Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL INIST-CNRS

Deep Insight Section

Y RNA in cell cycle progression and cancer

Roberto Piergentili

Department of Biology and Biotecnology - Charles Darwin, Sapienza University of Rome - Istituto Genetica, room 1-07 - P.Le A.Moro 5 00185 Roma, Italy roberto.piergentili@cnr.it

Published in Atlas Database: February 2020
Online updated version : http://AtlasGeneticsOncology.org/Deep/YRNAID20152.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/70820/02-2020-YRNAID20152.pdf
DOI: 10.4267/2042/70820

Abstract

A growing amount of evidence demonstrates the role of non-coding RNAs (ncRNA) in the etiopathogenesis of cancer. ncRNA are the product of the transcription of genes which are not further translated into proteins, thus they exert their functions as they are or more frequently after post-transcriptional modifications. In the last decades, several different classes of ncRNA had been described, both long (lncRNA) and short (sncRNA). The former are molecules usually longer than 200 nucleotides (nt), while the latter usually include species of a few tens of nucleotides in length, although exceptions are present (for example, circRNA span a length of 100-1600nt; snoRNA are 60-300nt). Y RNA belong to the sncRNA family and are in the range of ca. 80-120nt. Here we summarize the current knowledge about Y RNA biology, their role in normal cellular homeostasis, and their expression variations in human cancers.

Keywords
hY1; hY3; hY4; hY5; RNY1; RNY3, RNY4; RNY5; cell cycle; DNA replication; RO60; ribonucleoprotein particle

Discovery, evolutionary conservation and structure

The first discovery of Y RNA (Lerner et al. 1981) has been made by immunopurification with auto-antibodies in patients affected by the autoimmune diseases systemic lupus erythematosus (SLE) and subsequently confirmed in (i) primary Sjogren syndrome, (ii) subacute cutaneous lupus erythematosus, (iii) neonatal lupus erythematosus, (iv) ANA-negative lupus erythematosus, and (v) systemic lupus erythematosus-like disease. These diseases are characterized by having as autoantigen targets, among the others, the soluble ribonucleoproteins (RNP) (also known as SSA or TROVE2 - TROVE domain family, member 2) (Deutscher et al. 1988; Ben-Chetrit et al. 1989) and (small RNA-binding exonuclease protection factor - also known as La) (Chambers et al. 1988). Y RNA are small non-coding RNAs that were originally identified as the RNA component of RO60 and SSB in these patients (Lerner et al. 1981; Hendrick et al. 1981). Y RNA, like other small RNAs, are transcribed by RNA Polymerase III (Pol III) (Hendrick et al. 1981; Wolin and Steitz 1983). After transcription, they may either remain inside the nucleus or be exported in the cytoplasm (Kowalski and Krude 2015). They were originally termed as 'Y' RNA to distinguish their cytoplasmic localization from that of the nuclear 'U' RNA (Lerner et al. 1981). There are four known Y RNA members in humans, named hY1 (length: 112 nucleotides, nt), hY3 (101nt), hY4 (93nt) and hY5 (83nt) RNA; the presence of hY2 RNA was later confuted, as it was found that it is a degradation product of hY1. According to ENSEMBL 75, there are also an additional 52 transcripts which are pseudogenes based on the 4 human Y RNA, and a further 966 hYRNA pseudogenes (Perreault et al. 2005), with 878 predicted transcripts, that make up the Y RNA category. In the most common use, hY1-5 are the names of the RNAs, while the HGNC approved gene symbol for the four genes are RNY1-5, respectively (i.e. , , and).

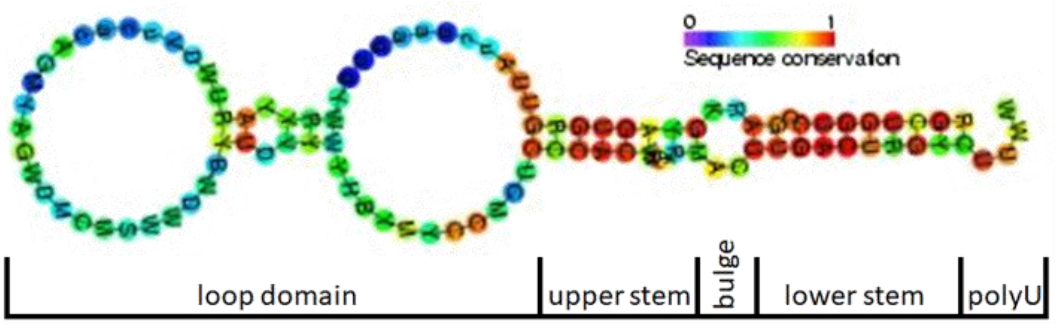

Figure 1: structure of a generic human Y RNA. For the structure of specific genes, please see for example (Köhn et al. 2013); note that the loop domain is the less conserved both in length and structure, among all studied organisms and among the four human RNAs. Image taken from the Rfam database release 9.1 (http://rfam.xfam.org/family/RF00019) and partially modified (picture rotation; indication of domains). Nucleotide coloring indicates sequence conservation between the members of this family.

Y RNA have two recognized functions: repressors of RO60 and other Ro proteins, and initiation factors for DNA replication (Christov et al. 2006; Zhang et al. 2011; Hall et al. 2013). Y RNA are conserved molecules, and confirmed (true Y RNA) or putative (stem-bulge RNAs, sbRNA (Boria et al. 2010)) members of this family are found in mammals, birds, amphibians, fishes, worms, insects, tunicates and even bacteria (Mosig et al. 2007; Perreault et al. 2007; Boria et al. 2010; Duarte Junior et al. 2015, 2019). However, in some lower organisms such as Caenorhabditis elegans (CeY RNA), Branchiostoma floridae (BfY RNA) and Deinococcus radiodurans (DrY RNA) the sequence similarity to vertebrate Y RNA is only partial and does not include the upper stem domain (Gardiner et al. 2009); moreover, their function is not essential in them, since mutant organisms with missing Y RNA are viable. To date, only plants and fungi do not have any candidate Y RNA or sbRNA, thus the evolution of these molecules is still a debated topic in eukaryotes.

The stem-loop organization of Y RNA is conserved as well, and it is schematically reported in Figure 1. Four specific regions can be identified. (i) A poly-uridine tail that is important for SSB binding and for Y RNA stabilization (target of exonucleases); moreover, some authors suggest that, at least hY1 and hY3, potentially contain a variety of 3' ends, with the most abundant species being at positions -5 and -4 relative to the previously mapped 3' ends (Shukla and Parker 2017). (ii) A lower stem domain, which is the binding site of RO60 and is important for nuclear export; this region is frequently flanked by a bulged region that is essential for RO60 binding and separates the lower stem from (iii) an upper stem domain, which is important for the initiation of DNA replication. Finally, (iv) a loop domain, which is the most variable portion of the Y RNA. In particular, the loop domain length and sequence are the most discriminating parameters among the four human Y RNA, the longest loop being that of hY1 (65 nt) and the shortest that of hY5 (31 nt). Also the three-dimensional folded structure of the loops differ significantly among the four hY RNA: it is likely very flexible (Teunissen 2000) and fulfills different tasks such as modulation of chromatin association, protein binding site (such as those reported in Table 1) (Fabini et al. 2001; Fouraux et al. 2002; Belisova et al. 2005; Hogg and Collins 2007; Gallois-Montbrun et al. 2008; Sim et al. 2012; Köhn et al. 2013, 2015; Shukla and Parker 2017; Donovan et al. 2017) and site of cleavage for the formation of YsRNA (Y RNA-derived small RNAs, stretches of 22-36 nucleotides that are produced in apoptotic cells - see the specific section below) (van Gelder et al. 1994; Teunissen 2000; Kowalski and Krude 2015). It is expected that Y RNA contemporarily bind at least two proteins, one of which is a core protein bound on the stem domain (such as RO60) and another on the loop domain; indeed, experiments using gel filtration show that Y RNP range in size from 150 to 550 kDa (see (Köhn et al. 2013) and references therein). All human Y RNA genes map inside the region 7q36.1 (Maraia et al. 1994; Maraia 1996) and, in particular, RNY3 is on the opposing DNA strand from the gene RNY1 (Wolin and Steitz 1983); interestingly, despite their high homology, these two RNAs do not cross-hybridize (Wolin and Steitz 1983). This clustering of Y RNA coding genes on chromosomes has been described also in other vertebrates (O'Brien et al. 1993; Farris et al. 1996; Mosig et al. 2007).

Role of Y RNA in RO60 function

Ro ribonucleoproteins (Ro RNP) are implicated in RNA processing and quality control (Hogg and Collins 2007; Sim and Wolin 2011), as well as in intracellular transport, bringing other Y RNA binding proteins to their specific targets (Belisova et al. 2005). It has been recently proposed that an evolutionarily conserved function of non-coding RNAs (ncRNA), including Y RNA, might be the assembly and function of RNP complexes; in this case, these molecules could act as scaffolding factors necessary to form functional RNP (Täuber et al. 2019).

Protein (HGNC)	Synonyms	Interacting Y RNA	Domain involved	Function
	CEM15	1, 3, 4, 5	unknown	unknown
	NEB1	1, 3	loop	histone pre-mRNA processing
	EXOSC11	(1), (3)	polyU tail	Y RNA stabilization
	DIS3L1	1, 3	polyU tail	Y RNA degradation and turnover
	PMSCL2	1, 3, 4, 5	polyU tail	Y RNA trimming, stabilization
	HNRPK	1, 3	loop	unknown
	C20ORF183	(1), 3	loop	nuclear Export of RO60 and Y3
	nucleolin, C23	1, 3	loop	unknown
	DAN	1, 3, 4, 5	polyU tail	Y RNA trimming, stabilization
	hnRNP I, PTB	1, 3	loop	unknown
	RoBP1, FIR	(1), (3), 5	unknown	unknown
	PRCA1, RNS4	1, (3), 4, 5	loop	cell cycle arrest and apoptosis
	La, LARP3	1, 3, 4, 5	polyU tail	nuclear localization, protection of Y RNA 3' ends
	PAPD5	1, 3, 4, 5	polyU tail	Y RNA oligoadenylation, degradation
	PCH7	1, (3)	polyU tail	Y RNA degradation and turnover
	TROVE2, Ro60, SSA	1, 3, 4, 5	lower stem	stabilization, nuclear export, RNA quality control

Table 1 - Y RNA binding proteins. Numbers inside parentheses indicate unconfirmed data or minor effects. Protein names (column 1) are those approved by the HUGO (Human Genome Organisation) Gene Nomenclature Committee (HGNC). Proteins are listed in alphabetical order according to data in column 1.

RO60 is a 60kDa ring-shaped RNA-binding protein (Stein et al. 2005) important in the response to environmental stress, such as exposure to UV radiation or heat, in both animal cells and bacteria. It is highly conserved (Sim and Wolin 2011; Wolin et al. 2013), able to bind aberrant non-coding RNAs such as mis-folded 5S rRNA or U2 snRNA (O'Brien and Wolin 1994; Chen et al. 2003) and possibly acting as a cellular stress sensors (reviewed in (Kowalski and Krude 2015; Boccitto and Wolin 2019)).

Structural and biochemical studies have shown that the binding affinity of Y RNA for RO60 is higher than that of mis-folded RNA, suggesting that Y RNA might act as a RO60 repressor (Stein et al. 2005; Fuchs et al. 2006), although some evidence support the hypothesis that these molecules (or, at least, hY5) might also enhance the recognition of mis-folded ncRNA (Hogg and Collins 2007).

It has been suggested that the interaction of Y RNA with nucleolin (NCL), polypyrimidine tract-binding proteins (PTB) and Z-DNA binding protein 1 (ZBP1) (Köhn et al. 2013) might modulate the subcellular localisation of RO60 (Sim and Wolin 2011).

Indeed, RO60 can move between nucleus and cytoplasm, in a Y RNA-dependent way (Sim et al. 2009; Sim and Wolin 2011) and, in turn, RO60 protects them from degradation and allows their accumulation in several species (Chen and Wolin 2004). Consequently, some authors suggest a model where Y RNA and bound RO60 can dissociate under certain conditions, so that RO60 can act in cellular recovery by salvaging mis-folded RNAs. In this context, it is possible to hypothesize that other RNA-binding proteins could complex Y RNA in a similar fashion, to fulfill additional tasks, such as mRNA regulation (Köhn et al. 2013).

Role of Y RNA in DNA replication

Y RNA functions during DNA replication seem quite distinct from those related to RO60 functions (Langley et al. 2010). Indeed, Langley and collaborators showed that immunodepletion of RO60 and SSB RNP from human cytosolic extracts does not inhibit DNA replication in human cell nuclei (Langley et al. 2010). Similarly, deletion of RO60 and SSB binding sites on the lower stem domain of vertebrate Y RNA does not inhibit the DNA replication activity of the mutant Y RNA (Christov et al. 2006; Gardiner et al. 2009) indicating that the role of Y RNA in DNA replication is uncoupled from Ro RNP binding. Instead, RNA interference (RNAi)-mediated depletion of either hY1, hY3, or hY4 RNA in cell cultures eliminates or reduces DNA replication in these cells (Christov et al. 2006, 2008; Krude et al. 2009; Collart et al. 2011), and DNA replication is restored back by artificial reintroduction of any of them; the only exception being for hY5, which is consequently thought to be refractory to RNAi. Similarly, functional inactivation of Y RNA (sbRNA in worms (Boria et al. 2010)) via microinjection of antisense morpholino oligonucleotides (MOs) in embryos, is sufficient to impair DNA replication in Xenopus laevis, Danio rerio and Caenorhabditis elegans, where this treatment impairs DNA replication and causes cell cycle arrest and embryonic lethality (Collart et al. 2011; Kowalski et al. 2015). In this context, it is not surprising that Y RNA are over-

expressed in some human solid tumors (Christov et al. 2008) (see also the specific sections below).
Y RNA function in DNA replication is fulfilled by the upper stem domain (Gardiner et al. 2009; Wang et al. 2014; Kowalski et al. 2015) which is important also for the recognition of specific chromatin domains and DNA replication initiation proteins (Zhang et al. 2011; Collart et al. 2011). Interestingly, however, this interaction does not include replication fork proteins (Zhang et al. 2011) suggesting that the interaction is restricted to the DNA replication initiation complex (Kheir and Krude 2017). Indeed, Y RNA localize inside nuclei in G1, before DNA replication, and they are displaced upon DNA replication initiation (Zhang et al. 2011). To date, there is no certainty about their role in this process, and only hypotheses may be drawn (Kowalski and Krude 2015). Interestingly, although all Y RNA localize inside the nucleus, only hY1, hY3 and hY4 co-localize with each other on early-replicating euchromatin; instead, hY5 is prevalently localized in nucleoli (Zhang et al. 2011). This different behavior of hY5 is recurrent also in some of the tumors described below. This localization is controlled, in all Y RNA, by the loop domain. Differently, the nuclear export of Y RNA is controlled by the lower stem domain and is dependent on the small GTPase Ran (Rutjes et al. 2001).

Y RNA derivatives

Intracellular localization of Y RNA is dependent on cellular stress (Chen and Wolin 2004); specifically, both RO60 and Y RNA are up-regulated and accumulate inside the nucleus following UV irradiation, starvation, heat stress, γ-irradiation, and desiccation (Sim et al. 2009, 2012; Boccitto and Wolin 2019). However, it has been noted that this phenomenon could also be just a byproduct of the inhibition of RanGTP gradient under stress conditions (Köhn et al. 2013). The RNA component of Ro RNP is partly degraded during apoptosis and generates the so called Y RNA-derived small RNAs (YsRNA), such as miR-1975 and miR-1979. However, is not required for the production of these YsRNA (Nicolas et al. 2012; Langenberger et al. 2013) and indeed, after their identification as byproducts of Y RNA degradation, miR-1975 and miR-1979 were removed from miRBase (http://www.mirbase.org/), the primary database for micro RNAs. These shorter fragments are specifically, abundantly and rapidly generated from all four Y RNA during apoptosis, in a caspase-dependent manner (Rutjes et al. 1999), but it is not yet clear if they have any causal role in these phenomena, or are just a product of apoptosis-mediated cellular changes (Rutjes et al. 1999; Meiri et al. 2010). These Y RNA degradation products remain bound to the RO60 protein and, in part, also to the SSB protein (Rutjes et al. 1999). This suggests that the rapid degradation of these molecules might occur at an early step during the systemic deactivation of the dying cell. Despite the role of these molecules is currently unknown, YsRNA have been identified both in healthy tissues (Nicolas et al. 2012; Yamazaki et al. 2014) and in precursor B cells of acute lymphoblastic leukaemia patients (Schotte et al. 2009) as well as in solid tumors (Meiri et al. 2010); for these reasons, they are under investigation as possible biomarkers in cancer and/or other conditions (Meiri et al. 2010; Nicolas et al. 2012; Dhahbi 2014; Vojtech et al. 2014; Ikoma et al. 2018). Indeed, these fragments - especially those derived from hY4 - are particularly abundant in plasma, serum (Dhahbi et al. 2013; Yeri et al. 2017; Umu et al. 2018) and other biofluids (Vojtech et al. 2014; Godoy et al. 2018), where they circulate as part of a complex with a mass between 100 and 300 kDa but not included in exosomes or microvesicles (Dhahbi et al. 2013). Some authors suggest that, beyond what described before, Y RNA and their derivatives might also fulfill a signaling (Dhahbi et al. 2013) or a gene regulation (Van Balkom et al. 2015) function; actually, a role in gene regulation has also been described for the maturation of histone mRNA through hY3 and its derivative, hY3** (a smaller 60nt-long Y RNA) (Köhn et al. 2015; Köhn and Hüttelmaier 2016). Noteworthy, these fragments are not confined inside cells, but can be found also in blood circulation, with a specific enrichment of hY4 derivatives (Dhahbi et al. 2013), and inside extracellular vesicles (EV) for hY5 derivatives (Chakrabortty et al. 2015). More detailed descriptions of these fragments can be found in the following specific sections on human tumors.

Y RNA and human cancer

The role of Y RNA in DNA replication (and, consequently, in the regulation of cell cycle) sets the basis to hypothesize their possible role in cancer etiology. Indeed, there are reports showing that Y RNA are significantly up-regulated (4- to 13-fold for hY4 and hY1, respectively) in human cancer tissues (carcinomas and adenocarcinomas of the lung, kidney, bladder, prostate, , and) compared to normal tissues (Christov et al. 2008), and are also required for the proliferation of cancer cells, since their RNA interference (RNAi)-mediated degradation results in a significant cytostatic (but not cytotoxic) effect in cell lines, probably by inducing a significant inhibition of chromosomal DNA replication in cultured human cells (Christov et al. 2008). Interestingly, hY5 seems under control of an independent mechanism since its cellular amount is frequently different from that of the other three Y RNA, although over-expressed as well in at least some tumors (Christov et al. 2008).
As said, it has been reported in 2008 that hY1 and hY3 are highly over-expressed in (Christov et al.

2008). Instead, in 2017 Tolkach and collaborators reported that all Y RNA are down-regulated in BC (Tolkach et al. 2017), with the low abundance of hY1, hY3 and hY4 typical of muscle-invasive bladder cancer (MIBC) compared to non-muscle-invasive bladder cancer (NMIBC) and that low amount of hY1, hY3 and hY4 also correlates with lymph node metastases and advanced grade. No correlation was found with age or gender. Further studies are needed to assess with certainty if, in bladder cancer, Y RNA are indeed down-regulated.

Dhabi and collaborators detected inside the serum and plasma the presence of RNA fragments, including YsRNA (Dhahbi et al. 2013). Using this approach, they later verified if their abundance can be related to (Dhahbi et al. 2014). They found a major population of 30-33nt long fragments mostly derived from Y RNA 5' end, and a minor population of 25-29nt long fragments almost exclusively derived from their 3' end. Interestingly, some fragments increase while other decrease their amount, in a specific pattern. This result is in good agreement with a previous study describing an enrichment of 3'-end fragments - derived from human hY5 - detected in MCF 7 (mammary adenocarcinoma) cells (Nicolas et al. 2012). More recently (Guo et al. 2018), another study on (TNBC) showed similar results for RNY1, RNY5 and, above all, RNY4 expression, while another group (Tosar et al. 2015) found fragments of 31-33nt greatly and significantly enriched in the extracellular space of cultured breast cancer cells, suggesting that this fragments are specifically excreted by these cells.

As for (the most common tumor of the brain), to date, only one manuscript was published, dealing with Y RNA (Wei et al. 2017). In glioma cells, all extracellular fractions, especially non-vesicular RNPs, are highly enriched in specific Y RNA fragments ca. 32nt in length, especially belonging to hY1, hY4 and hY5.

Martinez and collaborators reported that in (HNSCC), Y RNA-derived small RNAs are significantly deregulated in the sera of patients (Martinez et al. 2015). These patients have, among the others, an enrichment of 30-33nt-long fragments deriving from Y RNA degradation, and these fragments proportion either increases or decreases significantly for specific RNA species, suggesting a remodeling of the small non-coding RNA networks in HNSCC. Recently, Dhahbi and coworkers analyzed Y RNA fragments in (OSCC), a form of HNSCC and the most common type of head and neck cancer (Dhahbi et al. 2019). Also in this case, the authors found that multiple 5' Y RNA fragments displayed significant differential expression levels in circulation and/or tumor tissue, as compared to their control counterparts.

Bernatsky and collaborators demonstrated that many cancer types, and hematologic malignancies in particular, are substantially increased in patients affected by systemic lupus erythematosus (Bernatsky et al. 2013). Chakrabortty and coworkers (Chakrabortty et al. 2015) demonstrated that primary cell cultures are sensitive to apoptosis induction either by treatment with K562 cells EV, or by the ectopic over-expression of 31nt-processed fragments of hY5. Instead, this treatment is inefficient on cancer cells, suggesting that this might be a way for cancer cells to create a favorable microenvironment (Chakrabortty et al. 2015). More recently, a study on (CLL) (Haderk et al. 2017) revealed that (i) hY4 is highly enriched in exosomes; (ii) it is sufficient to activate cytokine release in monocytes and trigger in these cells the activation of Toll-like receptor 7 ( ), (iii) the pharmacologic inhibition of endosomal TLR attenuates CLL development in vivo; (iv) in CLL patients, the PD-L1 pathway is activated, allowing the tumor cells to escape the immune response.

It has been shown (Nientiedt et al. 2018) that in (ccRCC) patients, the expression of RNY3 and RNY4 is significantly increased and that the expression levels of RNY4 alone is inversely correlated with ccRCC stage and the presence of lymph node metastases.

In (ADC) and (SQCC) patients, Li and collaborators (Li et al. 2018) showed that 5' hY4-derived fragments have a significantly higher expression in plasma EV compared to controls, while they are down-regulated inside cancer; moreover, over-expressing hY4 inhibits the proliferation of lung cancer cell line A549, suggesting for hY4 fragments a role of tumor suppressors in this pathology. These results show evident differences from those reported before (Christov et al. 2008), thus a further validation of either data is advisable.

The analysis of ncRNA content of EV of the cell line MML-1 (Lunavat et al. 2015) demonstrated that there is a specific signature of Y RNA present in EV, with hY1, hY4 and hY5 significantly more abundant in EV than inside melanoma cells, while hY3 amount is similar inside EV and MML-1 cells. These data were partly validated by the recent work of Sole and collaborators (Sole et al. 2019) who found an enrichment of hY4 and, to a lesser extent, of hY1 and hY3, but only in patients with stage 0 disease.

Quantification of Y RNA in samples (Tolkach et al. 2018) revealed a down-regulation of these molecules two to fourfold, compared to normal tissue. The authors also found that higher RNY5 expression is associated with poor prognosis, measured as biochemical recurrence-free survival. Interestingly, these results are in contrast with those found for bladder cancer (see above), further supporting the use of Y RNA as a valid biomarker for cancer identification. Also for prostate cancer, these data contrast with those reported before (Christov et al. 2008) thus a more in depth analysis is required to validate either results.

References

Belisova A, Semrad K, Mayer O, Kocian G, Waigmann E, Schroeder R, Steiner G. RNA chaperone activity of protein components of human Ro RNPs. RNA. 2005 Jul;11(7):1084-94

Ben-Chetrit E, Gandy BJ, Tan EM, Sullivan KF. Isolation and characterization of a cDNA clone encoding the 60-kD component of the human SS-A/Ro ribonucleoprotein autoantigen. J Clin Invest. 1989 Apr;83(4):1284-92

Bernatsky S, Ramsey-Goldman R, Labrecque J, Joseph L, Boivin JF, Petri M, Zoma A, Manzi S, Urowitz MB, Gladman D, Fortin PR, Ginzler E, Yelin E, Bae SC, Wallace DJ, Edworthy S, Jacobsen S, Gordon C, Dooley MA, Peschken CA, Hanly JG, Alarcón GS, Nived O, Ruiz-Irastorza G, Isenberg D, Rahman A, Witte T, Aranow C, Kamen DL, Steinsson K, Askanase A, Barr S, Criswell LA, Sturfelt G, Patel NM, Senécal JL, Zummer M, Pope JE, Ensworth S, El-Gabalawy H, McCarthy T, Dreyer L, Sibley J, St Pierre Y, Clarke AE. Cancer risk in systemic lupus: an updated international multi-centre cohort study. J Autoimmun. 2013 May;42:130-5

Boccitto M, Wolin SL. Ro60 and Y RNAs: structure, functions, and roles in autoimmunity. Crit Rev Biochem Mol Biol. 2019 Apr;54(2):133-152

Boria I, Gruber AR, Tanzer A, Bernhart SH, Lorenz R, Mueller MM, Hofacker IL, Stadler PF. Nematode sbRNAs: homologs of vertebrate Y RNAs J Mol Evol 2010 Apr;70(4):346-58

Chakrabortty SK, Prakash A, Nechooshtan G, Hearn S, Gingeras TR. Extracellular vesicle-mediated transfer of processed and functional RNY5 RNA RNA 2015 Nov;21(11):1966-79

Chambers JC, Kenan D, Martin BJ, Keene JD. Genomic structure and amino acid sequence domains of the human La autoantigen J Biol Chem 1988 Dec 5;263(34):18043-51

Chen X, Smith JD, Shi H, Yang DD, Flavell RA, Wolin SL. The Ro autoantigen binds misfolded U2 small nuclear RNAs and assists mammalian cell survival after UV irradiation Curr Biol 2003 Dec 16;13(24):2206-11

Chen X, Wolin SL. The Ro 60 kDa autoantigen: insights into cellular function and role in autoimmunity J Mol Med (Berl) 2004 Apr;82(4):232-9

Christov CP, Trivier E, Krude T. Noncoding human Y RNAs are overexpressed in tumours and required for cell proliferation Br J Cancer 2008 Mar 11;98(5):981-8

Collart C, Christov CP, Smith JC, Krude T. The midblastula transition defines the onset of Y RNA-dependent DNA replication in Xenopus laevis Mol Cell Biol 2011 Sep;31(18):3857-70

Deutscher SL, Harley JB, Keene JD. Molecular analysis of the 60-kDa human Ro ribonucleoprotein Proc Natl Acad Sci U S A 1988 Dec;85(24):9479-83

Dhahbi J, Nunez Lopez YO, Schneider A, Victoria B, Saccon T, Bharat K, McClatchey T, Atamna H, Scierski W, Golusinski P, Golusinski W, Masternak MM. Profiling of tRNA Halves and YRNA Fragments in Serum and Tissue From Oral Squamous Cell Carcinoma Patients Identify Key Role of 5' tRNA-Val-CAC-2-1 Half Front Oncol 2019 Sep 26;9:959

Dhahbi JM. Circulating small noncoding RNAs as biomarkers of aging Ageing Res Rev 2014 Sep;17:86-98

Dhahbi JM, Spindler SR, Atamna H, Boffelli D, Martin DI. Deep Sequencing of Serum Small RNAs Identifies Patterns of 5' tRNA Half and YRNA Fragment Expression Associated with Breast Cancer Biomark Cancer 2014 Dec 8;6:37-47

Donovan J, Rath S, Kolet-Mandrikov D, Korennykh A. Rapid RNase L-driven arrest of protein synthesis in the dsRNA response without degradation of translation machinery RNA 2017 Nov;23(11):1660-1671

Duarte Junior FF, de Lima Neto QA, Rando Fdos S, de Freitas DV, Pattaro Júnior JR, Polizelli LG, Munhoz RE, Seixas FA, Fernandez MA. Identification and molecular structure analysis of a new noncoding RNA, a sbRNA homolog, in the silkworm Bombyx mori genome Mol Biosyst 2015 Mar;11(3):801-8

Fabini G, Raijmakers R, Hayer S, Fouraux MA, Pruijn GJ, Steiner G. The heterogeneous nuclear ribonucleoproteins I and K interact with a subset of the ro ribonucleoprotein-associated Y RNAs in vitro and in vivo J Biol Chem 2001 Jun 8;276(23):20711-8

Farris AD, Gross JK, Hanas JS, Harley JB. Genes for murine Y1 and Y3 Ro RNAs have class 3 RNA polymerase III promoter structures and are unlinked on mouse chromosome 6 Gene 1996 Sep 26;174(1):35-42

Fouraux MA, Bouvet P, Verkaart S, van Venrooij WJ, Pruijn GJ. Nucleolin associates with a subset of the human Ro ribonucleoprotein complexes J Mol Biol 2002 Jul 12;320(3):475-88

Fuchs G, Stein AJ, Fu C, Reinisch KM, Wolin SL. Structural and biochemical basis for misfolded RNA recognition by the Ro autoantigen Nat Struct Mol Biol 2006 Nov;13(11):1002-9

Gallois-Montbrun S, Holmes RK, Swanson CM, Fernández-Ocaña M, Byers HL, Ward MA, Malim MH. Comparison of cellular ribonucleoprotein complexes associated with the APOBEC3F and APOBEC3G antiviral proteins J Virol 2008 Jun;82(11):5636-42

Gardiner TJ, Christov CP, Langley AR, Krude T. A conserved motif of vertebrate Y RNAs essential for chromosomal DNA replication RNA 2009 Jul;15(7):1375-85

Godoy PM, Bhakta NR, Barczak AJ, Cakmak H, Fisher S, MacKenzie TC, Patel T, Price RW, Smith JF, Woodruff PG, Erle DJ. Large Differences in Small RNA Composition Between Human Biofluids Cell Rep 2018 Oct 30;25(5):1346-1358

Guo Y, Yu H, Wang J, Sheng Q, Zhao S, Zhao YY, Lehmann BD. The Landscape of Small Non-Coding RNAs in Triple-Negative Breast Cancer Genes (Basel) 2018 Jan 10;9(1)

Haderk F, Schulz R, Iskar M, Cid LL, Worst T, Willmund KV, Schulz A, Warnken U, Seiler J, Benner A, Nessling M, Zenz T, Göbel M, Dürig J, Diederichs S, Paggetti J, Moussay E, Stilgenbauer S, Zapatka M, Lichter P, Seiffert M. Tumor-derived exosomes modulate PD-L1 expression

in monocytes Sci Immunol 2017 Jul 28;2(13)

Hall AE, Turnbull C, Dalmay T. Y RNAs: recent developments Biomol Concepts 2013 Apr;4(2):103-10

Hendrick JP, Wolin SL, Rinke J, Lerner MR, Steitz JA. Ro small cytoplasmic ribonucleoproteins are a subclass of La ribonucleoproteins: further characterization of the Ro and La small ribonucleoproteins from uninfected mammalian cells Mol Cell Biol 1981 Dec;1(12):1138-49

Hogg JR, Collins K. Human Y5 RNA specializes a Ro ribonucleoprotein for 5S ribosomal RNA quality control Genes Dev 2007 Dec 1;21(23):3067-72

Ikoma M, Gantt S, Casper C, Ogata Y, Zhang Q, Basom R, Dyen MR, Rose TM, Barcy S. KSHV oral shedding and plasma viremia result in significant changes in the extracellular tumorigenic miRNA expression profile in individuals infected with the malaria parasite PLoS One 2018 Feb 9;13(2):e0192659

Köhn M, Pazaitis N, Hüttelmaier S. Why YRNAs? About Versatile RNAs and Their Functions Biomolecules 2013 Feb 8;3(1):143-56

Kheir E, Krude T. Non-coding Y RNAs associate with early replicating euchromatin in concordance with the origin recognition complex J Cell Sci 2017 Apr 1;130(7):1239-1250

Kowalski MP, Krude T. Functional roles of non-coding Y RNAs Int J Biochem Cell Biol 2015 Sep;66:20-9

Krude T, Christov CP, Hyrien O, Marheineke K. Y RNA functions at the initiation step of mammalian chromosomal DNA replication J Cell Sci 2009 Aug 15;122(Pt 16):2836-45

Langenberger D, akir MV, Hoffmann S, Stadler PF. Dicer-processed small RNAs: rules and exceptions J Exp Zool B Mol Dev Evol 2013 Jan;320(1):35-46

Langley AR, Chambers H, Christov CP, Krude T. Ribonucleoprotein particles containing non-coding Y RNAs, Ro60, La and nucleolin are not required for Y RNA function in DNA replication PLoS One 2010 Oct 27;5(10):e13673

Lerner MR, Boyle JA, Hardin JA, Steitz JA. Two novel classes of small ribonucleoproteins detected by antibodies associated with lupus erythematosus Science 1981 Jan 23;211(4480):400-2

Li C, Qin F, Hu F, Xu H, Sun G, Han G, Wang T, Guo M. Characterization and selective incorporation of small non-coding RNAs in non-small cell lung cancer extracellular vesicles Cell Biosci 2018 Jan 10;8:2

Lunavat TR, Cheng L, Kim DK, Bhadury J, Jang SC, Lässer C, Sharples RA, López MD, Nilsson J, Gho YS, Hill AF, Lötvall J. Small RNA deep sequencing discriminates subsets of extracellular vesicles released by melanoma cells--Evidence of unique microRNA cargos RNA Biol 2015;12(8):810-23

Maraia R, Sakulich AL, Brinkmann E, Green ED. Gene encoding human Ro-associated autoantigen Y5 RNA Nucleic Acids Res 1996 Sep 15;24(18):3552-9

Maraia RJ, Sasaki-Tozawa N, Driscoll CT, Green ED, Darlington GJ. The human Y4 small cytoplasmic RNA gene is controlled by upstream elements and resides on chromosome 7 with all other hY scRNA genes Nucleic Acids Res 1994 Aug 11;22(15):3045-52

Meiri E, Levy A, Benjamin H, Ben-David M, Cohen L, Dov A, Dromi N, Elyakim E, Yerushalmi N, Zion O, Lithwick-Yanai G, Sitbon E. Discovery of microRNAs and other small RNAs in solid tumors Nucleic Acids Res 2010 Oct;38(18):6234-46

Mosig A, Guofeng M, Stadler BM, Stadler PF. Evolution of the vertebrate Y RNA cluster Theory Biosci 2007 Aug;126(1):9-14

Nicolas FE, Hall AE, Csorba T, Turnbull C, Dalmay T. Biogenesis of Y RNA-derived small RNAs is independent of the microRNA pathway FEBS Lett 2012 Apr 24;586(8):1226-30

Nientiedt M, Schmidt D, Kristiansen G, Müller SC, Ellinger J. YRNA Expression Profiles are Altered in Clear Cell Renal Cell Carcinoma Eur Urol Focus 2018 Mar;4(2):260-266

O'Brien CA, Wolin SL. A possible role for the 60-kD Ro autoantigen in a discard pathway for defective 5S rRNA precursors Genes Dev 1994 Dec 1;8(23):2891-903

Perreault J, Perreault JP, Boire G. Ro-associated Y RNAs in metazoans: evolution and diversification Mol Biol Evol 2007 Aug;24(8):1678-89

Rutjes SA, Lund E, van der Heijden A, Grimm C, van Venrooij WJ, Pruijn GJ. Identification of a novel cis-acting RNA element involved in nuclear export of hY RNAs RNA 2001 May;7(5):741-52

Rutjes SA, van der Heijden A, Utz PJ, van Venrooij WJ, Pruijn GJ. Rapid nucleolytic degradation of the small cytoplasmic Y RNAs during apoptosis J Biol Chem 1999 Aug 27;274(35):24799-807

Schotte D, Chau JC, Sylvester G, Liu G, Chen C, van der Velden VH, Broekhuis MJ, Peters TC, Pieters R, den Boer ML. Identification of new microRNA genes and aberrant microRNA profiles in childhood acute lymphoblastic leukemia Leukemia 2009 Feb;23(2):313-22

Shukla S, Parker R. PARN Modulates Y RNA Stability and Its 3'-End Formation Mol Cell Biol 2017 Sep 26;37(20)

Sim S, Weinberg DE, Fuchs G, Choi K, Chung J, Wolin SL. The subcellular distribution of an RNA quality control protein, the Ro autoantigen, is regulated by noncoding Y RNA binding Mol Biol Cell 2009 Mar;20(5):1555-64

Sim S, Wolin SL. Emerging roles for the Ro 60-kDa autoantigen in noncoding RNA metabolism Wiley Interdiscip Rev RNA 2011 Sep-Oct;2(5):686-99

Sim S, Yao J, Weinberg DE, Niessen S, Yates JR 3rd, Wolin SL. The zipcode-binding protein ZBP1 influences the subcellular location of the Ro 60-kDa autoantigen and the noncoding Y3 RNA RNA 2012 Jan;18(1):100-10

Sole C, Arnaiz E, Manterola L, Otaegui D, Lawrie CH. The circulating transcriptome as a source of cancer liquid biopsy biomarkers Semin Cancer Biol 2019 Oct;58:100-108

Stein AJ, Fuchs G, Fu C, Wolin SL, Reinisch KM. Structural insights into RNA quality control: the Ro autoantigen binds misfolded RNAs via its central cavity Cell 2005 May 20;121(4):529-539

Täuber H, Hüttelmaier S, Köhn M. POLIII-derived non-coding RNAs acting as scaffolds and decoys J Mol Cell Biol 2019 Oct 25;11(10):880-885

Teunissen SW, Kruithof MJ, Farris AD, Harley JB, Venrooij WJ, Pruijn GJ. Conserved features of Y RNAs: a comparison of experimentally derived secondary structures Nucleic Acids Res 2000 Jan 15;28(2):610-9

Tolkach Y, Niehoff EM, Stahl AF, Zhao C, Kristiansen G, Müller SC, Ellinger J. YRNA expression in prostate cancer patients: diagnostic and prognostic implications World J Urol 2018 Jul;36(7):1073-1078

Tolkach Y, Stahl AF, Niehoff EM, Zhao C, Kristiansen G, Müller SC, Ellinger J. YRNA expression predicts survival in bladder cancer patients BMC Cancer 2017 Nov 10;17(1):749

Tosar JP, Gámbaro F, Sanguinetti J, Bonilla B, Witwer KW, Cayota A. Assessment of small RNA sorting into different extracellular fractions revealed by high-throughput sequencing of breast cell lines Nucleic Acids Res 2015 Jun 23;43(11):5601-16

Umu SU, Langseth H, Bucher-Johannessen C, Fromm B, Keller A, Meese E, Lauritzen M, Leithaug M, Lyle R, Rounge TB. A comprehensive profile of circulating RNAs in human serum RNA Biol 2018 Feb 1;15(2):242-250

Victoria Martinez B, Dhahbi JM, Nunez Lopez YO, Lamperska K, Golusinski P, Luczewski L, Kolenda T, Atamna H, Spindler SR, Golusinski W, Masternak MM. Circulating small non-coding RNA signature in head and neck squamous cell carcinoma Oncotarget 2015 Aug 7;6(22):19246-63

Vojtech L, Woo S, Hughes S, Levy C, Ballweber L, Sauteraud RP, Strobl J, Westerberg K, Gottardo R, Tewari M, Hladik F. Exosomes in human semen carry a distinctive repertoire of small non-coding RNAs with potential regulatory functions Nucleic Acids Res 2014 Jun;42(11):7290-304

Wang I, Kowalski MP, Langley AR, Rodriguez R, Balasubramanian S, Hsu ST, Krude T. Nucleotide contributions to the structural integrity and DNA replication initiation activity of noncoding y RNA Biochemistry 2014 Sep 23;53(37):5848-63

Wei Z, Batagov AO, Schinelli S, Wang J, Wang Y, El Fatimy R, Rabinovsky R, Balaj L, Chen CC, Hochberg F, Carter B, Breakefield XO, Krichevsky AM. Coding and noncoding landscape of extracellular RNA released by human glioma stem cells Nat Commun 2017 Oct 26;8(1):1145

Wolin SL, Belair C, Boccitto M, Chen X, Sim S, Taylor DW, Wang HW. Non-coding Y RNAs as tethers and gates: Insights from bacteria RNA Biol 2013 Oct;10(10):1602-8

Wolin SL, Steitz JA. Genes for two small cytoplasmic Ro RNAs are adjacent and appear to be single-copy in the human genome Cell 1983 Mar;32(3):735-44

Yamazaki F, Kim HH, Lau P, Hwang CK, Iuvone PM, Klein D, Clokie SJ. pY RNA1-s2: a highly retina-enriched small RNA that selectively binds to Matrin 3 (Matr3) PLoS One 2014 Feb 18;9(2):e88217

Yeri A, Courtright A, Reiman R, Carlson E, Beecroft T, Janss A, Siniard A, Richholt R, Balak C, Rozowsky J, Kitchen R, Hutchins E, Winarta J, McCoy R, Anastasi M, Kim S, Huentelman M, Van Keuren-Jensen K. Total Extracellular Small RNA Profiles from Plasma, Saliva, and Urine of Healthy Subjects Sci Rep 2017 Mar 17;7:44061

Zhang AT, Langley AR, Christov CP, Kheir E, Shafee T, Gardiner TJ, Krude T. Dynamic interaction of Y RNAs with chromatin and initiation proteins during human DNA replication J Cell Sci 2011 Jun 15;124(Pt 12):2058-69

van Balkom BW, Eisele AS, Pegtel DM, Bervoets S, Verhaar MC. Quantitative and qualitative analysis of small RNAs in human endothelial cells and exosomes provides insights into localized RNA processing, degradation and sorting J Extracell Vesicles 2015 May 29;4:26760

van Gelder CW, Thijssen JP, Klaassen EC, Sturchler C, Krol A, van Venrooij WJ, Pruijn GJ. Common structural features of the Ro RNP associated hY1 and hY5 RNAs Nucleic Acids Res 1994 Jul 11;22(13):2498-506

This article should be referenced as such:

Piergentili R. Y RNA in cell cycle progression and cancer. Atlas Genet Cytogenet Oncol Haematol. 2020; 24(10):379-386.