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SnoRNAs and the emerging class of sdRNAs: multifaceted players in oncogenesis

Yoann ABEL^{1,2}, Mathieu REDERSTORFF^{1,*}

¹ Université de Lorraine, CNRS, IMoPA, F-54000 Nancy, France

² Current address: IGMM, F-34000 Montpellier, France

* Corresponding author. Tel.: +33 3727 4650.

E-mail address: mathieu.rederstorff@univ-lorraine.fr

ABSTRACT

Small nucleolar RNAs are generally involved in the modification of target ribosomal RNAs. Other possible functions recently emerged with the discovery of the novel class of snoRNA-derived RNAs or sdRNAs. Since then, additional data has revealed the involvement of both snoRNAs and sdRNAs in tumorigenesis.

After briefly introducing snoRNA families and functions, this mini-review summarises recently acquired knowledge on snoRNA-related mechanisms associated with cancer. Despite the rapid increase in the number of studies, exactly how snoRNAs lead to cancer remains unclear. However, exciting new research is paving the way for future diagnostic or therapeutic strategies.

Keywords: small nucleolar RNAs (snoRNAs), sno-derived RNAs (sdRNAs), microRNAs (miRNAs), small nucleolar RNA host genes (SNHG), cancer, p53

1. Housekeeping snoRNAs got freshened up

1.1. SnoRNA families

The first small nucleolar RNAs (snoRNAs) were identified more than 50 years ago (1,2) and their biogenesis, complex assembly pathway into ribonucleoprotein particles (RNPs) and canonical functions have since been studied in detail (3,4). More than 700 snoRNAs or snoRNA-like entities have been listed to date (5–8).

Most snoRNAs can be classified in three families, C/D box- and H/ACA box snoRNAs, named after the conserved consensus boxes they contain, and the RNA moiety of RNase MRP (mitochondrial RNA processing) (9,10). Additional RNAs, such as microRNAs (miRNAs), can be found in the nucleolus, transiently or not, but are not listed as snoRNAs (11). Here, we focus on members of the C/D box- and H/ACA box snoRNA families (Figure 1). To be comprehensive, one should also mention that some small Cajal-body RNAs (scaRNAs), generally involved in guiding modifications of small nuclear RNAs (snRNAs) of the spliceosome, contain C/D, H/ACA or both types of conserved boxes (12,13), while the RNA moiety of the telomerase complex (hTR/TERC), involved in the maintenance of chromosome ends, features an H/ACA box (14).

1.2. SnoRNA functions

Within snoRNPs, snoRNAs guide posttranscriptional RNA modifications of other non-coding RNAs (ncRNAs) thanks to their complementary sequences (Figure 1). Most snoRNAs target ribosomal RNAs (rRNAs) for modification, but recently, novel types of targets, such as messenger RNAs (mRNAs), have also been described (15), and it has also been proposed that some snoRNAs regulate alternative splicing of their target mRNAs (16–18). Rather than guiding enzymatic modifications, some snoRNAs, including U3 and U8, are involved in processing pre-rRNAs (19,20). Finally, a few snoRNAs are still considered orphan snoRNAs, as no functions or targets have been identified (8).

C/D box snoRNAs guide 2'-O-methylation reactions of their target RNA. They are associated with the four core proteins, SNU13, NOP56, NOP58 and the methyltransferase fibrillarin (FIB). Recently, two orphan C/D box snoRNAs were also unexpectedly shown to guide KRE33-mediated acetylation of two residues in yeast 18S pre-RNA (15,21).

H/ACA box snoRNAs, the second big family of snoRNAs, guide isomerisation of uridine residues into pseudouridines. They are associated with four different core proteins, NHP2, GAR1, NOP10 and the pseudouridine synthase, dyskerin (DKC1) (4).

In both C/D and H/ACA box snoRNA families, assembly of the snoRNA moiety with their cognate core proteins relies on a complex stepwise mechanism which is now relatively well understood, involving numerous assembly factors and chaperone proteins, reviewed in (4).

1.3. Processing of snoRNAs

Last but not least, in the late 2000s, a further unexpected function of snoRNAs was discovered, shedding an exciting new light in the field. In a study aimed at identifying novel classes of small ncRNAs using unbiased sequencing, the authors observed stable short RNA species derived from snoRNAs for the first time (22). Later, a search for novel small RNA substrates of human Argonaute (hAgo) proteins identified many novel RNAs corresponding to short, snoRNA-derived molecules (23). The most abundant one, which derived from the H/ACA box scaRNA ACA45, was even shown to be processed by Dicer, and its behaviour resembled that of miRNAs, by targeting a mRNA for silencing (23). At the same time, similar sno-derived RNAs or sdRNAs, sometimes referred to as processed snoRNAs (psnoRNAs) or even sno-microRNAs (sno-miRs), were identified in protozoa (24). SdRNAs were next observed in most if not all species' genomes containing snoRNA genes with conserved processing profiles, suggesting their functional relevance and prompting further investigations to understand their roles (25–30).

2. SnoRNAs and cancer: from early observations of differential expression to laying the foundations for understanding molecular mechanisms

2.1. Differential expression of snoRNAs in cancer

In 2002, the expression of a newly identified snoRNA targeting 5S rRNA was reported to be strongly decreased in meningioma (31). Since this very first observation, a connection between snoRNA and cancer has been increasingly reported, and the number of publications in the field is still growing (32–36). Early studies were generally limited to the observation of differential expression levels of snoRNAs in cancer and in normal tissues, with snoRNAs being reported either as tumour suppressors or oncogenes (Figure 2).

For example, deletion of chromosome 6q was a commonly observed feature in several types of cancer, including prostate and breast cancers, suggesting the presence of tumour suppressor elements in the region. Among the numerous genes located on the deleted fragment, surprisingly, the only mutation was identified in a non-protein coding gene, SNORD50, highlighting its tumour suppressor function (37,38).

Conversely, gene amplification of oncogenic regions is a frequent mechanism leading to tumour progression (39). Again, several studies pointed to a cluster of snoRNAs with increased expression levels in non-small-cell lung cancer tissues, including SNORA42 (40–43).

These first observations reflected the versatility of snoRNAs in cancer progression, but also stressed the lack of understanding of the mechanisms underlying snoRNA-dependent tumour progression or prevention.

2.2. Towards understanding the contribution of snoRNAs to tumorigenesis

Recently some evidence was put forward for molecular pathways connecting differentially expressed snoRNAs to cancer.

For instance, in a protein microarray analysis performed in human, SNORD50, a tumour-suppressor snoRNA, was shown to directly bind to the K-RAS oncogenic protein (44). This binding inhibited the activity of the GTPase. Indeed, the authors showed that loss of SNORD50 was associated with increased amounts of active, GTP-bound K-RAS, subsequently increasing MAPK/ERK signalling and consequently, tumorigenesis (Figure 2).

The opposite effect was recently described for SNORA74B, which induces cell proliferation by promoting the AKT/mTOR signalling pathway, via negative regulation of an AKT inhibitor, PHLPP (45). However, in this case, the exact molecular mechanisms were not clearly established.

The role of SNORA42, one of the most frequently expressed snoRNAs in lung tumours, in tumorigenicity mechanisms was also investigated. It was shown that the snoRNA inhibited caspase-3 activity in some non-small cell lung cancers and therefore reduced apoptosis, in a possibly p53-dependent manner, but elucidation of the full mechanism, again, is still pending (42,43).

In both cases, SNORA74 and SNORA42, and probably many others, different hypotheses are conceivable, including direct RNA-protein interactions, like for SNORD50 and K-RAS, but unknown mechanisms are also possible.

The possible implication of small nucleolar RNA host genes (SNHG5) in tumorigenesis is also an interesting research pathway. For example, the long non-coding RNA transcribed from the SNHG5 locus (lncSNHG5), which also encodes SNORD50, was demonstrated to suppress cell proliferation, invasion and migration in gastric cancer by directly trapping and retaining the metastasis-associated protein MTA2 in the cytosol, thereby increasing histone and p53 acetylation levels (46). Like several other lncSNHG5s, lncSNHG5 was also shown to

sponge certain miRNAs, revealing a novel regulatory mechanism with possible connections to cancer, given the roles miRNAs play in tumorigenesis (Figure 2) (47–49).

Another possible mechanism could be direct epigenetic suppression of certain genes involved in cancer by lncSHNGs or snoRNAs (50,51). No such mechanism has been observed yet, but, in *Drosophila*, several snoRNAs have been identified as being tightly associated with chromatin via the chromatin decondensation factor 31, adding to the growing list of snoRNAs non-canonical functions (51).

2.3. *SdRNAs and cancer*

Many snoRNAs have been shown to be further processed into sno-derived RNAs (22,23), and the study of specific sdRNAs whose behaviour resembles that of miRNAs, with identified targets, have produced more data. Regulation of p53 by snoRNA-dependent mechanisms is a remarkable example.

The tumour suppressor protein p53 is a key actor in cancer development. P53 negatively regulates transcription of many genes, including snoRNA host genes. One of them, SNHG1, which produces several snoRNA-derived miRNA-like molecules, is particularly interesting. The most frequently expressed sdRNA from SNHG1, sno-miR-28 produced from SNORD28, silences TAF9B, a protein known to stabilise p53 (52). In this regulatory feedback loop, the transcriptional target of p53, sno-miR-28, indirectly targets p53, while in a similar loop concerning miRNAs, the miRNAs generally directly target the p53 mRNA. Interestingly, the lncSNHG1, SNORD28 and sno-miR-28 were shown to be overexpressed in breast tumours (Figure 2) (52).

A similar situation was described earlier for miR-605, an H/ACA box snoRNA-derived miRNA-like molecule (29). The authors of that study showed that miR-605 targeted the ubiquitin ligase MDM2, a direct inhibitor of p53 (53), while both MDM2 and miR-605 are transcriptionally activated by p53. Under stress conditions, this feedback loop could be a way for p53 to rapidly accumulate, thereby escaping MDM2 negative effects. Interestingly, miR-605 was also shown to target INPP4B, a phosphatase required for the activation of the AKT oncogene, in melanoma (54) and EN2, a regulator of the PI3K/AKT pathway, in prostate cancer (55).

2.4. *SnoRNAs, ribosomes and cancer*

The growing list of sdRNAs involved in tumorigenesis through non-canonical functions could mask the implication of snoRNAs in cancer aetiology via their canonical functions (see paragraph 1) (3,20,56–58).

Increased production and activity of ribosomes is a strong indicator of cancer cells dividing actively, often associated with abnormal numbers of - or abnormally sized - nucleoli (59,60), and is crucially dependent on snoRNAs activity, either guiding modification or processing of rRNAs (Figure 1). Indeed, a first study reported abnormally high 2'-O-methylation of 28S rRNA in breast cancer (61), associated with increased 45S pre-rRNA transcription and non-canonical processing patterns. These observations were concomitant with decreased IRES-dependent translation of p53. In the same way, the same group later showed that p53 repressed expression of the 2'-O-methyltransferase fibrillarin, one of the core proteins associated with C/D box snoRNAs (62). More recently, another study revealed the prevalence of enhanced C/D box snoRNPS expression in leukaemogenesis (63).

H/ACA box snoRNAs or dyskerin defects are no exception. Dyskerin mutations and subsequently decreased rRNA pseudouridylation are characteristic of X-linked dyskeratosis congenita (ribosomopathy) (64), and patients display a clear increase in susceptibility to cancers (65). Interestingly, like C/D box snoRNAs or fibrillarin defects, dyskerin mutants and pseudouridylation impairment are again associated with decreased IRES-dependent translation of p53 mRNA (66).

Dyskerin is also part of the telomerase RNP, as TERC RNA shares an H/ACA box with the snoRNA family of the same name (67,68), and telomerase upregulation is a common feature of many cancers. Mutation within the H/ACA box of the TERC RNA was also observed in several dyskeratosis congenita patients (69).

Finally, and not obviously, as such a study had never been previously conducted in human, a key later work showed that snoRNAs U3 and U8, which are involved in processing of, respectively, pre-18S and pre-28S, and thus in the synthesis of the small and large ribosomal subunits, were essential for ribosome biogenesis (70). U3 and U8 had previously been shown to be highly expressed in cancer (71). The same work also showed that individual snoRNAs, specifically U3 or U8, were required for tumorigenesis and that their depletion led to an antitumoral response via increased levels of p53 and apoptosis (70), and subsequently to the impairment of ribosome biogenesis.

3. Future leads

Although the involvement of snoRNAs in tumorigenesis is now widely acknowledged and new publications appear almost daily, linking snoRNAs or sdRNAs to diseases and tumorigenesis (see 33–36 for a review), how snoRNA precisely contribute to cancer is still rather poorly understood and molecular details remain relatively scarce, with many ways still to be explored. While the canonical functions of snoRNAs in ribosome biogenesis seem to be of paramount importance in the tumorigenesis process, non-canonical functions, especially borne by sdRNAs, also require careful investigation.

Yet, excitingly, and like miRNA (72,73), sdRNAs expression signatures alone recently made it possible to classify patients from distinct cancer types with very high resolution (74).

SnoRNAs, as well as lncSNHG, and their targets, therefore appear to be promising diagnostic tools or targets and could eventually lead to the development of efficient and original therapeutic strategies.

Contributors

M.R. had the idea of the review, Y.A. and M.R. wrote the draft manuscript, M.R. reviewed the final manuscript.

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Figure legends

Figure 1. C/D and H/ACA box snoRNA families. Schematic representation of C/D (left) and H/ACA (right) box snoRNAs. Consensus box sequences are highlighted in green. C/D and C'/D' boxes form kink-turn 3D structures, featuring Watson-Crick base pairs (solid lines), U-U (dotted lines) and G-A (dashed lines) non-canonical base pairs. The targeted RNAs are in red, base-paired to their respective antisense element on the snoRNA. The 2'-O-methylated positions guided by C/D box snoRNAs, which consist in the 5th base-paired nucleotides upstream from D or D' boxes, are indicated. For H/ACA box snoRNAs, the first unpaired nucleotides in each pseudouridylation pocket are indicated. Pseudouridylation can occur in one or two distinct targets.

Figure 2. SnoRNAs contribute to tumorigenesis. The possible implications of snoRNAs in tumorigenesis are summarized. SnoRNAs, snoRNA host genes and sno-derived RNAs can play either tumor suppressor or proto-oncogenic roles. Up- or down-regulation of their expression can have a positive or negative regulatory effect at different levels, including cell proliferation, apoptosis, etc. Additional direct effects have been documented, such as snoRNAs or SNHG long non-coding RNAs directly binding proteins.

Like miRNAs, sno-derived RNAs were also shown to target mRNAs, while miRNAs sponging on SNHG long non-coding RNAs was also observed.

Although these mechanisms have only been described on specific occasions, it is likely that many more snoRNAs intervene in tumorigenesis through similar mechanisms.

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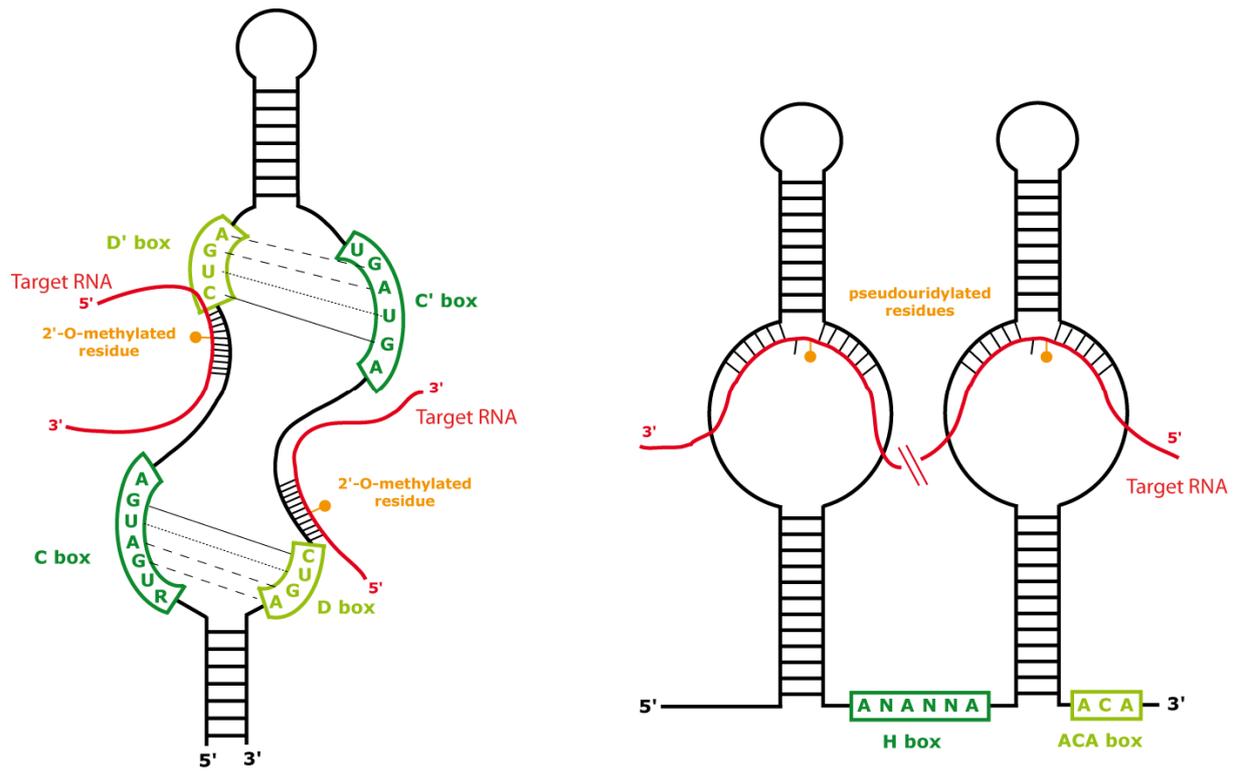


Figure 1

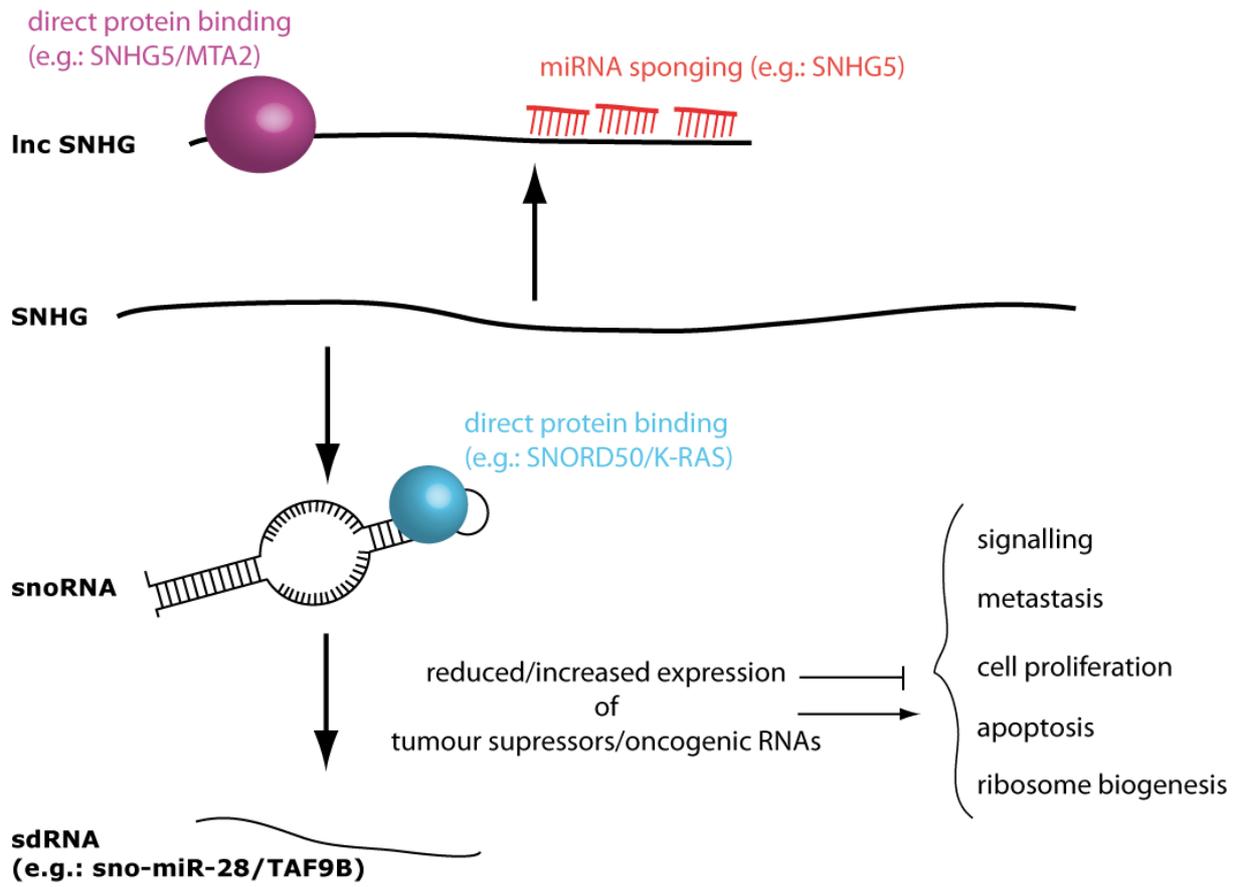


Figure 2