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EXTRA VIEW

New roles for Dicer in the nucleolus and its relevance to cancer

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ABSTRACT

The nucleolus is a distinct compartment of the nucleus responsible for ribosome biogenesis. Misregulation of nucleolar functions and of the cellular translation machinery has been associated with disease, in particular with many types of cancer. Indeed, many tumor suppressors (p53, Rb, PTEN, PICT1, BRCA1) and proto-oncogenes (MYC, NPM) play a direct role in the nucleolus, and interact with the RNA polymerase I transcription machinery and the nucleolar stress response. We have identified Dicer and the RNA interference pathway as having an essential role in the nucleolus of quiescent *Schizosaccharomyces pombe* cells, distinct from pericentromeric silencing, by controlling RNA polymerase I release. We propose that this novel function is evolutionarily conserved and may contribute to the tumorigenic pre-disposition of DICER1 mutations in mammals.

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The nucleolus specializes in ribosomal transcription and assembly

The nucleolus is the nuclear compartment in which RNA (rRNA) is transcribed, processed, and assembled into ribosomal subunits during interphase, that are then exported to form mature ribosomes. The nucleolus is formed by the process of ribosome biogenesis[1] and organizes into 3 main zones: the fibrillar(s) center(s) (FC), the dense fibrillar component (DFC), and the granular component (GC). DNA (rDNA) is present within the FC, at the periphery of which pre-rRNA is actively transcribed and elongates into the DFC. RNA processing occurs co-transcriptionally and rRNA assembles with ribosomal proteins, to form immature ribosomes in the GC[2,3] (Fig. 1). A specific RNA polymerase, RNA polymerase I, specializes in transcription of the DNA (rDNA) locus. The resulting 48S pre-rRNA is processed by a series of cleavages to obtain the 18S, 5.8S and 28S mature rRNAs, while RNA polymerase III transcribes the fourth rRNA species, 5S rRNA, outside the nucleolus, where it is then imported along with small nucleolar RNAs (snoRNAs) important for rRNA processing. The major transcriptional burden of a growing cell lies in ribosome biosynthesis—rRNAs can represent 80% of cellular RNAs—and is heavily correlated with rates of protein synthesis, highlighting its central importance in cellular metabolism. Understandably, nucleolar transcription is tightly regulated according to the phase of the cell cycle, nutritional availability, environment, and growth status of the cell.[4] Conversely, multiple ribosomal quality control mechanisms provide feedback for cell cycle progression.[5]

The rDNA promoter

The initiation of rDNA transcription requires several basal transcription factors in addition to the multi-subunit RNA polymerase I complex. Active rDNA promoters are organized in a configuration free of nucleosomes,[3] bound by dimers of UBF (Upstream Binding Factor), a multi-functional HMGB-box protein which activates transcription[6] and forms a structure termed the 'enhancosome'.[7] Furthermore, UBF spreads across the rDNA locus and contributes to its structural organization.[8,9]

The core rDNA promoter is bound by 2 basal transcription initiation factors, TIF-IA/RRN3 and TIF-IB/SL1, which are necessary for the formation of the RNA polymerase I pre-initiation complex (PIC). The TIF-IB/SL1 complex comprises the TATA-binding protein (TBP) in a specific complex with TAF proteins (TBP-associated factors: TAF1A, TAF1B, TAF1C, TAF1D),[10] which confers promoter specificity. TIF-IA/RRN3 recruits initiation-competent RNA polymerase I complexes to the rDNA promoter, and interacts directly with TAF1B and TAF1C in the SL1 complex.[11] Binding of SL1 to the rDNA promoter further stabilizes UBF.[12] Budding yeast and fission yeast form a functionally equivalent TBP-TAF complex (RRN6, RRN7, RRN11),[13] while the upstream element (UCE) of the rDNA promoter is bound by an additional complex, the Upstream Activating Factor (UAF).[14] The promoter and the terminator regions of rDNA are brought in close contact via binding of TTF-I, which participates in RNA polymerase I transcription termination and re-initiation.[15,16]

Regulatory mechanisms of ribosomal transcription

RNA polymerase I transcription is tightly regulated to couple the translational capability of the cell to its requirements according to its growth status. The size and organization of the nucleolus is particularly dependent on the phase of the cell cycle, as well as environmental conditions.[3,17] Regulation of

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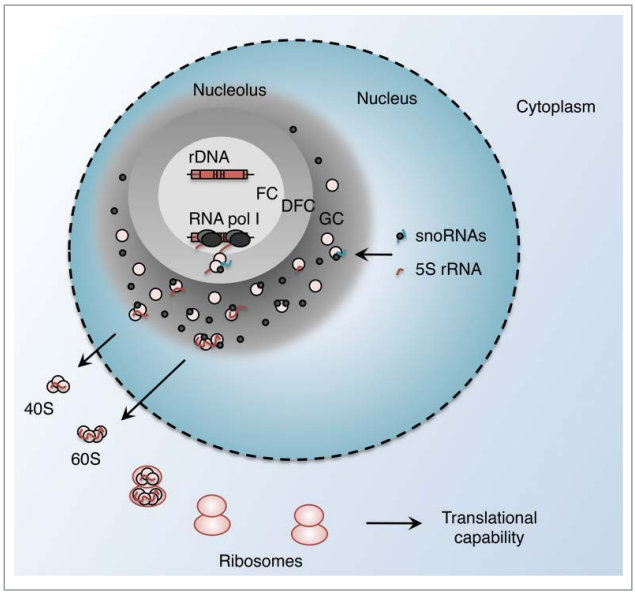

Figure 1. Overview of nucleolar structure and function. RNA polymerase I transcribes the rDNA repeats at the interface between the fibrillar center (FC) and the dense fibrillar component (DFC). rRNA molecules and ribosomal proteins associate in complexes in the granular component (GC), and are exported outside of the nucleolus as immature ribosomal particles, which are then assembled into ribosomes.

RNA polymerase I transcription occurs at several key-points, in particular at the level of the formation of the pre-initiation complex, and it has been proposed that the rate-limiting step of RNA polymerase I transcription is promoter clearance subsequent to PIC formation,[18] although other studies also pointed to transcription elongation, depending on growth conditions.[19]

The phosphorylation status of TIF-IA/RRN3 is regulated by nutrient availability through the TOR signaling pathway,[20,21] mitogen-activated kinase (MAPK) cascades,[22] and RNA polymerase I activity is modulated by several key signaling pathways such as PI3K,[23] AKT,[24] GSK3β,[25] the RAS-family protein RasL11a.[26] The inputs of these different signaling pathways converge to fine-tune RNA polymerase I transcription, integrating growth factors, nutrient availability and energetic capability.[27]

Another layer of regulation lies within the repetitive structure of the rDNA. The rDNA repeats form at least 3 fractions differing in their transcriptional status: active rDNA repeats undergoing RNA polymerase I transcription, silent rDNA repeats packed into heterochromatin, and poised/inactive rDNA repeats that, while not actively being transcribed, do not present heterochromatic marks and may constitute a readily-available 'buffer' of repeats.[28,29] UBF is an important player in determining the active/inactive rDNA repeat ratio.[30]

Two key phases of the cell cycle when RNA polymerase I activity needs to be regulated are mitosis and quiescence. During mitosis, RNA polymerase I transcription is halted until G1 via phosphorylation of UBF and the TAF1C subunit of SL1.[31] Cells alternate between phases of quiescence and division, for example, to maintain stem cell populations in mammals,[32] or to survive conditions of nutritional scarcity in microbial eukaryotes.[33] In non-dividing quiescent cells that retain metabolic and transcriptional activity,[32,34] RNA polymerase I remains essential for maintaining basal levels of rRNAs to ensure translation of transcripts necessary for quiescence maintenance, but is strongly downregulated. Quiescent fibroblasts down-regulate transcripts of genes involved in ribosomal biogenesis.[35] This regulation is conserved in eukaryotes; for example, in the fission yeast *Schizosaccharomyces pombe*, a model organism for the cell cycle and cellular quiescence,[33] rDNA occupancy of RNA polymerase I is greatly decreased in quiescent cells,[36] and conversely, rDNA transcription and ribosomal proteins are upregulated upon re-entry into the cell cycle.[37]

Misregulation of the nucleolus is central to cancer

Misregulation of ribosome biosynthesis, the central function of the nucleolus, is a recurrent feature in cancer, as well as in a distinct set of rare genetic diseases known as ribosomopathies.[38] Early on, an enlarged nucleolus has been recognized as a hallmark of cancer cells/cellular transformation,[39] and higher numbers of silver-stained nucleolar organizer regions (NORs) correlate with cell proliferation rate and tumor prognosis.[40] This correlation can be interpreted as a cause or as a consequence of the increased translational burden of cancer cells due to their uncontrolled proliferation. On the one hand, the inability to exit the cell cycle would leave the cell in a constant state of growth and division, requiring heavy transcription and translation and therefore large amounts of ribosomal synthesis. On the other hand, the existence of a nucleolar feedback on the cell cycle[4] indicates that uncontrolled rDNA transcription and misregulation of RNA polymerase I activity could by itself be a major factor promoting cellular proliferation by providing the first step to unwarranted G0-G1 transition, a hallmark of cancer.[41] Accordingly, recent evidence now clearly recognizes nucleolar misregulation as an important contributor to cancer and many key proto-oncogenes and tumor suppressors appear to play a direct role in the nucleolus and in RNA polymerase I transcription.[17,42-46]

Proto-oncogenes and tumor suppressors linked to nucleolar function

The proto-oncogene c-Myc is a major activator of RNA pol I transcription, is expressed in proliferating cells at a level correlating with rRNA[47,48] and almost absent from quiescent cells.[48] c-Myc binds directly to rDNA at the promoter region and at the transcription initiation region, as well as near a transcription termination site, and physically associates with the TBP-containing SL1 complex.[48] Modulating c-Myc levels directly affects levels of SL1 and UBF binding at the rDNA.[48] Another MYC family transcription factor frequently mutated in small cell lung cancer, L-Myc, also promotes pre-rRNA synthesis.[49] The nucleolar function of MYC is evolutionarily conserved as its Drosophila ortholog dMyc also plays an essential role controlling rRNA synthesis during development.[50] In addition to this direct role at the rDNA, MYC binds and up-regulates ribosome biogenesis genes[51] and activates RNA polymerase III transcription of tRNAs and 5S rRNA genes.[52,53] MYC therefore appears to be a key growth regulator that directly affects transcription by all RNA polymerases to modulate the translational capacity of the cell.

Nucleophosmin, a nucleolar proto-oncogene found mutated in several cancer types,[54] affects the nucleolar function of MYC. In particular, c-Myc transformation is enhanced by expression of nucleophosmin,[55] and nucleophosmin is essential for c-Myc nucleolar localization and rDNA transcription.[56] An important partner of nucleophosmin is ARF/p14, a major tumor suppressor, which has recently been found to have a nucleolar function in addition to cell cycle inhibition via the MDM2-p53 pathway. ARF binds to the rDNA promoter,[57] binds UBF in a p53-independent manner,[58] and directly affects nucleolar chromatin organization by masking the nucleolar localization sequence of TTF-I.[59] The other major tumor suppressors Rb, and the Rb-like protein p130, in addition to their role in G1/S cell cycle progression inhibition via sequestering E2F factors, also directly repress RNA polymerase I transcription by binding and inactivating UBF.[60-62]

The major tumor suppressor p53 also plays an important role coordinating ribosome biogenesis and the cell cycle/proliferation via signaling nucleolar stress. Signals such as oncogenic activation and DNA damage trigger nucleolar stress, and nucleolar disruption is a key event for p53 activation.[63] Nucleolar stress triggers the nucleoplasmic export of the ribosomal proteins RPL5 and RPL11, which bind MDM2 and block MDM2-mediated p53 degradation, resulting in p53 activation, cell cycle arrest and apoptosis.[64] p53 is then recruited to the FCs of the nucleolus,[65] where it represses RNA polymerase I by directly binding to TBP and TAF-IC in the SL1 complex, disrupting its interaction with UBF.[66,67] p53 furthermore directly represses c-Myc expression,[68] along with RPL5/RPL11.[69] PICT1, a nucleolar protein with mutations found in cancer, is a key DNA damage sensor at the rDNA that signals nucleolar stress through the RPL5/11-MDM2-p53 pathway[70] and inhibits RNA polymerase I transcription.[71]

Other examples include PTEN, a tumor suppressor that inhibits cellular proliferation both by inhibiting the AKT/PI3K pathway and by affecting the rDNA occupancy of the SL1 complex, thereby repressing RNA polymerase I transcription,[72] in association with GSK3β.[25] It has also been reported that a PTEN isoform, PTENβ, physically associates with nucleolin and the 2 core subunits shared by RNA polymerase I and RNA polymerase III, AC40^{POLR1C} and AC19^{POLR1D} to repress ribosomal transcription.[73] BRCA1, a key tumor suppressor, interacts directly at the rDNA repeats with UBF, the SL1 complex and RNA polymerase I, and the interaction is decreased in response to DNA damage.[74] CTCF, a key insulator and multi-functional tumor suppressor involved in chromatin organization,[75] also binds unmethylated DNA upstream of the rDNA promoter and interacts with UBF as well as RNA polymerase I,[76] and CTCF expression correlates with pre-rRNA levels.[77] In Drosophila, CTCF knock-down results in defects of rDNA silencing and nucleolar fragmentation.[78] Overall, it appears that many proto-oncogenes and tumor suppressors have a nucleolar function and that generally, oncogenic proteins increase RNA polymerase I transcription, while tumor suppressors repress it.

Targeting RNA polymerase I is anti-tumorigenic

As might be expected, RNA polymerase I transcription has emerged as a key target in cancer therapy.[79] For example, the RNA polymerase I inhibitors CX-5461 and CX-3543 (quarfloxin) have undergone early clinical trials after indications of anti-tumor activity.[80,81] Both drugs bind and stabilize G-quadruplexes at the rDNA, which in addition to inhibiting RNA polymerase I initiation, results in the displacement of nucleolin to the nucleoplasm, where it binds to a G-quadruplex structure in the MYC promoter leading to repression of its expression.[82,83] CX-5461 targets MYC in myeloma in a p53-independent manner,[84] and L-Myc with strong tumor inhibition in a mouse model of small cell lung cancer.[85] The G-quadruplex stabilization activity of CX-5461 and CX-3543 also leads to selective lethality in BRCA-deficient tumors, including tumors resistant to PARP inhibitors.[86] Several other small molecules, BMH-9, -21, -22 and -23, which were originally identified in a screen for activators of the p53 pathway and found to do so in a DNA damage-independent manner,[87] were subsequently found to inhibit RNA polymerase I via degradation of its main catalytic subunit RPA1, conferring them potent antitumoral activity across several cancer cell types.[88,89]

A better understanding of nucleolar pathways in cancer will improve our understanding of cross-reactions in combinatorial treatments, and devise efficient and synergistic drug combinations; for example, mTOR inhibitors also inhibit the p53-dependent nucleolar stress pathway, an effect that may not be beneficial,[90] while combining RNA polymerase I inhibition with drugs targeting MYC signaling[91] or ATM/ATR signaling[92] has yielded promising results.

RNA interference: A new player in nucleolar function?

We have recently discovered that Dicer plays a novel essential function specifically in quiescent cells by targeting RNA polymerase I.[36] The fission yeast *Schizosaccharomyces pombe* is an excellent model organism for quiescence,[33] and mutants in RNA interference (RNAi) such as Dicer (*dcr1*Δ), Argonaute (*ago1*Δ) and RNA-dependent RNA polymerase (*rdp1*Δ) lose viability specifically in G0. Intriguingly, this novel function of RNAi is largely independent of heterochromatin formation at pericentromeric repeats.[93] We found that in quiescence, Dicer mutants are defective in RNA polymerase I release, resulting in the accumulation of stalled RNA pol I over the rDNA repeats, DNA damage (visualized using γH2AX, which is bound by Crb2^{53BP1}), and extensive silencing of the rDNA repeats by the H3K9 methylation machinery.[36] This defect has striking parallels in cycling cells, where Dicer mutants fail to release RNA polymerase II from pericentromeres, highly expressed genes and rDNA, also resulting in DNA damage.[94,95] This parallel is further strengthened by the observation that mutants in corresponding subunits of RNA polymerase I (A12) and RNA polymerase II (Rpb9+TFIIS) suppress specifically Dicer's G0 and cycling cell silencing defects, respectively,[36,96] prompting us to propose that the RNA interference machinery is tightly associated with, and regulates, the transcription machinery of all RNA polymerases.

Is this novel function of Dicer evolutionarily conserved? The association of RNA polymerase I transcription with cancer, and evidence that DICER1 is a tumor suppressor, suggest further investigation of this possibility. Importantly this function might be independent of Dicer's role in the biosynthesis of

microRNA (miRNA), which are absent from *S. pombe* and most fungi. In accordance with this hypothesis, Dicer in mammalian cells promotes stem cell quiescence[32] and can be found in the nucleolus binding to both active and silent rDNA repeats.[97] Similarly, human AGO2 binds to numerous rRNA sites and binding is DICER-dependent.[98] While AGO2 knockdown does not impact rRNA processing,[98] Dicer and Drosha mutants accumulate 5.8S rRNA precursors, and Dicer but not Drosha mutants have a drastic effect on nucleolar morphology.[99] Dicer also interacts with SIRT7,[100] a sirtuin that associates with RNA polymerase I and UBF in mammals.[101] In Drosophila, RNA interference is necessary for nucleolar organization,[102] and in the model plant *Arabidopsis thaliana*, a specific set of RNA interference proteins comprising RDR2, DCL3, AGO4, DRD1 and the specialized RNA polymerase IV co-localize to nucleolar Cajal bodies.[103,104] In *Candida albicans*, Dicer is necessary for 3′ETS cleavage of pre-rRNA,[105] a function borne by the related RNase III enzyme Rnt1 in yeast.[106] These observations strongly suggest that a nucleolar function of RNA interference—in particular of Dicer—is conserved in eukaryotic evolution.

Dicer is a tumor suppressor

There is now a well-described association between human DICER1 (14q32.13) mutations and cancer risk.[107] Germline mutations in DICER1 (summarized in Fig. 2)[108-117] result in a predisposition to develop a wide variety of otherwise rare cancers—the "DICER1 syndrome"—such as pleuropulmonary blastoma (PPB),[118] cystic nephroma (CF),[116,119] uterine cervix rhabdomyosarcoma,[120] ovarian Sertoli-Leydig cell tumors (SL),[109] thyroid cancer,[121] multinodular goiter,[108,122] pineoblastoma,[123] ocular medulloepithelioma,[110,124] and Wilms tumors (nephroblastoma).[120,125] In many cases of PPB and SL, there is a frequent co-occurrence of 2 mutations;[126] affected patients most frequently inherit a null allele (frameshift or stop truncation) in the germline and subsequently acquire a mutation on the second allele at hotspot residues in catalytic and metal-binding residues of the RNAse IIIb domain (Fig. 2).[115,127-129] In a survey of 350 confirmed PPB cases, 66% patients carried a germline DICER1 mutation.[130] Mutations in DICER1 are frequently associated with biallelic loss of TP53 in PPB[131] as well as in Wilms tumors,[132] suggesting that Dicer loss may trigger p53 activation resulting in increased selective pressure to mutate p53 in the tumorigenic tissue. In accordance with this, in mouse fibroblasts, Dicer deletion results in p53 activation and induction of senescence,[133] and co-ablation of Dicer and p53 results in multiple skin carcinomas with increased DNA damage.[134] Furthermore, Dicer has been described as a key target of the tumor suppressor p63; p63-null mice develop metastatic tumors with low Dicer and miR-130b expression, and re-expression of Dicer suppresses this phenotype.[135]

Dicer mutants are affected in development

The frequent heterozygous profile of DICER1 mutations suggests that this gene is a haploinsufficient tumor suppressor. Dicer is essential in mammals: Dicer-null mice die before gastrulation.[136] In a mouse model of PPB, loss of DICER1 is sufficient for tumor development,[137] and deletion of DICER1 in the female reproductive tract not only impaired its development, but also causes cystic nephromas.[136] In a mouse retinoblastoma-sensitized model, monoallelic, but not biallelic, loss of Dicer increases tumorigenesis,[138] and complete Dicer deletion is selected against during tumorigenesis,[139-141] suggesting that low levels of Dicer protein are able to support most of its functions. In accordance with this, Dicer hypomorphic mice (10–30% expression level depending on tissue) have been reported to show few developmental defects, which were mostly limited to pancreatic morphological abnormalities.[142]

Conditional Dicer knockout is lethal during the development of many tissues, such as lung epithelia,[143] Sertoli cells,[144] male germ cells,[145] haematopoietic stem cells and in erythroid lineage development,[146] neuronal development,[147] cerebellar development,[148] and B-cell development.[149] Knockdown of Dicer results in defects in oocyte maturation.[150]

Which molecular function underlies Dicer's tumor suppressor role?

One model to explain the tumorigeneticity of DICER1 hotspot mutations is that mutations are hypomorphic and the resulting enzyme is still able to generate miRNAs, though with a cleavage bias for one strand of the pre-miRNA. The RNase IIIa and RNase IIIb domains respectively cleave the 3′ (3p) and the 5′ (5p) end of the double-stranded RNA in the miRNA hairpin precursor, and the Dicer RNase IIIb mutants result in a strong loss of 5p miRNAs.[127,151,152] Conversely, Dicer RNase IIIa mutants result in a strong loss of 3p miRNAs.[151,153] Among 5p miRNAs, the let-7 family plays a tumor suppressor role by

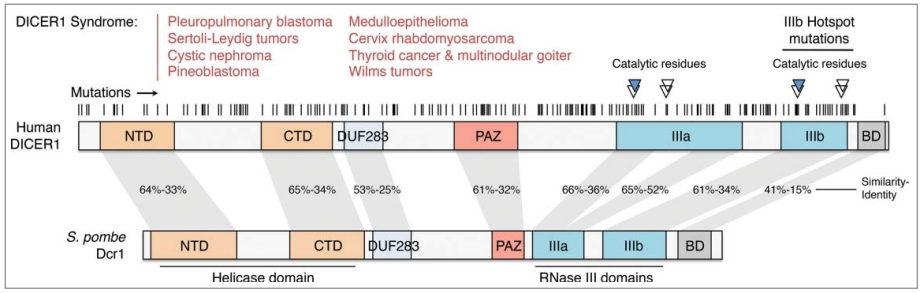

Figure 2. DICER1 is frequently mutated in cancer. Overview of DICER1 mutations found in several cancer types, as described in[108-130] and in NCBI ClinVar. The majority of mutations are predicted to be heterozygous germline loss-of-function alleles, while the hotspot for somatic mutations is located at the RNase IIIb domain catalytic residues.

repressing several targets including MYC (reviewed in[154]), leading to propose that let-7 dysregulation in DICER1 mutants is at the core of its promoting cancer stem cell stemness.[155] In *C. elegans*, let-7 regulates nucleolar size by affecting mRNA levels of ncl^{-}1, a translational inhibitor of fibrillarin and thereby of rRNA transcription and processing.[156]

While the RNase IIIb domain is a clear hotspot for second-hit mutations in DICER1 tumors, screening of somatic mutations in DICER1 syndromes should not be limited to sequencing this domain as particularly interesting mutations over the rest of the gene have been detected. For example, a RNase IIIa mutation was found in one Wilms tumor,[125] a homozygous G803R mutation (between the DUF283 and PAZ domains) in another Wilms tumor,[117] and a compound mutation with both alleles truncating the protein before the RNase IIIa domain in pineoblastoma.[123] These mutations suggest that the oncogenicity of DICER1 hypomorphic mutants may be more complex than reduction of 5p miRNAs.

DICER1 is able to cleave a variety of double-stranded RNA (dsRNA) substrates including endogenous siRNAs,[157] as well as secondary structure-forming RNAs such as RNAs containing triplet-repeats,[158] tRNAs,[159] snoRNAs,[160,161] the 7SL RNA component of the signal recognition particle (SRP) complex,[162,163] and was shown recently to also play a role in DNA repair via DNA damage-induced small RNAs (ddRNAs).[164,165] Importantly, the biologic function of many of these substrates is not well understood. Phenotypically, that DICER1 can have miRNA-independent roles is also shown by its requirement for murine oocyte development, while DROSHA is not required.[166] Canonical miRNA production is abolished in DROSHA mutant cells, while in the absence of Dicer many miRNAs are still produced by loading pre-miRNAs directly into Argonaute, where they are trimmed.[167]

Dicer in the nucleolus: A potential link underlying its tumor suppressor role

Is there a link between the conserved role of Dicer in the nucleolus and the pro-tumorigenic consequences of nucleolar misregulation? The selection for hypomorphic RNase IIIb mutants in DICER1 cancers is presumably explained by the fact that Dicer is essential for cell survival, precluding biallelic loss-of-function i.e. it acts as a haploinsufficient tumor suppressor.[139] But in the presence of reduced Dicer function in polymerase release, RNA polymerase I may undergo stalling and DNA damage at the rDNA, triggering activation of the nucleolar stress pathway and p53. Selective pressure to inactivate p53 could result in the frequent appearance of p53 null-mutants in Dicer hypomorphs, as has been observed.[131,132] Similarly, several ribosomopathies display both sustained activation of p53 and cancer predisposition.[4]

To assess this possibility, a particularly interesting line of study would be to assay the phenotypic consequences of conserved RNase IIIa and RNase IIIb mutations found in cancer on nucleolar functions. In particular, as fission yeast has no miRNA, mutants could be assayed in fission yeast for RNA polymerase I stalling and formation of DNA damage at the rDNA. In that regard, while the dual catalytic-mutant (IIIa + IIIb, *dcr1–5* allele in *S. pombe*) has an identical phenotype to the full deletion *dcr1*Δ,[36] the contribution of each RNase III domain independently has not yet been assayed. However, it is also possible that specific miRNAs underlie the nucleolar function of Dicer, especially given that miRNA analogs are predicted along the primary rRNA transcript.[168] A set of miRNAs is found within the nucleolus, although they appear to be Dicer- and RNA polymerase I-independent.[169] Besides, many miRNA precursors form a structure similar to the C/D box of snoRNAs, and are able to bind fibrillarin, including let-7 g.[170]

Targeting Dicer's nucleolar function in cancer

One novel strategy for specific targeting of cancer cells is by taking advantage of negative epistatic interactions (synthetic lethals).[171] In other words, a pathway that is not essential in wild-type can become essential in a cancerous cell; targeting this pathway would specifically kill the cancer cell (negative epistasis is often referred to as "oncogene addiction"). This strategy has been successful in the identification of PARP inhibitors for targeting tumors with BRCA1/2 mutations, leading to FDA approval of the drug Olaparib for ovarian cancer.[172] Several new negative epistasis candidates have been proposed, through large screens using yeast and mammalian cells in a combinatorial approach.[171]

Identifying genes that are negatively epistatic with DICER1 mutations would be an interesting approach toward therapeutic prevention of DICER1 syndrome. Examples from fission yeast suggest that DNA repair, particularly homologous recombination repair, represents a significant negative epistatic target in Dicer mutant cycling cells.[94,173] A similar approach could be taken during cellular quiescence, which could underlie Dicer's tumor suppressor function in regulation of RNA polymerase I. Candidates could then be tested in mammalian cancer models.[171] For example, we have found that the G_0 defects of Dicer mutants can be rescued by alleviating RNA polymerase I stalling. One way to do so is via lowering RNA pol I recruitment to the rDNA, for example in the TBP mutant *tbp1*-D156Y.[36] *dcr1*Δ*tbp1*-D156Y double-mutants show a strong reduction in DNA damage at rDNA repeats and suppress the synthetic sickness/lethality between *dcr1*Δ and *rad51*Δ in both dividing and non-dividing cells.[36,94] Suppression was also conferred by deleting the non-essential subunit Spp27 of the rDNA UAF complex (Upstream Activation Factor), a SWI/SNF domain-containing protein that is involved in RNA polymerase I transcription initiation (unpublished observations). Another way to alleviate stalling is to destabilize RNA polymerase I itself, using a deletion mutant of its non-essential subunit A12, which suppresses *dcr1*Δ G_0 defects.[36] Stalling of RNA polymerase I results in the unchecked silencing of rDNA repeats, resulting in accumulation of H3K9 methylation. Targeting this latter step using mutants in the H3K9 methylation pathway, H3K9R histone substitution mutants, or HP1 mutants also suppresses G_0 lethality, although it occurs downstream and cells therefore still undergo RNA polymerase I stalling and DNA damage. Conversely, overexpression of the H3K9 methyltransferase Clr4 (ortholog of SUV39H1) enhances the phenotype, and is lethal in quiescent cells.[36]

Interestingly, no epistasis was observed between *dcr1*Δ and the deletion mutant of the yeast ortholog of UBF, *hmo1*Δ (unpublished observations), suggesting suppression might be limited to the TBP and UAF complexes. In an adenocarcinomal cell

line, knock-down of Dicer results in loss of cisplatin resistance,[174] potentially indicating that Dicer mutants may act independently of UBF for RNA polymerase I transcription regulation. If this hypothesis is true, then Dicer mutant cells may be more sensitive to targeting the SL1 complex, or RNA polymerase I itself. Reducing the accumulation of stalled polymerases may alleviate the tumorigenicity of Dicer-mutated cancer cells. Therefore, drugs that inhibit RNA polymerase I transcription by targeting the SL1 complex, such as 9-hydroxyellipticin,[175] or by triggering degradation of RPA1, such as BMH-9, -21, -22 and -23,[88,89] would therefore be of particular interest to test on Dicer mutant cells. As 9-hydroxyellipticin is p53-independent[175] while BMH compounds trigger p53 activation,[88,89] their action could be synergistic, and bypass the frequent p53 loss found in Dicer tumors.[131,132]

Dicer has distinct roles in both quiescence and proliferation

Epistatic interactions can be different in cycling and G_0 cells. For example, we found a very strong inhibition of growth in double-mutants of Dicer and TTF-I, but this did not affect the viability of quiescent cells.[36] The mechanism underlying this epistatic interaction is likely linked to DNA replication; TTF-I bound to the rDNA terminator sites provides an unidirectional block of the DNA replication fork, insuring that rDNA replication and rRNA transcription occur in the same direction during S-phase to avoid replication-transcription collisions.[176,177] Dicer is involved in collision resolution in fission yeast, and could become essential for timely completion of replication in the absence of TTF-1.[94,95] It is therefore important to assay epistatic interactions during both growth and quiescence. Ideally, targets can be combined to achieve growth inhibition in both actively-dividing and non-dividing cells. In the context of a tumor, if the treatment of the majority of actively-dividing cells does not result in complete tumor elimination, it is important to specifically target non-dividing and slow-dividing cancer cells responsible for relapse and metastasis.[178] In this regard fission yeast would be an ideal model system for conducting such a screen and identifying negative epistasis targets of nucleolar functions of RNA interference and DICER1, in both cycling and quiescent cells, which would provide potential targets of therapeutic significance.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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