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Midsize noncoding RNAs in cancers: a new division that clarifies the world of noncoding RNA or an unnecessary chaos?

Kacper Guglas[1–3], Joanna Kozłowska-Masłoń[1–4], Tomasz Kolenda[1, 3], Anna Paszkowska[1, 3, 5], Anna Teresiak[1, 3], Renata Bliźniak[1, 3], Katarzyna Lamperska[1, 3]

[1]Laboratory of Cancer Genetics, Greater Poland Cancer Centre, Poznan, Poland
[2]Postgraduate School of Molecular Medicine, Medical University of Warsaw, Warsaw, Poland
[3]Research and Implementation Unit, Greater Poland Cancer Centre, Poznan, Poland
[4]Faculty of Biology, Institute of Human Biology and Evolution, Adam Mickiewicz University, Poznan, Poland
[5]Faculty of Biology, Adam Mickiewicz University, Poznan, Poland

ABSTRACT

Most of the human genome is made out of noncoding RNAs (ncRNAs). These ncRNAs do not code for proteins but carry a vast number of important functions in human cells such as: modification and processing other RNAs (tRNAs, rRNAs, snRNAs, snoRNAs, miRNAs), help in the synthesis of ribosome proteins, initiation of DNA replication, regulation of transcription, processing of pre-messenger mRNA during its maturation and much more. The ncRNAs also have a significant impact on many events that occur during carcinogenesis in cancer cells, such as: regulation of cell survival, cellular signaling, apoptosis, proliferation or even influencing the metastasis process. The ncRNAs may be divided based on their length, into short and long, where 200 nucleotides is the "magic" border. However, a new division was proposed, suggesting the creation of the additional group called midsize noncoding RNAs, with the length ranging from 50–400 nucleotides. This new group may include: transfer RNA (tRNA), small nuclear RNAs (snRNAs) with 7SK and 7SL, small nucleolar RNAs (snoRNAs), small Cajal body-specific RNAs (scaRNAs) and YRNAs. In this review their structure, biogenesis, function and influence on carcinogenesis process will be evaluated. What is more, a question will be answered of whether this new division is a necessity that clears current knowledge or just creates an additional misunderstanding in the ncRNA world?

Key words: noncoding RNA; midsize noncoding RNA; tRNA; snRNA; snoRNA; scaRNA; YRNA; cancer

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Introduction

Most of the human genome consists of noncoding RNAs and despite not coding any proteins, they play crucial roles in protein coding genes regulation [1–3]. Traditionally, the noncoding RNAs were divided into two groups based on their length: short, noncoding RNA (less than 200 nucleotides) and long, noncoding RNA (more than 200 nucleotides) [1, 2, 4, 5]. However, a new division was proposed, a midsize, noncoding RNAs that are 50-400 nucleotides long [6]. In this new category, multiple RNA types may be distinguished: transfer RNA (tRNA); small, nuclear RNA (snRNA); small, nucleolar RNA (snoRNA); small Cajal body-specific RNA (scaRNA) and YRNA [2, 7–18]. In this

Address for correspondence: Kacper Guglas, Research and Implementation Unit, Greater Poland Cancer Centre, Poznan, Poland; e-mail: kacper.guglas@wco.pl

review, each of midsize noncoding RNAs will be analyzed in terms of their structure, biogenesis, function and influence on cancer in order to systematize current knowledge in the field. We also try to answer the question of whether additional division of noncoding RNAs is a necessity or just a further difficulty in its understanding.

Transfer RNAs: structure, biogenesis and functions

Transfer RNAs, also known as tRNAs, are transcribed from a precursor (pre-tRNA) by RNA Polymerase III and, after a series of complex processing reactions and modifications, form mature tRNAs [9, 19, 20]. The pre-tRNA contains 5'-leader and 3'-trailer sequences and in less than 10% of cases introns in the anticodon loop. After the pre-tRNA was transcribed by the RNA Polymerase III, the 5'-leader sequence is processed by RNase P. The 3'-trailer sequence is processed by RNase Z and at the 3' end a CCA triplet is added by TRNT1 enzyme. Pre-tRNA containing introns in the anticodon loop are processed by a nuclear tRNA splicing endonuclease (TSEN) complex which cuts off the intron sequence and ligates 5' and 3' exon regions of tRNA forming a mature tRNA. In most cases the introns degrade rapidly but in some pathological cases they may accumulate [21–23], (Fig. 1). During the pre-tRNA and mature tRNA processing various additional fragments are produced such as: tRNA-derived small RNAs (tsRNAs), tRNA halves (tiRNA) and tRNA-derived fragments (tRFs) [9, 22–24]. tsRNAs are generated in the nucleus as a consequence of the pre-tRNA 3' end cleavage and tiRNAs are generated from mature tRNAs by cytoplasmic angiogenin (ANG) activated in response to stress (oxidative stress, UV radiation, heat shock). The biogenesis of tRFs is currently under investigation, but a Dicer-dependent cleavage of mature tRNAs in the cytoplasm has been proposed as highly probable, also tRFs are formed from tiRNAs by ANG [9, 21], (Fig. 1). Although tRNA derived pieces are heterogeneous in size (10–45 nucleotides), they are not products of random tRNA cleavage or degradation, because their ends are precisely defined by RNA cleavage sequence determinants [21]. However, tsRNAs, tiRNA and tRFs due to their much shorter length compared to mature tRNAs are classified as short, noncoding RNAs. Mature tRNAs consist of 73–95 nucleotides and are characterized by specific "clover" secondary structure as well as an L-shaped tertiary structure. Interestingly, more than 500 genes encode over 40 different tRNAs. The most conserved function of tRNAs is helping ribosomes in synthesizing proteins by decoding nucleotide triplets as a result linking nucleotide information on mRNA to an amino acid sequence. However, tRNA is also found to take part in various other processes such as: cell survival, cell signaling, apoptosis, metabolism of amino acids and stress response programs [9, 21–23]. Interestingly, tRNAs play an important role in aging and lifespan, the serum levels of mitochondrial tRNAs and ribosomal RNAs (rRNAs) will increase with age, which may be related to mitochondrial dysfunction during the aging process [20].

Transfer RNAs and cancer

A number of previous studies have shown that tRNAs are often dysregulated in many cancer types [22, 25–27]. In general, tRNAs seem to be upregulated in cancers, they were found downregulated only in senescent or differentiating cells [25]. It has also been indicated that the expression of target tRNAs contribute to tumor aggressiveness due to oncogenes which selectively induced target tRNAs. However, the mechanisms of this phenomenon are not fully understood [25]. It should be noted that serine (Ser), threonine (Thr) and tyrosine (Tyr) tRNA isoacceptors were the most commonly upregulated in tumors. In HER-2 positive breast cancer it was found that oncogenes influence tRNA expression profiles resulting in apoptosis resistance and increased cell proliferation. Also breast cancer stem cells are enriched in proteins involved in tRNA biosynthesis [25]. Another study showed that tRNAs are overexpressed in breast cancer cells compared to normal cells and are highly upregulated in metastatic breast cancer cells [28]. In metastatic breast cancer cells $tRNA^{Glu}UUC$ and $tRNA^{Arg}CCG$ were noted as the most upregulated of indicated tRNA isoacceptors [25]. In the case of triple negative breast cancer, tRNAs were also found to be highly expressed, and $tRNA^{Val}CAC$, $tRNA^{Gly}GCC$, $tRNA^{Val}ACC$, $tRNA^{Glu}CTC$, $tRNA^{Lys}CTT$, $tRNA^{Gly}CCC$ and $tRNA^{His}GTG$ were the most commonly (approximately 95%) present [27].

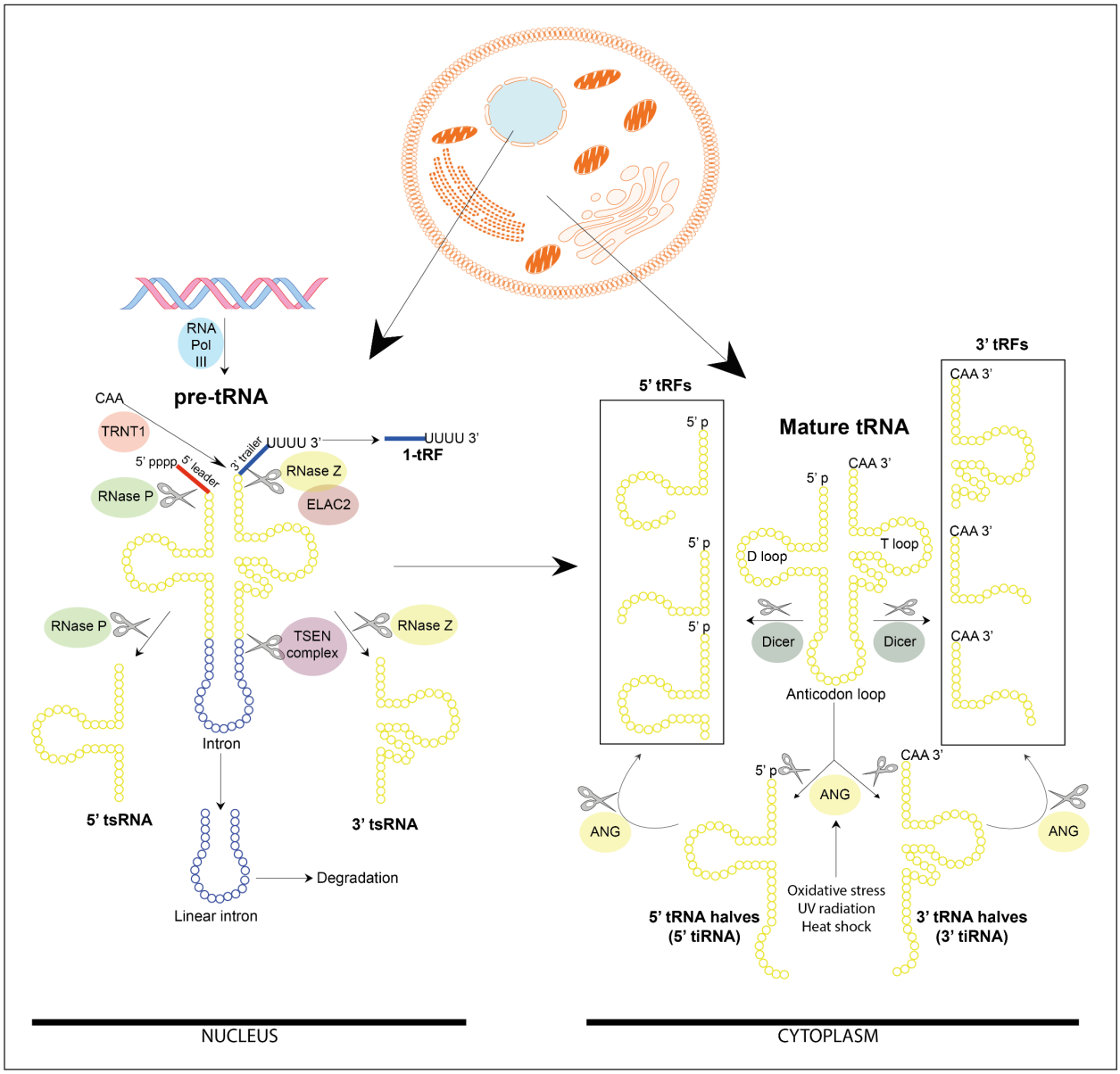

Figure 1. Transfer RNA (tRNA) and tRNA-derived fragments biogenesis. ANG — angiogenin

The initiator methionine tRNA ($tRNAi^{Met}$) in cancer-associated fibroblasts were found to be highly upregulated leading to modifying the cellular microenvironment to accelerate tumor progression through type II collagen secretion, which is known for favoring endothelial migration, angiogenesis and tumor growth [22, 29]. Furthermore, in melanoma, $tRNAi^{Met}$ overexpression was correlated with a higher migration rate, invasiveness and higher lung metastasis capacity. On the other hand, $tRNAi^{Met}$ displayed a smaller impact on cell proliferation and primary tumor growth in melanoma [22, 25]. It was shown that upregulated levels of telomerase reverse transcriptase (TERT) cause increased levels of tRNAs resulting in rising the proliferation abilities of melanoma cancer cells, suggesting that TERT promotes cancer cell proliferation through elevation of different tRNA expression ($tRNA^{Ala}$, $tRNA^{Cys}$, $tRNA^{Asn}$, $tRNA^{Thr}$, $tRNA^{Glu}$, $tRNA^{Arg}$, $tRNA^{Lys}$) [22]. Similar mechanism may be observed in lung cancer where tRNAs overexpressed by TERT were correlated with carcinogenesis processes [22, 30]. Moreover, abnormally increased tRNA also promoted translation of highly active proteins in multiple myeloma. tRNAs were also found to be higher expressed in cervical cancer and in pancreatic cancer. In these cancers, tRNA functions as the modulator of MEK2 function to regulate

cancer cellular behavior [22]. Interestingly, it was indicated that mitochondrial tRNAs (mt-tRNAs) were involved in lung cancer [22] and breast cancer tumorigenesis [22, 31]. Mutations in mt-tRNAs DNA caused disruption of the secondary structure of mt-tRNAs resulting in a decrease of mitochondrial protein synthesis, as a result contributing to carcinogenesis of lung and breast cancers [22, 30, 31]. What is more, several studies also suggested tRNAs as potential prognostic markers [25, 32–34]. Upregulation of $tRNA^{Arg}CGT$ and $tRNA^{Arg}AGA$ and downregulation of $tRNA^{Thr}ACA$ and $tRNA^{Pro}C$-CA result in significantly worse overall survival in kidney renal clear cell carcinoma [25, 32]. In lung adenocarcinoma dysregulated tRNAs correlate with increased recurrence risk [33] and in breast cancer samples 76 different tRNAs were found to be used as markers to distinguish normal cells from breast cancer cells [25, 34]. Interestingly, recent papers have showed that tRNA-derived fragments are abundantly dysregulated in many cancer types, such as: pancreatic cancer [35, 36], breast cancer [9, 22, 26, 37, 38], uveal melanoma [39], chronic lymphocytic leukemia [9,40], non-small cell lung cancer [41], lung cancer [9, 22], hepatocellular carcinoma [42], colorectal cancer [27, 43–45], ovarian cancer [46], cervical carcinoma [47], prostate cancer [48, 49], urinary bladder carcinoma [50] and colon cancer [51, 52]. Analyzing all the studies considering tRNA and tRNA-derived fragments, it may be assumed that they have a potent impact not only on normal cells but also on cancer cells, leading to carcinogenesis and processes combined with it. It should be noted that tRNAs and tRNA-derived fragments show many features of potential prognostic biomarkers as well as therapeutic targets.

Small nuclear RNAs, 7SK and 7SL: structure, biogenesis and functions

snRNAs associate with a number of different proteins forming small nuclear ribonucleoprotein particles (snRNPs). This process occurs in the cytoplasm and fully formed snRNPs are transferred back to the nucleus to perform one of their many functions. Genes for the major snRNAs are transcribed by Pol II and the most common are U1, U2, U4 and U5 molecules [10, 53]. Interestingly, U6 spliceosomal RNAs, 7SK and 7SL, are transcribed by RNA Pol III [10, 54–57]. The snRNA genes have a less complex promoter in contrast to protein-coding ones. It should be noted that a distal signal element (DSE) acts as an enhancer and proximal signal element (PSE) is the core promoter involved in the transcription process of these molecules. The transcripts do not contain introns and are not polyadenylated, similarly to other ncRNAs, but additionally carry a 3' box that is responsible for creating the 3' end of the pre-snRNA. In the next step of biogenesis, the pre-snRNA is processed into a mature form of snRNA [10, 53] (Fig. 2A). Interestingly, DSE and PSE work as *cis*-acting elements for RNA Pol II and RNA Pol III action [10, 53]. Several factors activate the transcription of snRNA as well as mRNA: Oct1, Sp1, NF1 and Staf. These factors bind to sequences in the DSE, which have properties of transcriptional enhancer, resulting in transcription activation of snRNA and mRNA [10, 53]. Transcription factors, Oct1, Sp1, NF1 and Staf, bind to DSE and enhance the snRNA gene expression. They stabilize three different proteins binding to PSE: PSE binding protein (PBP), PSE binding transcription factor (PTF) and snRNA activating protein complex (SNAPc) (Fig. 2B). The PTF recruits TATA-binding protein (TBP) and TBP-associated factors (TAFs) such as: TAF6, TAF7, TAF8, TAF9, TAF11, TAF13 and more. It should be underlined that such a process occurs only if there is a TATA box present in the promoter sequence. TATA box converts transcription from RNA Pol II to RNA Pol III and this biogenesis pathway is specific for 7SK, U6 and mRNA. Most of the snRNAs are transcribed by RNA Pol II [10, 53–57]. The RNA Pol II also requires additional proteins such as: TFIIA (transcription factor II A), TFIIB (transcription factor II B), TFIIE (transcription factor II E), TFIIF (transcription factor II F) and TFIIH (transcription factor II H), (Fig. 2B) [10, 53]. However, the role of TFIIH for transcription of snRNAs is not fully understood yet. The RNA Pol II also requires an integrator complex which consists of 14 subunits and is necessary for the recognition of the 3' box and the RNA cleavage that produces pre-snRNA [10, 53]. What is more, during snRNA transcription, a phosphorylation of a CTD (C-terminal domain) of RNA Pol II results in obtaining transcription and RNA processing factors at the right point of the transcription cycle [10, 53]. Furthermore, phosphorylation of CTD of RNA

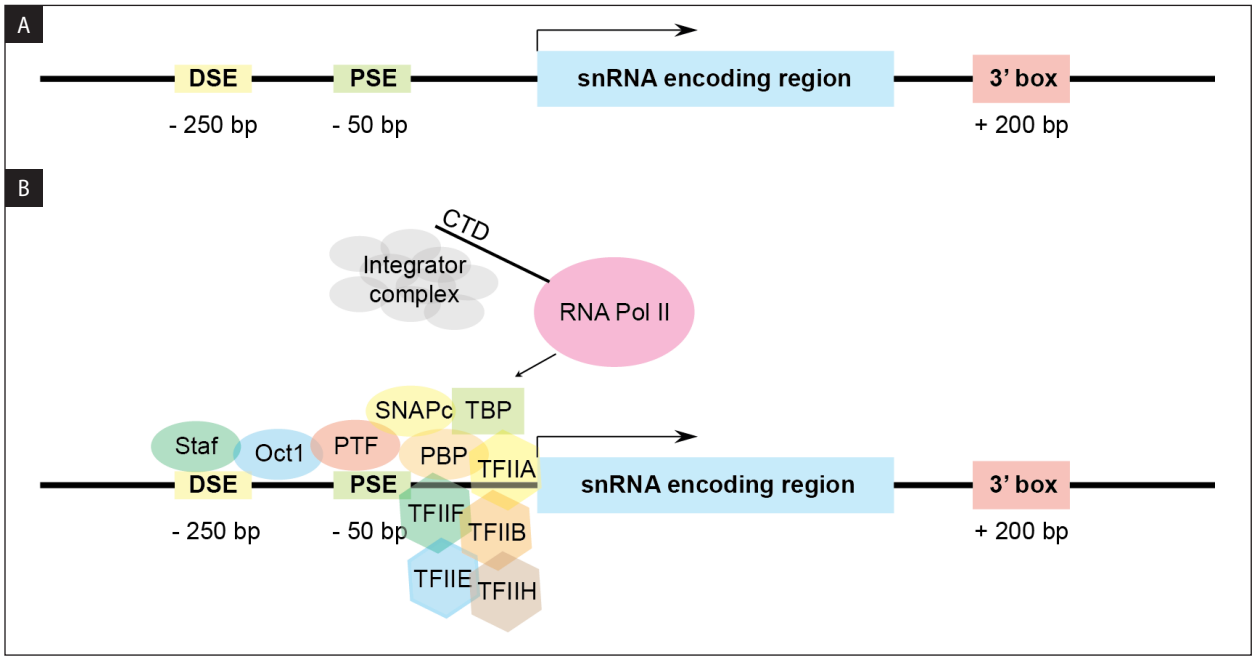

Figure 2. Transcription of small nuclear RNA (snRNA). **A.** A scheme depicting a structure of snRNA genes transcribed by RNA Pol II; **B.** A scheme depicting complexes, transcription factors and proteins needed for snRNA biogenesis

Pol II is essential for 3' box dependent RNA 3' end formation. The 3' box is an element consisting of 14–16 nt and it determines the production of a 3' extended pre-snRNA, which after transport to cytoplasm is further processed generating a mature 3' end of snRNA [10, 53].

The primary function of the snRNAs is their influence on processing pre-messenger RNA (hnRNA) in the nucleus [58]. However, some specific snRNAs carry characteristic functions such as 7SK, 7SL or spliceosome-related snRNAs. The first one, 7SK is a longer type of snRNA consisting of approximately 330 nucleotides. This snRNA plays a role in regulating transcription by controlling the positive transcription elongation factor P-TEFb [10, 54–57]. The second one, 7SL RNA, is also a long snRNA and it consists of approximately 300 nt. 7SL forms a ribonucleoprotein complex with signal recognition particle (SRP), which mediates co-translational and post-translational translocation of proteins to the endoplasmic reticulum [59]. However 7SL, free of SRP proteins, is a well-known component of virus particles [59–61].

Interesting group of snRNAs are spliceosome-related molecules. The U1 is the most abundant of all snRNAs, which is crucial for production of full-length RNA polymerase II transcripts from protein coding genes, as well as from long, noncoding RNA [58]. U1, U2, U4, U4atac, U5, U11, U12 snRNAs take part in the expression of intron-containing protein coding genes. U7 is crucial for 3' formation of replication-activated histone mRNA and U3 is required for rRNA processing [10].

snRNA, 7SK and 7SL in cancers

The snRNAs, 7SK and 7SL were previously found to be altered in many types of cancer. 7SL RNA was found to be highly expressed in cancer tissues of the liver, lung, stomach, breast compared to normal adjacent tissue and its silencing resulted in the reduction of cellular proliferation [62]. 7SL RNA, alongside 7SK and different snRNAs, were found to be overexpressed in triple negative breast cancer [26]. On the other hand, 7SK was found to be downregulated in tongue squamous cell carcinoma patients and its expression level was negatively correlated with tumor size [56]. Another study considering the role of 7SK in HEK 293T cells (human embryonic kidney cells) stated that 7SK is highly overexpressed in these cells and decreases their viability [57]. Also overexpressed 7SK RNA promotes caspase-dependent apoptosis in HEK 293T cells and inhibits cancer cell proliferation [57]. On the other hand, 7SK RNA was found to be significantly downregulated in the breast, blood and colon

cancer tissue samples as well as in human mesenchymal stem cells and embryonic stem cells [55]. It was indicated that U1 snRNP regulates cancer cell migration and invasion *in vitro* in cervical cancer, lung adenocarcinoma and breast cancer cell lines [58, 63]. Moreover, the expression of U6 snRNA in breast cancer plasma patients was observed to be overexpressed in comparison to healthy subjects [63]. in a review describing diagnostic potency of different ncRNAs, Wang et al. indicated that U2 snRNA fragments (RNU2-1f) could function as diagnostic biomarkers in colorectal cancer and cholangiocarcinoma [27]. The expression of U1, U2 and U5 in tumor-educated platelets (TEP) were found to be significantly downregulated and correlated with lung cancer progression making them potentially useful biomarkers for lung cancer [64]. Previous studies have implicated that alterations in the splicing process of snRNPs have been found in many different types of cancer and cancer cell lines. Such alterations in different snRNPs result in tumorigenesis promotion by allowing the cells to gain proliferative properties, overcome hypoxia, become more metastatic and invasive, acquire the antiapoptotic ability and achieve independence from growth factor [65].

Small nucleolar RNA: structure, biogenesis and functions

Small nucleolar RNAs (snoRNAs) consist of 60-300 nucleotides and most are encoded in intronic or other noncoding regions of protein coding genes involved in ribosome synthesis. All snoRNAs form complexes with different proteins generating functional small nucleolar ribonucleoproteins (snoRNPs) [12, 63, 66, 67]. Two major groups of snoRNA may be distinguished: C/D box and H/ACA box. The first one, C/D box (SNORD), consists of 60-200 nucleotides long and directs rRNA modification by 2'-O-ribose methylation. The other one, H/ACA (SNORA) box, consists of 120–250 nucleotides and is involved in pseudouridylation of essential regions for the ribosomal function [12, 63, 66–69]. It should be noted that the H/ACA snoRNA is characterized by two hairpin structures, two boxes, box H and box ACA, and pseudouridylation pocke, (Fig. 3A). However, to gain its functions the H/ACA form a complex with four different proteins, dyskerin, Nop10, Nhp2, and Gar1, which results in creating a H/ACA snoRNP complex (Fig. 3B). The dyskerin mainly promotes pseudouridylation, and Nop10 and Nhp2 are needed for H/ACA stability and function, and Gar1 enhances the catalytic activity of dyskerin and facilitates the release of target RNA [67–73]. Moreover, dyskerin binding with the H/ACA box also prevents aggregation, degradation and binding to the premature RNA [15]. Dyskerin is bound to chaperone Shq1 and has to be released by the R2TP complex before assembling to the H/ACA [15]. Next characteristic feature of the C/D snoRNA is a stem-bulge-stem structure and a box C and box D conserved sequences in contrast to C' and D' boxes which are less-conserved elements. The antisense elements of the box D/D' are complementary to target RNA and form a recognition component (Fig. 3C). Similarly to H/ACA, the C/D snoRNA binds with different proteins, Fibrillarin, Nop58, Nop56, 15.5kD and Naf1, forming the C/D snoRNP complex (Fig. 3D). Fibrillarin facilitates 2'-O-ribose-methylation of target RNAs and Naf1 is responsible for processing stability and nucleolar localization. Nop58, Nop56 and 15.5 kD proteins are responsible for the localization, maturation and stability of the C/D snoRNP complex [67–73]. Additionally, 15.5 kD protein initiates the assembly of C/D box RNPs [15]. Interestingly, in H/ACA snoRNAs biogenesis four different proteins — Nhp2, Nop10, Dyskerin, and Naf1 which is replaced with Gar1 at the end of the process — must be present to initiate the transcription of H/ACA box. However, in C/D box biogenesis the proteins are added during the different stages of its origin [15] (Fig. 4). All in all, RNP proteins define the termini of the snoRNA by protecting them from the exonucleases activity, making them essential for correct processing and metabolic stability of the mature snoRNAs [67–69, 71–74]. It should be noted that the majority of snoRNAs are transcribed from introns by RNA Pol II, embedded in protein coding genes related to ribosome function and biogenesis. However, some snoRNAs are transcribed from the introns of noncoding genes, such as GAS5 and SNHG1, encoding for 11 and 9 snoRNAs, respectively. Next, the snoRNAs bind to proteins and factors, Naf1, Shg1, described above, which are crucial for processing stability and nucleolar localization. Fully formed snoRNPs are transported to Cajal bodies for additional maturation and processing. Finally, snoRNPs

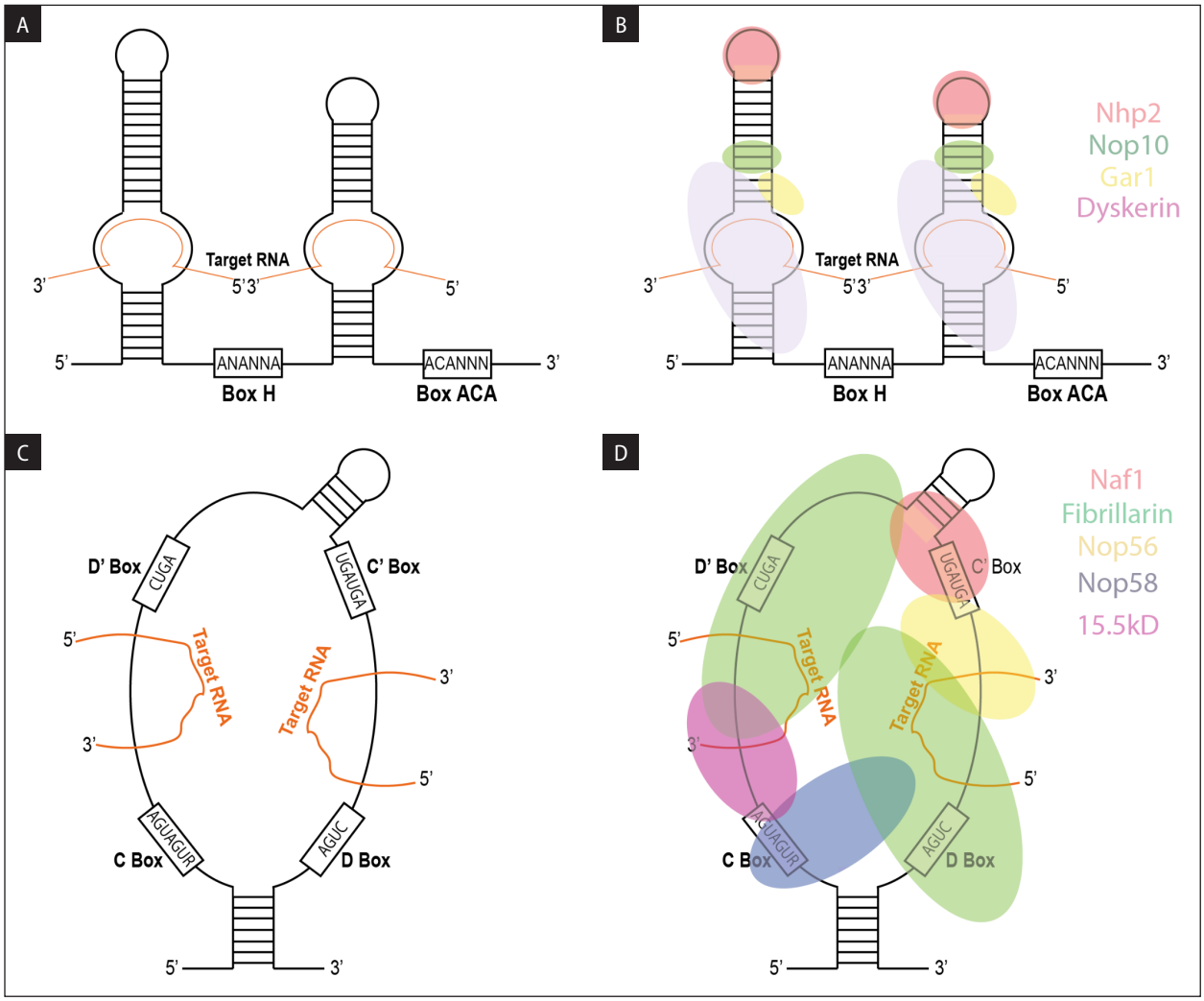

Figure 3. A. The H/ACA small nucleolar RNA (snoRNA) structure; **B.** The structure of the H/ACA snoRNP complex, a combination of H/ACA snoRNA and proteins that allow the H/ACA functioning. **C.** The characteristic structure of C/D snoRNA; **D.** The structure of the C/D snoRNP complex

are delivered to nucleoli to perform their functions [67–71, 73]. However, two snoRNA groups, snR30 (H/ACA box snoRNA) and U3 and U14 (C/D box snoRNA), which are probably not involved in methylation and pseudouridylation, are essential for cleavage of the pre-ribosomal RNAs at the early processing stages [67]. SnoRNAs carry very diverse functions in cells. The main function of snoRNAs is modification and processing of ribosomal RNA. However, snoRNAs also influence the modification of other cellular RNAs, such as snRNAs and miRNAs, and directly affect mRNA splicing and alternative splicing in serotonin receptor subtype 2C and DPM2, PBRM1, RALGPS1, TAF1, and CRHR1 pre-mRNA [12, 63]. Another study also proposed that snoRNAs regulate splicing of the E2F7 transcriptional factor [75]. SnoRNAs are also involved in the response to oxidative stress in tumorigenesis and in cell death in diabetes [63, 67]. What is more, snoRNAs are involved in the PI3K/ACT, p53, and Wnt/β-catenin cell-signaling pathways [12,66]. Finally, a number of studies report the presence of snoRNA-derived miRNAs. The H/ACA box and C/D box snoRNAs are cut by nucleolytic enzymes into smaller products, 20–25 nucleotides long. Similarly to miRNAs, these fragments associate with Argonaute proteins and target specific mRNAs [67, 76–78]. Interestingly, some miRNAs, such as miR-605, are derived from the H/ACA box snoRNA, and it is an important factor in stress induced stabilization of the p53 tumor suppressor protein [79].

snoRNAs and cancer

Enhanced nucleolar activity, enlarged nucleoli and enhanced ribosome biogenesis are known as tumor aggression markers [63]. Some snoRNAs may function as tumor suppressors, U50, h5sn2, RNU43, RNU44, RNU48, RNU6B, SNORD113-1, whereas some may function as oncogenes, SNORD33, SNORD66, SNORD76, SNORD42, SNORA42 [63, 67]. SnoRNAs were previously reported to be altered in a vast number of different cancers [27, 66] including: breast cancer [12, 67, 80, 81], prostate cancer [67, 82], lung cancer [67, 71, 83, 84], head and neck squamous cell carcinoma [66, 67], hepatocellular carcinoma [67, 85] and clear cell renal cell carcinoma [86]. In prostate cancer it was discovered that SNORA74A, SNORA42 and SNORA64 carry nucleotide deletions and substitutions leading to tumorigenesis [87]. Also a mutated snoRNAU50 was found significantly decreased in prostate cancer [67]. Similar situation is with SNORA42 in non-small cell lung cancer (NSCLC), where also its higher expression levels were correlated with significantly poorer prognosis, increased cell growth and colony formation [12, 67, 71]. In addition, C/D box snoRNAs, SNORD33, SNORD66, SNORD76, SNORD73B and SNORD78 were found to be significantly upregulated in NSCLC [67]. In head and neck squamous cell carcinoma (HNSCC), substitution mutations were discovered [71] and a decreased expression of RNU43, RNU44, RNU48 and RNU6B were associated with poor prognosis of HNSCC patients [67]. In breast cancer, as in HNSCC, the same snoRNAs, RNU43, RNU44, RNU48, RNU6B were found to be significantly decreased. Interestingly, also snoRNAU50 was discovered to be decreased and SNORD44 overexpressed, suggesting that in the same cancer type, different snoRNAs may function as tumor suppressors as well as oncogenes [12, 67, 81]. It was indicated in the case of colon cancer and renal cancers that hypermethylation of CpG islands is correlated with silencing of H/ACA snoRNA on the transcriptional level [71]. Next, SNORD113-1, a tumor suppressor snoRNA, was significantly decreased in hepatocellular carcinoma (HCC). SNORD113-1 inhibits cell growth and proliferation in human HCC cells, so the loss of SNORD113-1 correlates with HCC tumor development and its activity contributes to tumor growth suppression [66, 67]. The H/ACA box snoRNA h5sn2 is known to be significantly decreased in meningioma [71]. Interestingly, some snoRNAs, such as SNORD33 may function as both tumor suppressor and oncogene, depending on a tumor type. SNORD33 in clear cell renal cell carcinoma (ccRcc) acts as tumor suppressor and in breast cancer as oncogene [66,86]. More snoRNAs and their changes in different types of cancer may be found in Table 1.

Table 1. Small nucleolar RNAs (snoRNAa) and their role in cancers based on different studies [12, 26, 27, 66–68, 80–90]

snoRNA	Cancer type	Function	snoRNA class	Expression level
SNORD114-10	Ovarian Cancer	Tumor suppressor	C/D box	Decreased
SNORD35B (RNU35B/U35B)	Head and neck squamous cell carcinoma	Tumor suppressor	C/D box	Decreased
SNORD76 (U76)	Glioblastoma	Tumor suppressor	C/D box	Decreased
SNORD47 (RNU47/U47)	Glioblastoma	Tumor suppressor	C/D box	Decreased
SNORA74B (U19-2)	Gallbladder cancer	Tumor suppressor	H/ACA box	Decreased
SNORD24 (RNU24/U24)	Adenocarcinoma	Oncogene	C/D box	Decreased
SNORA23 (ACA23)	Pancreatic ductal adenocarcinoma	Oncogene	H/ACA box	Increased
SNORD113-1	Hepatocellular carcinoma	Tumor suppressor	C/D box	Decreased
SNORA47 (HBI-115)	Hepatocellular carcinoma	Oncogene	H/ACA box	Increased
SNORD76 (U76)	Hepatocellular carcinoma	Oncogene	C/D box	Increased
ACA11 (SCARNA22)	Hepatocellular carcinoma	Oncogene	H/ACA box	Increased
SNORD126 (MiR1201/MiRN1201)	Hepatocellular carcinoma	Oncogene	C/D box	Increased
SNORA18L5	Hepatocellular carcinoma	Oncogene	H/ACA box	Increased

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Table 1. Small nucleolar RNAs (snoRNAa) and their role in cancers based on different studies [12, 26, 27, 66–68, 80–90]

snoRNA	Cancer type	Function	snoRNA class	Expression level
SNORD94 (RNU94/U94)	Osteosarcomas	Oncogene	C/D box	Increased
SNORA70 (RNU70/U70/DXS648E)	Osteosarcomas	Oncogene	H/ACA box	Increased
SNORD10 (mgU6-77)	Osteosarcomas	Oncogene	C/D box	Increased
SNORA13 (ACA13)	Osteosarcomas	Oncogene	H/ACA box	Increased
SNORA38 (ACA38)	Osteosarcomas	Oncogene	H/ACA box	Increased
SNORA79 (ACA65A)	Osteosarcomas	Oncogene	H/ACA box	Increased
SNORA46 (ACA46)	Osteosarcomas	Oncogene	H/ACA box	Increased
SNORD117 (U83)	Prostate cancer	Tumor suppressor	C/D box	Decreased
SNORD116 (HBII-85)	Prostate cancer	Tumor suppressor	C/D box	Decreased
SNORD82 (RNU82/U82/Z25)	Prostate cancer	Tumor suppressor	C/D box	Decreased
SNORD59A (RNU59A/U59A)	Prostate cancer	Tumor suppressor	C/D box	Decreased
SNORA55 (ACA55)	Prostate cancer	Oncogene	H/ACA box	Increased
SNORA42 (MBI-43)	Non-small cell lung cancer and Colorectal cancer	Oncogene	H/ACA box	Increased
SNORD78 (U78)	Non-small cell lung cancer and Prostate cancer	Oncogene	C/D box	Increased
SNORD50A (RNU50/U50)	Breast cancer and Prostate cancer	Tumor suppressor	C/D box	Decreased
SNORD114-1	Acute promyelocytic leukemia	Oncogene	C/D box	Increased
SNORD112-114	Acute promyelocytic leukemia	Oncogene	C/D box	Increased
SNORD43 (RNU43/U43)	Acute myeloid leukemia	Oncogene	C/D box	Increased
SNORD14D	Acute myeloid leukemia	Oncogene	C/D box	Increased
SNORD74 (U74/Z18)	Acute myeloid leukemia	Oncogene	C/D box	Increased
SNORD35A (RNU35/RNU35A/U35)	Acute myeloid leukemia	Oncogene	C/D box	Increased
U3 (SNORD3)	Breast cancer	Oncogene	C/D box	Increased
SNORD118 (U8/LCC)	Breast cancer	Oncogene	C/D box	Increased
SNORD44 (RNU44/U44)	Breast cancer	Tumor suppressor	C/D box	Decreased
SNORD43 (RNU43/U43)	Breast cancer	Tumor suppressor	C/D box	Decreased
SNORD48 (RNU48/U48)	Breast cancer	Tumor suppressor	C/D box	Decreased
SNORD29 (RNU29/U29)	Breast cancer	Oncogene	C/D box	Increased
SNORD34 (RNU34/U34)	Breast cancer	Oncogene	C/D box	Increased
SNORD67 (HBII-166)	Breast cancer	Oncogene	C/D box	Increased
SNORD33 (RNU33/U33)	Breast cancer	Oncogene	C/D box	Increased
SNORA44 (ACA44)	Breast cancer	Oncogene	H/ACA box	Increased
SNORA21 (ACA21)	Colorectal cancer	Oncogene	H/ACA box	Increased
SNORA15 (ACA15)	Colorectal cancer	Oncogene	H/ACA box	Increased
SNORA41 (ACA41A)	Colorectal cancer	Oncogene	H/ACA box	Increased
SNORD33 (RNU33/U33)	Colorectal cancer	Tumor suppressor	C/D box	Decreased

Small Cajal body-specific RNA: structure, biogenesis and functions

Small Cajal body-specific RNAs (scaRNAs) are the base of small Cajal body-specific ribonucleoprotein (scaRNPs) which modify snRNA in Cajal bodies (CBs) [16]. The CBs are subnuclear organelles without lipid bilayer that take part in biogenesis of different types of ribonucleoproteins such as snRNPs or scaRNPs. The CBs are also responsible for rRNA processing, splicing, telomerase maintenance and DNA damage repair. The CBs in DNA damage repair function by concentration of components and CB-associated proteins in one area.

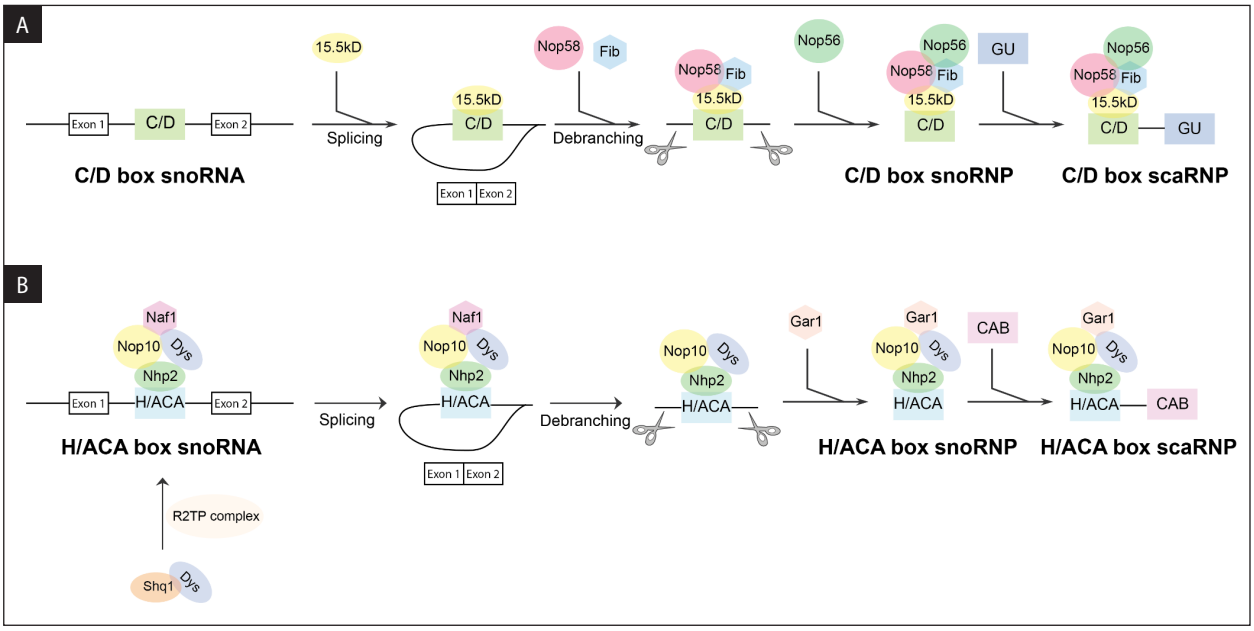

Figure 4. Biogenesis of small nucleolar RNAs (snoRNAs), small Cajal body-specific RNAs (scaRNAs), snoRNPs and scaRNPs. **A.** Biogenesis of C/D box snoRNP and C/D box scaRNP. C/D box scaRNP requires additional long GU repeat, which represents the Cajal body localization signal and results in binding to TCAB1 protein and transport to Cajal body; **B.** Biogenesis of H/ACA box snoRNP and H/ACA box scaRNP, which requires additional CAB motif for binding TCAB1 and transporting to Cajal body. The detailed biogenesis description and protein function may be found in the main text. Dys — dyskerin, Fib — fibrillarin

This concentration occurs due to telomerase Cajal body protein 1 (TCAB1/WRAP53/WDR79) [12, 14, 15, 69, 91]. Next, scaRNAs are very similar to previously described snoRNAs, however scaRNAs are longer and more complex. Interestingly, scaRNAs are bound to the same proteins as snoRNAs, but depending on a type of scaRNA, forming scaRNPs. What is more, they consist of C/D boxes and H/ACA boxes, however, with additional long GU repeat on a C/D box, or CAB motif on a H/ACA box (Fig. 4). These additional components allow TCAB1 protein to bind and transport scaRNPs to the CBs for their further maturation and transport scaRNPs to the CBs for their further maturation and correct function [12, 14, 15, 69, 91]. Additionally, TCAB1 is required for telomerase trafficking to CBs and for telomere maintenance. There are twenty-four different scaRNAs found which may be divided into three groups: C/D box scaRNA (4 scaRNAs) that guide 2'-O-methylation, and H/ACA box scaRNA (16 scaRNAs) that direct pseudouridylation, and mixed domain scaRNA (4 scaRNAs) that carry both functions [14, 15]. Most scaRNAs are encoded in the introns of host genes and just like snoRNA they share the same biogenesis pathway: synthesized in nucleoplasm, processed and assembled with proteins and transported to CBs (Fig 4). There are three scaRNAs (scaRNA 2,9,17) that, unlike the rest, do not accumulate in CBs, but are processed into small, nucleolar enriched fragments of 70-80 nucleotides [15, 91]. They are found accumulated in the nucleus and in nucleoplasm and their function is still unclear [91]; however, it was proposed that by altering snoRNP activity they influence the level of modifications in rRNA [16]. scaRNAs even carry similar functions to snoRNAs such as direct modification of rRNA, snRNA, mRNA and tRNA [12, 14, 15, 91]. scaRNAs are essential for ribosome functioning by protecting them from cleavage, maturation, rRNA folding, stability and probably nucleolar localization. Furthermore, scaRNAs take part in maturation of spliceosomal snRNAs by methylation, resulting in increasing their stability. scaRNAs also play a crucial role in mRNA alternative splicing and in pseudouridylation of tRNAs [12, 14, 15, 91]. Several studies also indicate that miRNAs may evolve from snoRNAs and scaRNAs or that their sequences are a primary mechanism behind the miRNAs formation in some cases, such as SCARNA15 [69]. Finally, scaRNAs TERC, are believed to play a role in telomerase functioning, however, more studies

are needed to fully understand this phenomenon [12, 14, 15, 91].

scaRNA and cancer

Since scaRNAs are very similar to snoRNAs in biogenesis and function these RNA types are often taken together in terms of disease and cancers. There are only a few studies considering specific scaRNAs and their function in cancers [15, 92–95]. Considering scaRNAs globally, they are dysregulated in different types of cancers [68, 96, 97]. Previous studies concerning HCC have shown that a significantly low expression of SCARNA16 is strictly associated with poor patients' survival and more advanced clinical status. These results show that SCARNA16 may possibly function as an biomarker in HCC [95]. On the other hand, SCARNA15 was discovered to be highly overexpressed in leukemic and breast cancer cell lines compared with healthy controls. Overexpression of SCARNA15 is correlated with MYC alterations in many cancers causing cancer cells' growth and survival. What is more, SCARNA15 guides the conversion of a key Ψ residue in U2 snRNA, which, as a result, directs gene-specific alternative splicing and impacts tumor suppressor pathways [94]. In chronic lymphocytic leukemia, SCARNA17 and SCARNA9 were significantly downregulated in a high risk group of patients, together with 17 different snoRNAs [15, 93]. Finally, SCARNA22 (ACA11) was significantly overexpressed in multiple myeloma, which contributes to carcinogenesis by evasion of chemotherapy, offering protection from oxidative stress and modulating the Wolf-Hirschhorn syndrome candidate 1 gene (WHSC1)[15, 92].

YRNA: structure, biogenesis and functions

YRNAs are noncoding RNAs whose genes are clustered on a single chromosomal locus 7q36. Four YRNAs are distinguished: YRNA1 (112 nt), YRNA3 (101 nt), YRNA4 (93 nt) and YRNA5 (83 nt). The YRNAs are highly conserved among species. These noncoding RNAs are characterized by a very specific stem-loop structure, consisting of a loop domain, upper stem, lower stem and polyuridine tail [1–3, 17, 18, 98]. Loop domain is actually the least conservative part of the YRNA and is responsible for binding proteins (nucleolin, ZBP1, PTB), modulating chromatin association and carrying a cleavage site to generate YRNA-derived fragments (YsRNAs). Upper stem and lower stem are the most conservative elements of YRNAs. Upper stem is vital for DNA replication initiation, creating new DNA replication forks, and the lower stem is crucial for nuclear export and also carries a Ro60 binding site. Finally, the polyuridine tail is a La protein binding site. Two main proteins that bind with YRNAs and that determine their function are Ro60, SSA or TROVE2-TROVE domain family member 2, and La protein, SSB — small RNA binding exonuclease protection factor [1-3,17,18,98]. The Ro60 protein promotes nuclear export of YRNAs, stabilizes its structures in the cytoplasm and protects YRNAs from exonucleolytic degradation. The La protein also protects YRNAs from exonucleolytic degradation, but is also responsible for nuclear retention and is vital for accurate and efficient termination of RNA pol III transcription. The YRNAs are transcribed in the nucleus by RNA pol III, bound with proteins (Ro60/La protein) and are exported from the nucleus to carry different functions. The intracellular localization of YRNAs depends on cellular stress, cell type and type of Ro60-YRNA complex. For example Ro60-YRNA5 is mostly found in the nucleus, while the rest of YRNAs are mostly found in cytoplasm [1–3, 17, 18, 98]. Interestingly, YRNAs and Ro60 accumulate in the nucleus after oxidative stress or exposure to UV. YRNAs may also be found in extracellular vesicles and viruses (murine leukemia virus/human immunodeficiency virus). YRNAs, similarly to other types of noncoding RNAs, may form YRNA-derived fragments. These fragments are usually derived from YRNA3 (27–36 nt) and YRNA5 (22–25 nt) in apoptotic cells due to YRNAs degradation by a caspase-3 dependent pathway. YsRNAs may also be formed by poly I:C-mediated activation of the innate immune system or by RNAse L in response to UV exposure. They may be found in the cell as well as in body fluids [1–3, 17, 18, 98]. This type of derived RNA fragments are important factors in the promotion inflammation process in monocytes/macrophages and in apoptosis. Interestingly, extracellular YsRNAs induce caspase-3 dependent cell death and NF-kB dependent inflammation in monocytes/macrophages, however, intracellular ones carry the same function but through Toll-like receptor 7 (TLR7) [1–3, 17, 18, 98, 99]. YRNAs themselves are mainly components of Ro60 RNP which is vital for intracellular

transport of RNA-binding proteins, response to environmental stress, RNA quality control and binds aberrant or miss-folded noncoding RNAs, such as U2 snRNA or 5S rRNA. The YRNA-Ro60 RNP complexes also bind with autoantigens, forming a target for the immune system in autoimmune diseases (Sjogren's syndrome and systemic lupus erythematosus). YRNAs are also involved in sustaining cell proliferation and downregulation results in cell proliferation inhibition. What is more, YRNAs are crucial for DNA replication initiation forming new DNA replication forks. They also bind with many different proteins determining their localization and function, such as: processing and splicing mRNA transcripts, binding AU-rich elements in mRNA transcripts, and mediate 3' end processing of human histone H3 mRNA. They are also involved in viral infections, innate immunity and much more [1–3, 17, 18, 98]. The detailed structure and biogenesis figures may be found in our previously published paper [2].

YRNA and cancer

YRNAs were previously found to be associated with a vast number of different processes in healthy human cells and because of so many processes that they are involved in YRNAs are significantly dysregulated in many cancer types [1–3, 17, 18, 98]. YsRNAs are also found to be dysregulated in many cancers [2, 100], however, since they are very short, YsRNAs are not included in this review. In bladder cancer (BCA), all four YRNAs (YRNA1, YRNA3, YRNA4 and YRNA5) were found to be significantly downregulated in tumor tissue compared with healthy bladder tissue making them potential disease biomarkers. What is more, YRNA3 and YRNA4 correlated with metastasis, tumor grade and disease progression. These findings also show that YRNAs may function as bladder cancer progression biomarkers [2]. Then, all four YRNAs were also dysregulated in cervix cancer, however, contrary to findings considering bladder cancer, all were significantly increased [2]. Interestingly, in FFPE samples derived from cervix cancer patients only YRNA1 was significantly upregulated [2]. YRNAs may also function as possible disease biomarkers in prostate cancer (PCA) where all YRNAs were found to be downregulated compared to healthy prostate tissue. The same study also proposed them to be possible PCA progression biomarkers. Interestingly, in benign prostate hyperplasia, (BPH) YRNA4 and YRNA5 were significantly downregulated, showing that expression of YRNAs vastly differ among different tissue types [2]. Furthermore, it was previously suggested that YRNAs may also serve as a diagnostic utility in BRAF-mutated metastatic melanoma patients [2]. In glioma all four YRNAs were highly abundant not only in glioma cells, but also in extracellular vesicles and free RNPs [2]. YRNAs were also found to be highly dysregulated in head and neck squamous carcinomas (HNSCC), which also qualifies them as promising disease biomarkers [1, 7]. Especially, YRNA1 was significantly downregulated in HNSCC cells and in patients' serum. It was also indicated that higher expression of YRNA1 correlated with better disease-free survival and overall survival [1]. In a study concerning triple negative breast cancer (TNBC), apart from a vast number of other noncoding RNAs, all four YRNAs were found highly expressed in patients suffering from luminal androgen receptor (LAR) subtypes [26]. YRNAs were also dysregulated in pancreatic ductal adenocarcinoma (PDAC). In FFPE samples derived from PDAC patients YRNA1 and YRNA3 were significantly overexpressed [2]. Interestingly, in PDAC tissue samples, compared to normal tissue, it was indicated that expression of Ro60 is also significantly higher and its knockdown resulted in significant decrease in cell proliferation and invasion. These findings show Ro60 as a potential target for silencing in PDAC [2]. Furthermore, YRNAs were discovered to be significantly overexpressed in colon cancer cell cultures, especially YRNA1 and YRNA3 [2]. In HCT116 cells YRNA5 was significantly overexpressed upon poly I:C treatment [2], and in the blood serum of rectal cancer patients, YRNA4 showed significantly high expression levels [2]. Finally, YRNAs were also examined in clear cell renal cell carcinoma. YRNA3 and YRNA4 were significantly overexpressed in tumor tissue and patients' serum compared to normal tissue and serum. Interesting fact is that a significant decrease in YRNA4 expression was found in patients with lymph node metastasis and more advanced clear cell renal cell carcinoma stages. It may be concluded that in ccRcc YRNA3 and YRNA4 may function as disease biomarkers, and YRNA4 itself as a disease pro-

gression biomarker [2]. All these previous studies show how much impact YRNAs have on different tumors and the diversely they are dysregulated, suggesting using them in the future as biomarkers and even therapeutic targets.

Conclusions

A huge number of previous studies considering the noncoding RNAs show that these molecules play many important roles in a vast number of processes in healthy and cancer cells [1–3, 9, 17–24, 54–74, 91, 98, 99]. Different types of ncRNAs have been found to be highly dysregulated in many cancers and other diseases, often correlating with carcinogenesis processes [2, 22, 25–52, 56–58, 62–57, 80–90, 92–97, 100]. The expression of tRNAs in cancers was associated with tumor aggressiveness, apoptosis resistance, increased cell proliferation, endothelium migration, angiogenesis, tumor growth and migration rate in many cancer types [22, 25–29]. Similarly, snRNA, 7SK, 7SL, scaRNA and YRNA also correlated with higher cell proliferation, metastasis, tumor growth, cell migration, invasion and cancer progression [2, 56, 58, 94, 95]. SnoRNA have a very similar impact on cancer cells (increased cell growth and colony formation); however, these RNA types may function as tumor suppressors and oncogenes. Oncogene snoRNAs impact the same processes as previously described noncoding RNAs; however, when they function as tumor suppressors snoRNAs can reduce tumor growth [63, 66, 67, 71, 86]. All the previous studies show many similarities between these RNAs, not only in function but also in their impact on developing different tumor types.

The noncoding RNAs were always divided into two groups based on their length: short noncoding RNAs (shorter than 200 nt) and long noncoding RNAs (longer than 200 nt) [1, 2, 4, 5]. Recently, a new division has been proposed, adding a new class of midsize noncoding RNAs (ranging from 50 to 200 nt) [6]. However, we are not fully convinced if that new class is really needed in the field of noncoding RNAs. Since all the noncoding RNAs carry similar functions in the human cells and in cancers, an additional division brings confusion and does not explain the world of noncoding RNAs better than the two-group division which has been very clear for researchers for decades. Additional argument is that almost all the above described noncoding RNAs (tRNA, snRNA, snoRNA, scaRNA, YRNA) form much shorter derivatives which were also found to play important roles in different cancers [2, 9, 35, 37, 38, 100]. In this newly proposed division these derivatives are associated in a different group (short noncoding RNAs), which brings more confusion. Whereas, in the two-group division, all these RNA types and their derivatives stay in the same group making them easier to understand. 7SK and 7SL RNAs do not produce derivatives and are 300 nucleotides long which brings even more confusion to the new division, it is more logical for them to be counted into long noncoding RNAs since they are significantly longer than other RNAs described in this work [10, 59]. Finally, some of these RNAs share similar pathways with miRNAs which are short noncoding RNAs and in the new division these RNAs are forced into separate groups despite the similarities between them [10, 12, 16, 63]. All that considered, we think that the new division creating midsize noncoding RNAs only brings confusion and chaos to the field and the old, two-group division is more fortunate and transparent in understanding the world of noncoding RNAs.

Authors' contributions

Conceptualization, T.K., K.L. and K.G.; Methodology, T.K., K.G.; Software, K.G.; Validation, K.G.; Formal Analysis, K.G., T.K.; Investigation, T.K., K.G., K.L.; Resources, K.G.; Data Curation, K.G., T.K; Writing — Original Draft Preparation, K.G.; Writing — Review & Editing, T.K., K.G., A.T., R.B.; Visualization, K.G.; Supervision, T.K., K.L.; Project Administration, K.L.; Funding Acquisition, K.L.

Conflict of interest

The authors declare no conflict of interest.

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Data availability statement

The data presented in this study are openly available online.

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