up-regulation of NKG2D ligands (including MICA and MICB). Some components of the DNA damage checkpoints, including ATM and ATR (two proteins involved in DNA damage detection), and Chk1 (a protein that transduces the DNA damage signal to effector proteins), are essential for the up-regulation of NKG2D ligands (Gasser S. et al, 2005; Tang KF. et al, 2008b). p53 is one of the effector proteins of the DNA damage checkpoints, but is not required for up-regulation of NKG2D ligands, as indicated by DNA damage-induced expression of the ligands in p53-deficient cell lines (Gasser S. et al, 2005). The fact that other components of the DNA damage response, such as ATR and Chk1, are rarely mutated in tumors might explain why NKG2D ligands are frequently up-regulated in cancer cells (Gasser S. & Raulet DH., 2006; Halazonetis TD., 2004). These findings suggest a possible role of the immune system, via the DNA damage response and NKG2D, in the elimination of precancerous cells and cancer cells.

In addition to promoting anti-tumor immune response, MICA and MICB can also suppress tumor immune surveillance. MICA associates with endoplasmic reticulum protein-5 (ERP5) on the surface of tumor cells, and the association is required for MICA shedding. Detailed analysis indicated that ERP5 and membrane-anchored MICA form transitory, mixed disulfide complexes, from which soluble MICA is released after proteolytic cleavage near the cell membrane. The secreted form of MIC molecules may bind to NKG2D receptor and inhibit the killing activity of effector cells (Kaiser BK. et al, 2007). NKG2D binding of MIC can induce endocytosis and degradation of NKG2D. In cancer patients, NKG2D expression was markedly reduced in both $CD8^+$ tumor-infiltrating T cells and in peripheral blood T cells, and the reduction of NKG2D expression is associated with increased level of circulating tumor-derived soluble MICA. Down-regulation of NKG2D severely impairs the function of tumor antigen-specific effector T cells (Groh V. et al, 2002). MICA can also mediate strong suppressive effects on T cell proliferation. Responsiveness to MICA-mediated suppression involves a receptor other than NKG2D. This finding might explain the observation that strong in vivo NKG2D ligand expression, such as in tumor cells, sometimes fails to support effective immune responses (Kriegeskorte AK. et al, 2005).

10. Conclusion

Dicer is misregulated in tumor tissues, and decreased Dicer expression induces the expression of MICA and MICB. MICA and MICB play important roles in anti-tumor immune response, and are frequently up-regulated in epithelial tumors of diverse tissue

origins. These observations suggest that the intracellular immune system and the innate immune system have a good synergistic or additive effect in tumor immune surveillance. In addition, decreased Dicer expression elicits DNA damage, which in turn induces cell apoptosis and senescence. However, disruption of Dicer in hepatocytes promotes hepatocarcinogenesis. Therefore, the role and mechanism of Dicer in tumorigenesis need further investigation.

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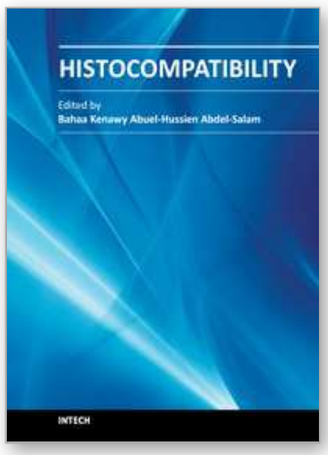
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