Y RNA

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Y RNA are a class of small non-coding RNA that are largely conserved. Although their discovery was almost 40 years ago, their function is still under investigation. This is evident in cancer biology, where their role was first studied just a dozen years ago. Since then, only a few contributions were published, mostly scattered across different tumor types and, in some cases, also suffering from methodological limitations. Nonetheless, these sparse data may be used to make some estimations and suggest routes to better understand the role of Y RNA in cancer formation and characterization.

Keywords: RNY1 ; RNY3 ; RNY4 ; RNY5 ; RO60 ; DNA replication ; cancer microenvironment ; cancer etiology

1. Introduction

The discovery of Y RNA goes back to 1981 [1], when Lerner and collaborators isolated them in patients affected by systemic lupus erythematosus using specific autoantibodies; this finding was subsequently confirmed in other autoimmune pathologies. The identified targets in these diseases include the soluble ribonucleoproteins (RNP) RO60 (also known as SSA or TROVE2—TROVE domain family, member 2) [2][3] and SSB (small RNA-binding exonuclease protection factor—also known as La) [4]. RNP are complex molecules that include both proteins and RNAs; in RO60 RNP, the RNA component is represented by Y RNA [1][5] which are small non-coding RNAs (sncRNA) that, like other sncRNA, are transcribed by RNA Polymerase III (Pol III) [5][6]. In humans, four genes (*RNY1, RNY3, RNY4,* and *RNY5*) encode for Y RNA; they are clustered on chromosome 7q36.1 [7][8] and their transcripts are named hY1 (112 nucleotides (nt)), hY3 (101 nt), hY4 (93 nt), and hY5 (83 nt), respectively.

The Y RNA family is not limited to the transcripts of the four canonical genes described above; there are other 966 hY RNA pseudogenes (368 for hY1, 442 for hY3, 148 for hY4, and 8 for hY5) scattered on all human chromosomes [9], with at least 878 predicted transcripts. Their distribution is generally proportional to the chromosome length, with the notable exceptions of chromosomes 1, 12, and 17 (excess) and Y (only one pseudogene, possibly because of its peculiar structure and content [10]. Interestingly, no pseudogene sequence is 100% identical to the corresponding hY functional RNA and, notably, although most sequence changes are randomly distributed along Y RNA entire sequence, there is a specific enrichment at specific positions [9], suggesting that these changes are not random, at least in some sequences.

Y RNA are conserved molecules [11][12][13][14][15] (Figure 1) and, in vertebrates, also their clustering is conserved [15][16][17]. A BLAST search shows that the sequence identity is higher than 90% in most vertebrates. Instead, in some non-vertebrate organisms and microorganisms, the sequence similarity with the vertebrate Y RNA is only partial [18] and in plants and fungi they have not been identified yet, thus their evolution is still debated.

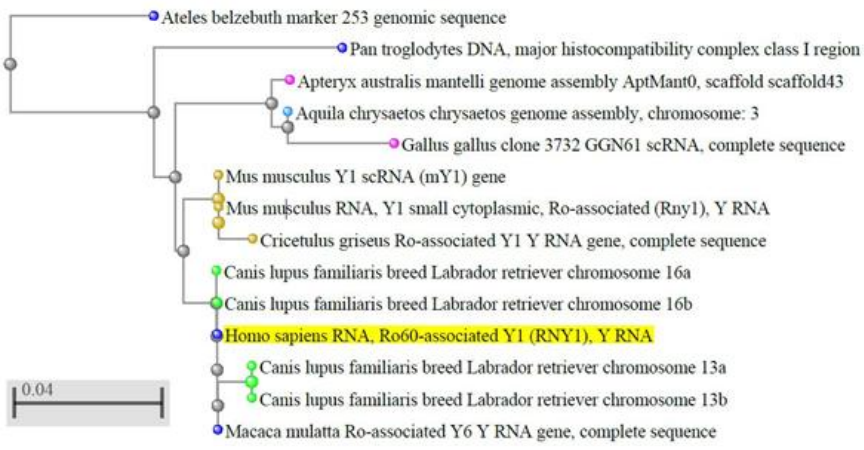

Figure 1. Evolutionary conservation of Y RNA in vertebrates. The dendrogram shows the conservation of human hY1 in monkeys, dogs, rodents, and birds; only best matches (identity >95%) were selected. The tree was obtained through the NCBI BLAST website (URL: https://blast.ncbi.nlm.nih.gov/Blast.cgi, accessed on April 2020), using default settings. Out of

the 100 results displayed, we selected only those coming from genome sequences, thus excluding predicted sequences, human pseudogenes, bacterial artificial chromosome (BAC) clones, and other constructs. The color codes, set by default by the NCBI website, are as follows: yellow highlight: query sequence; light blue dots: hawks and eagles; pink dots: birds; brown dots: rodents; blue dots: primates; green dots: carnivores; grey dots: nodes.

2. Y RNA Structure and Function

2.1. Y RNA Structure

Despite their relatively short length, Y RNA have a complex 3-D structure, including both double-helix rigid stems and single-strand flexible loops [19]; their structure can be roughly split into five major regions, represented by different colors in Figure 2. These regions are responsible for the binding activity of Y RNA with proteins, such as the above mentioned RO60 (which binds the lower stem and the bulge) and SSB (which recognizes the polyU tail). It was shown that the tail may be a variable portion of Y RNA, at least in hY1 and hY3, and that this might influence their intracellular stability, it being a target of exonucleases [20]. The upper stem domain is important for DNA replication, while the loop domain performs different tasks, such as modulation of chromatin association, protein binding, and cleavage for the formation of YsRNA (Y RNA-derived small RNAs) [19][21][22].

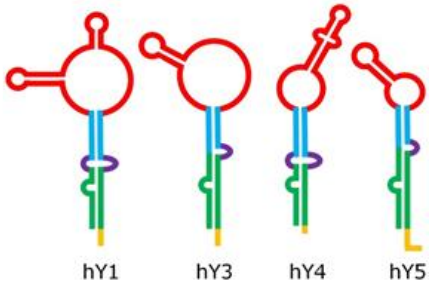

Figure 2. Structure of human Y RNA. The structure was retrieved from the literature [19][21][22], but alternative structures with minor differences have been reported as well [23][24]. The domains are the poly-U tail (yellow), the lower stem (green), the bulge (violet), the upper stem (blue), and the loop (red).

2.2. Y RNA Interacting Proteins

To date, several proteins have been identified that directly interact with either the entire Y RNA or Y RNA-derived fragments; the current knowledge about these interactions is summarized in Table 1, while the main steps in the life cycle of Y RNA are schematically depicted in Figure 3. It is likely that each Y RNA binds at the same time at least two proteins, one of which is a ‘core protein’ bound on the stem domain or the poly-U tail (such as RO60 or SSB) and another on the loop domain. Indeed, experiments using gel filtration show that Y-linked RNP range from 150 to 550 kDa (see [23] and references therein); this ample size variation likely reflects an equally ample variability in their composition. As shown in Table 1, the enrichment of RNA-processing/stabilizing proteins, including both sncRNA and mRNA is evident; this suggests that Y RNA have, potentially, multiple functions inside the cells, including the control of gene expression. This makes them promising potential targets for cancer therapy.

Table 1. Y RNA binding proteins. Data inside parentheses indicate unconfirmed data or minor effects. Protein names (column 1) are those approved by the HUGO (Human Genome Organization) Gene Nomenclature Committee (HGNC). Proteins are listed in alphabetical order according to data in column 1. References (refs) indicate the works that illustrate the protein binding to Y RNA (i.e., not the protein function). Y RNA between parentheses indicate weak or unconfirmed data; 1-3-4-5 is for hY1-hY3-hY4-hY5, respectively.

Protein (HGNC)	Synonym(s)	Interacting Y RNA	Y RNA Domain Involved	Protein Function	Refs
AGO1	EIF2C1, AGO	unknown	unknown	gene silencing through RNAi	[25]
APOBEC3F	ARP8	(1), (3), (4), (5)	unknown	antiviral activity	[26][27]
APOBEC3G	CEM15	1, 3, 4, 5	unknown	antiviral activity	[26][27]

CALR	CR, CRT	1, 3, 4, 5	unknown	formation of the RO60 RNP complex, calcium-binding chaperone	[28]
CPSF1	CPSF160	1, 3	loop	mRNA poly-adenylation	[29]
CPSF2	CPSF100	1, 3	loop	mRNA poly-adenylation	[29]
CPSF4	NEB1	1, 3	loop	histone pre-mRNA processing	[29]
DIS3	EXOSC11	(1), (3)	polyU tail	Y RNA stabilization	[20]
DIS3L	DIS3L1	1, 3	polyU tail	Y RNA degradation and turnover	[20]
EXOSC10	PMSCL2	1, 3, 4, 5	polyU tail	Y RNA trimming, stabilization	[20]
ELAVL1	HuR	3	unknown	mRNA stabilization	[29]
ELAVL4	HuD	3	loop	mRNA stabilization, mRNA translation	[30]
FIP1L1	FIP1-like 1	1, 3	loop	mRNA poly-adenylation	[29]
HNRNPK	HNRPK	1, 3	loop	pre-mRNA binding	[31]
IFIT5	RI58	5	unknown	innate immunity	[32]
MATR3	VCPDM	1, 3	upper and lower stem	nuclear matrix, transcription, RNA-editing	[29][33]
MOV10	gb110, KIAA1631	unknown	unknown	microRNA-guided mRNA cleavage	[34]
NCL	nucleolin, C23	1, 3	loop	association with intranucleolar chromatin	[35]
PARN	DAN	1, 3, 4, 5	polyU tail	Y RNA trimming, stabilization	[20]
PTBP1	hnRNP I, PTB	1, 3	loop	pre-mRNA splicing	[31]
PUF60	RoBPI, FIR	(1), (3), 5	(loop)	pre-mRNA splicing, apoptosis, transcription regulation	[32][36]
RNASEL	PRCA1, RNS4	1, (3), 4, 5	loop	cell cycle arrest and apoptosis	[37]
RO60	TROVE2, SSA	1, 3, 4, 5	lower stem	stabilization, nuclear export, RNA quality control	[38][39] [40]
RPL5	L5	5	loop	5S rRNA quality control	[32]

SSB	La, LARP3	1, 3, 4, 5	polyU tail	nuclear localization, protection of 3′ ends of pol-III transcripts	[39]
SYMPK	SYM, SPK	1, 3, (4), (5)	loop	mRNA poly-adenylation, histone pre-mRNA processing	[29]
TENT4B	PAPD5	1, 3, 4, 5	polyU tail	Y RNA oligoadenylation, degradation	[20]
TOE1	PCH7	1, (3)	polyU tail	Y RNA degradation and turnover	[20]
YBX1	NSEP1	1, 3, 4, (5)	unknown	mRNA transcription, splicing, translation, stability	[29][34]
YBX3	DBPA	unknown	unknown	cold-shock domain protein; DNA-binding domain protein	[34]
ZBP1	C20ORF183, IGF2BP1	(1), 3	loop	nuclear export of RO60 and Y3	[34][41]

Figure 3. A schematic representation of Y RNA life cycle. The light blue area represents the nucleus (the dotted line indicates the presence of nuclear pores) and the molecular events occurring inside it; the yellow area represents the cytoplasm; the white space represents the surrounding extracellular environment. Y RNA are transcribed by POLIII and, if bound by SSB/La, may remain inside the nucleus to perform specific tasks like promoting DNA replication or other functions, upon binding to specific proteins such as those reported in Table 1. In many cases, these additional functions are not fully understood, since Y RNA binding companions are known, but not their role. If Y RNA are bound by RO60 inside the nucleus, they can be exported into the cytoplasm with the help of specific carrier proteins. Once there, Y RNA may perform several tasks, either alone or in RNP complexes. Y RNA may be stabilized through their binding to SSB, RO60, or other proteins, and they may contribute to the stabilization of several target molecules. Moreover, they may also be excreted in the extracellular environment either as free and complete RNA, or as free RNP complexes, or inside micro vesicles. Y RNA excretion may also occur after a specific cleavage, that generates the YsRNA. Once in the extracellular environment, Y RNA may be internalized by target cells to perform additional tasks.

2.3. Role of Y RNA in RO60 Function

A special consideration, among Y RNA interacting proteins, should be given to RO60. This protein is a ring-shaped polypeptide [42] that specifically uses Y RNA as a scaffolding element [43]. Once assembled, this RNP complex fulfills several intracellular tasks, such as RNA quality control [32][44], intracellular transport of RNA-binding proteins [45], and response to environmental stress (reviewed in [22][24]). RO60 is highly conserved [44][46], and its functions include the binding of aberrant or mis-folded non-coding RNAs (ncRNA) such as 5S rRNA or U2 snRNA [47][48]. Due to the very high binding affinity of Y RNA for RO60, some authors hypothesize that Y RNA might act as RO60 repressors [42][49], although some evidence supports the hypothesis that these molecules (or, at least, hY5) might also enhance the recognition of mis-folded ncRNA [32]. Data show that the assembly of Ro RNP protects the particle itself from degradation in several organisms [50]. In addition, RO60 intracellular localization (nucleus/cytoplasm) is also driven by its binding to Y RNA [38][44], possibly through its interaction with other proteins such as nucleolin (NCL), polypyrimidine tract-binding proteins (PTB), and Z-DNA binding protein 1 (ZBP1) [23].

2.4. Role of Y RNA in DNA Replication

The role of—at least some—Y RNA in the initiation of DNA replication and cell cycle progression is well established. RNA-mediated depletion (RNAi) has been successfully used to knock down the intracellular amount of hY1, hY3, and hY4, demonstrating that this treatment on any of those is sufficient to halt or strongly reduce both processes, while the artificial re-expression of any of them in the same cells is sufficient to restore a pre-treatment situation [51][52][53][54]. Similar results were achieved by Y RNA inactivation mediated by antisense morpholino oligonucleotides (MOs) micro-injected in vertebrate and worm embryos, causing their death [53][55]. The role of Y RNA in DNA replication is uncoupled from that of

RO60 RNP; immuno-depletion in human cells of either RO60 or SSB is not sufficient to inhibit DNA replication [56] and the same happens in case of mutations deleting either the RO60 or SSB binding site inside Y RNA [18][57]. The additional finding that this process is driven by the upper stem domain of Y RNA [18] further supports the fact that Y RNA accomplish DNA replication independently of both RO60 and SSB, which have different binding sites (Table 1); moreover, it suggests that the initiation of DNA replication depends on different, yet currently unknown, binding proteins [57].

The different results obtained for hY5 (no effect on DNA replication upon RNAi treatment) may be explained in at least two ways. Some authors hypothesize that this Y RNA is just refractory to RNA-mediated depletion [51][52]. Alternatively, hY5 might play a marginal role in this process; this is suggested by its different intranuclear localization: hY1, hY3, and hY4 co-localize on early-replicating euchromatin, while hY5 is mostly localized inside nucleoli [58].

The role of Y RNA in promoting the initiation of DNA replication is in good agreement with their overexpression in various human solid tumors [52] (see also Section 3).

2.5. Y RNA Derivatives and Fragments

During the apoptosis, the RNA component of Ro RNP is partly degraded, generating the Y RNA-derived small RNAs (YsRNA); however, Dicer is not involved in their formation, thus their origin and function is not related to those of micro-RNAs [59][60]. These shorter fragments are specifically, abundantly, and rapidly generated from all four Y RNA through the action of caspases [61], yet their causal role in these phenomena (apoptosis and miR biogenesis), if any, is currently unclear [61][62]. These fragments remain bound to the RO60 protein and, in part, also to the SSB protein [61] suggesting their formation occurs early during the apoptotic process. YsRNA have been identified both in healthy tissues [33][59] and in cancer cells. These fragments—especially those derived from hY4—are particularly abundant in plasma, serum [63][64][65], and other biofluids [66][67], where they circulate either as free complexes with a mass between 100 and 300 kDa, or in exosomes and microvesicles [63], collectively called ‘extracellular vesicles’ (EV). Some authors suggest that Y RNA and their derivatives might also fulfill a signaling [63] or a gene regulation [68] function and act also on distant targets.

3. Y RNA and Human Cancer

The first comprehensive report about Y RNA quantification in human cancers was published by Christov and collaborators in 2008 [52] and, to date, it is still a major reference in this field. The examined solid tumors were carcinomas and adenocarcinomas of the lung, kidney, bladder, prostate, colon, and cervix. As a general rule, the authors showed that all four Y RNA are overexpressed, with a range between 4- and 13-fold (for hY4 and hY1, respectively). Despite its importance, the results of this work have been challenged by some authors in the last years, especially as for bladder and prostate cancers, while in other cases the results were only partially replicated. The major points of contrast are the choice of proliferation biomarkers, the missing differentiation of subtypes of cancer samples, the low numbers of tumor and control samples and the lack of distinction between the intracellular and extracellular—either free or embedded inside EV—amount of Y RNA. However, there are some points that have been lately confirmed by other studies, thus supporting the validity of this study [52], at least as a pilot. First, in all tumors analyzed and reported below, Y RNA expression is altered. Second, expression levels of Y RNA vary with tissue type, and there are patterns of mis-expression that are tissue-specific. Third, while the expression of hY1, hY3, and hY4 RNA are to some extent linked, the expression of hY5 RNA is somehow unlinked to the others, at least in some cancer types.

In 2010 Meiri and collaborators further analyzed the sncRNA profile of several solid tumor types [62]. In addition, this work suffers from evident limitations, the most important being the low sample number (in many cases this number is not reported), the non-fresh sources used for RNA quantification (23 human formalin-fixed paraffin-embedded (FFPE) samples), and the poor characterization of tumor histology (some samples, like lung, are a mix of various tumor types). Consequently, the study of Meiri et al. [62] should be considered a pilot study, similarly to [52].

Table 2 summarizes the present knowledge about Y RNA expression and tumor types/subtypes.

Table 2. Expression levels of Y RNA in various cancer types. Cancers are listed in alphabetical order according to the affected organ, irrespective of their histology, for which we refer the reader to the main text; KS means Kaposi’s sarcoma, a multi-organ cancer. The word ‘serum’ is used for short to indicate blood serum. An arrow pointing upward means overexpression; an arrow pointing downward means under-expression; a horizontal, double-headed arrow indicates no significant change; arrows between parentheses indicate weak evidence; mix indicates a complex situation with up- and down-regulation at the same time. N/A means that no data are available. Refs indicates bibliographic references, while ref gene indicates the gene(s) used for quantitative comparison. See the text for further details. Notes to Table2. FFPE are formalin-fixed paraffin-embedded tumor cells from stored samples of various ages; PE are paraffin-embedded cells from

fresh samples. qRT-PCR is quantitative Real Time PCR; HTS is high throughput sequencing. (a): the authors used simultaneously three methods (high throughput sequencing, microarray analysis and qRT-PCR) and compared the obtained results. 1: differences between EV and cancer cells; 2: differential up- and down-regulation (see text); 3: differences between blood serum and cells.

Cancer	hY1	hY3	hY4	hY5	Refs	Sample Type	Sample Number	Control Number	Method	Ref Gene	Notes
bladder	↑	↑	↔	(↑)	[52]	cell cultures	4	4	qRT-PCR	Ki-67, HPRT1	
	↑	↑	N/A	N/A	[62]	FFPE	5	1	(a)	hsa-miR-200b	
	↓	↓	↓	↓	[69]	FFPE	88	30	qRT-PCR	SNORD43, RNU6-2	
blood	N/A	N/A	N/A	↑	[70]	K562 cells EV	N/A	N/A	RNA-seq	N/A	1
	(↑)	N/A	↑	N/A	[71]	plasma EV	N/A	N/A	RNA-seq	N/A	1
brain	↑	↔	↑	↑	[72]	cell culture EV, free RNP	N/A	N/A	RNA-seq	N/A	
breast	↑	↑	N/A	N/A	[62]	FFPE	5	N/A	(a)	hsa-miR-200b	
	mix	mix	mix	mix	[73]	serum	5	5	RNA-seq	N/A	2
	N/A	N/A	↑	N/A	[74]	cell culture EV, free RNP	N/A	N/A	RNA-seq	N/A	
	↑	N/A	↑	↑	[75]	cell lines	26	N/A	RNA-seq	N/A	
cervix	↑	↑	↑	↑	[52]	cell cultures	4	4	qRT-PCR	Ki-67, HPRT1	
	N/A	N/A	N/A	↑	[59]	HeLa cells	N/A	N/A	northern blotting	N/A	
	↑	(↑)	N/A	N/A	[62]	FFPE	N/A	N/A	(a)	hsa-miR-200b	
colon	↑	↑	↑	↑	[52]	cell cultures	8	4	qRT-PCR	Ki-67, HPRT1	
	N/A	N/A	N/A	↑	[59]	HeLa cells	N/A	N/A	northern blotting	N/A	
	↑	↔	N/A	N/A	[62]	FFPE	N/A	7	(a)	hsa-miR-200b	
	N/A	N/A	↑	N/A	[76]	PE	96	N/A	HTS	miR-128a-3p, miR-92a-3p, miR-151a-3p	
esophagus	(↑)	↔	N/A	N/A	[62]	FFPE	N/A	N/A	(a)	hsa-miR-200b	
head/neck	mix	mix	mix	mix	[77]	serum	N/A	N/A	RNA-seq	N/A	2
	mix	mix	mix	mix	[78]	serum, tumor tissue	5+2	5+2	qRT-PCR	β2-microglobulin	2
kidney	↑	↑	↑	↑	[52]	cell cultures	15	4	qRT-PCR	Ki-67, HPRT1	3
	↔	↔	N/A	N/A	[62]	FFPE	N/A	N/A	(a)	hsa-miR-200b	
	↔	↑	↑	↔	[79]	tissue, serum	30+88	15+59	qRT-PCR	SNORD43	
liver	↑	↔	N/A	N/A	[62]	FFPE	N/A	3	(a)	hsa-miR-200b	
lymphatic system	N/A	N/A	↑	N/A	[80]	fresh, cell lines	20+5+44	5+19	RNA-seq	N/A	

Cancer	hY1	hY3	hY4	hY5	Refs	Sample Type	Sample Number	Control Number	Method	Ref Gene	Notes
lung	↑	↑	↔	↑	[52]	cell cultures	6	4	qRT-PCR	Ki-67, HPRT1	1
	↑	↑	N/A	N/A	[62]	FFPE	6	4	(a)	hsa-miR-200b	1
	N/A	N/A	↑	N/A	[81]	plasma EV, cell cultures	44+31	17	RNA-seq, qRT-PCR	U6 snRNA	
ovary	↑	↔	N/A	N/A	[62]	FFPE	N/A	N/A	(a)	hsa-miR-200b	
pancreas	↑	↑	N/A	N/A	[62]	FFPE	N/A	N/A	(a)	hsa-miR-200b	
prostate	↑	↑	↔	(↑)	[52]	cell cultures	5	4	qRT-PCR	Ki-67, HPRT1	
	↔	↑	N/A	N/A	[62]	FFPE	N/A	N/A	(a)	hsa-miR-200b	
	↓	↓	↓	↓	[82]	FFPE	56	36+28	qRT-PCR	SNORD43, RNU6-2	
skin	↑	(↑)	↑	↑	[83]	MML-1 cells	N/A	N/A	RNA-seq	N/A	1
	↑	↑	↑	N/A	[84]	plasma EV	118	99	RNA-seq, ddPCR	N/A	1
KS	↑	(↑)	↑	↑	[85]	plasma EV	8+28	19	RNA-seq	N/A	1
	↑	N/A	↑	N/A	[86]	plasma EV	N/A	N/A	RNA-Seq	N/A	1

4. Conclusions

The differential expression of Y RNA among different tissues, across different tumors and, sometimes, also between tumor cells and their released EV (Table 2) support their possible use in the identification and characterization of tumors, often without the use of invasive biopsies, but through a simple analysis of bodily fluids. However, this potential diagnostic strength is balanced by the complexity of Y RNA quantification demonstrated by the available literature, where several different approaches have been used to address this topic (Table 2). Further analysis of these elusive molecules in larger cohorts and the use of robust protocols may shed a new light in our understanding of Y RNA function in human cancers.

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