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Post-Transcriptional Control of RNA Expression in Cancer

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Abstract

Approximately 80% of the human genome contains functional DNA, including protein coding genes, non-protein coding regulatory DNA elements and non-coding RNAs (ncRNAs). An altered transcriptional signature is not only a cause, but also a consequence of the characteristics known as the hallmarks of cancer, such as sustained proliferation, replicative immortality, evasion of growth suppression and apoptotic signals, angiogenesis, invasion, metastasis, evasion of immune destruction and metabolic re-wiring. Post-transcriptional events play a major role in determining this signature, which is evidenced by the fact that alternative RNA splicing takes place in more than half of the human genes, and, among protein coding genes, more than 60% contain at least one conserved miRNA-binding site. In this chapter, we will discuss the involvement of post-transcriptional events, such as RNA processing, the action of non-coding RNAs and RNA decay in cancer development, and how their machinery may be used in cancer diagnosis and treatment.

Keywords: post-transcriptional control, splicing, microRNAs, long non-coding RNAs, mRNA decay

1. Introduction

The word cancer defines a group of diverse diseases, which share unique traits. Tumor cells display mechanisms of sustained proliferation, replicative immortality, evasion of growth

suppression and apoptotic signals, angiogenesis, invasion, metastasis, evasion of immune destruction and metabolic re-wiring [1]. These characteristics represent a great challenge to cancer treatment being both a cause and a consequence of an abnormal gene expression profile. Efforts to understand the consequences of these different expression profiles and the mechanisms underlying them contribute to clarify cancer biology and, consequently, to predict response to and optimization of therapeutic approaches [2–4].

There are several layers of gene expression modulation including epigenetics, transcriptional modulation, RNA expression control, translational regulation and post-translational modifications. All these mechanisms work in an orchestrated manner leading to specific expression signatures and phenotypes. In this chapter, we focus on RNA expression control mechanisms, which take place after RNA polymerase recognition of the gene promoter and start of RNA synthesis, discussing their implications to malignant transformation and cancer progression.

2. mRNA processing

RNA processing takes place after the start of transcription, resulting in a mature mRNA which is able to fulfill its function. This process comprises: 5′-Cap addition, splicing and poly(A) addition. RNA splicing is a process in which portions of the pre-RNA, denominated introns, are excised and the remaining portions (exons) are bound to form the mature RNA. Both *cis* and *trans* elements act to recognize exon/intron boundaries and/or to orchestrate the splicing machinery, the spliceosome, a complex of five small nuclear ribonucleoprotein particles (snRNP) and 100–200 non-snRNP proteins which catalyze the splicing reaction [5–7]. Recognition of the intron/exon boundaries is context-dependent; as a result, a single gene can originate several mature RNAs and, therefore, several proteins with independent or even opposite functions. This alternative splicing (AS) occurs by recognition of the alternative donor or acceptor splice sites, exon inclusion or exclusion, intron incorporation or combinatory mechanisms as mutually exclusive exons and so on. AS stands out as a major source for transcripts and proteins variability, occurring in approximately 59% of human genes [8] and almost 95% of the multi-exon genes [9]. Splicing factor genes are commonly mutated in different types of cancer and several splice variants have already been implicated in cancer development [10].

The splicing profile of a certain tissue changes dramatically when compared with malignant cells with their normal counterparts [11–13]. This difference may result from mutations or single-nucleotide polymorphisms (SNPs) on acceptor, donor splice sites, enhancing or silencing sequences which lead to alterations in the exon/intron boundary recognition; or due to deregulated expression or change of function mutation in a *trans* regulator (reviewed in [14, 15]). Serine-rich protein (SRP) and heterologous nuclear ribonuclear particle (hnRNP) are two protein families which are classically involved in splicing modulation by interacting with intronic or exonic enhancer or silencer sequences [16, 17]. The SRSF1 member of the SRP family is one of the most well characterized splice factor, being described as up-regulated in lung [18] and breast cancers [19, 20]. In the breast cancer model, SRSF1 association to

a sequence near to a donor splice site usually promotes exon inclusion, while its association in the vicinities of an acceptor splice site leads to exon skipping or inclusion [20]. Important cancer-related gene transcripts, such as Casp9 [21], CD44 [22] and VEGF [23], are among SRSF1 known targets.

Cell survival outcome is a perfect example of the influence of AS in basic cellular mechanisms, with alternative isoforms of several apoptotic-related gene transcripts displaying opposite roles, when compared to their canonical variant, shifting the cell status from apoptosis-prone to the survival state (reviewed in [24]). Upon an apoptotic stimulus, cytochrome C is released from the mitochondria and forms a complex with Apaf-1. The N-terminal portion of Apaf-1 interacts with the N-terminal pro-domain of pro-caspase-9, leading to Caspase-9 activation, which, in turn, activates the Caspase-3 and -7 effector proteases (reviewed in [25]). Caspase-9, a key player in this process, has an alternative-splicing variant in which exclusion of the exon cassette 3, 4, 5 and 6 leads to a protein isoform which lacks part of its large subunit. This Caspase-9b isoform retains the domain which interacts with Apaf-1, but lacks the Caspase-9 catalytic site, thus acting like a dominant negative and inhibiting the apoptotic pathway [26, 27]. The ratio between these two isoforms modulates the propensity of the cells to respond to death stimuli, altering their chemo-sensitivity and, potentially, the treatment's outcome. Interestingly, while Akt mediates exclusion of the exon cassette via phosphorylation of the RNA splicing factor SRp30a [28]; in this case, SRSF1 interacts with an intronic enhancer site at intron 6 favoring the exon cassette inclusion, which renders the cells more sensitive to chemotherapeutic agents as the combined therapy with daunorubicin and erlotinib [21]. Taking into account that SRSF1 is upregulated in non-small cell lung cancer cells, this case exemplifies the complexity of splicing as an expression regulator and how it can be explored to optimize therapy efficacy.

Another great source of transcripts variability is alternative polyadenylation (APA), since approximately 30% of human mRNAs display alternative polyadenylation sites [29]. Polyadenylation occurs in almost every mammalian transcript, a process in which an endonucleolytic cleavage is catalyzed by polyadenylation machinery proteins, immediately followed by polyadenylation (200–300 nucleotides, on average, in humans) of the 3′-end by poly(A) polymerases (reviewed in [30]). The resulting alternative transcripts will have different sizes, depending on the localization of the alternative poly(A) site, originating alternative 3′-untranslated regions (3′-UTR). Also, more rarely, when polyadenylation occurs inside the open reading frame region, it may originate truncated forms of the translated protein [31]. The 3′-UTR is extremely important to transcripts stability, localization and regulation by *trans* elements (such as miRNAs and RNA binding proteins), topics to be further discussed in this chapter and which have great implications for cancer development.

A shift in the polyadenylation global pattern occurs in tumor cells, with the proximal poly(A) sites being favored, when compared to their normal counterparts [29]. Also, highly proliferative murine T lymphocytes favor shorter 3′-UTRs, which is also observed in colorectal cancer, but only for certain groups of genes, including those involved in cell cycle, nucleic acid-binding and processing factors. It has been proposed that such shortening would restrict miRNA modulation over the transcripts, increasing their expression [32, 33]. Such

a mechanism is observed upon treatment of ER$^+$ breast cancer cells with the proliferation stimulant 17β-estradiol. This treatment leads to APA of the *CD6* transcript, which is essential for the start of DNA replication, originating a shorter 3′-UTR. The generated *CD6* variant is resistant to repression dependent on its 3′-UTR and is more efficiently translated, correlating with a higher rate of BrdU incorporation by the cells [34].

Curiously, mammalian RNAs can also be post-transcriptionally modified through a process called RNA editing. Well-known cases are the RNA editing enzymes adenosine and cytidine deaminases, which catalyze the conversion of adenine into inosine and of cytosine into ura-cil, respectively [35]. Adenosine deaminases acting on RNA (ADAR) enzymes act on double-stranded RNA regions, usually the secondary structure of a single mRNA molecule. Through a hydrolytic deamination at C6, ADAR enzymes catalyze adenine conversion into inosine, which pairs with cytosine. Cytidine deaminases are much more specific and different members of the APOBEC3 family are transcriptionally regulated by p53 [36]. Altered RNA editing signatures were found in different types of tumors, such as glioblastoma [37], breast [38] and gastric cancers [39, 40]. If located at a coding region, these editing events may cause a missense mutation. One example is ADAR-1 editing of the *Antizyme Inhibitor 1* (*AZIN1*), which leads to a serine-to-glycine substitution at residue 367 [41]. AZIN1 is an inactive homolog of ornithine decarboxylase (ODC) that competitively binds to antizymes [42]. ADAR-1 editing increases AZIN1 affinity to antizyme, leading to a decrease in ODC antizyme-mediated degradation and promoting polyamines biosynthesis, with consequent cell proliferation and a more aggressive behavior in hepatocellular carcinoma cells [41]. Although editing on consensus splicing sites are rare, ADAR enzymes alter the global splicing pattern of the cell by editing splicing regula-tory *cis* elements and, possibly, indirectly, by altering the activity of *trans* elements [43, 44].

The interaction of transcripts with long non-coding RNAs (lncRNAs) and microRNAs are important post-transcriptional regulatory mechanisms which will be further addressed in this chapter. RNA edition adds a layer of complexity to this apparatus. It is estimated that over 70% of potential editing sites within long non-coding RNAs may lead to changes in their secondary structure, a feature which is crucial for its target recognition [45]. If the editing takes place in a precursor miRNA, it can lead to alterations in its biosynthesis and target rec-ognition, increasing their range of action [46–48]. Alterations in the mRNA 3′-UTR may alter its recognition by a specific miRNA or lncRNA [37, 40, 47]. Furthermore, RNA editing may also modulate RNA expression by regulating RNA decay. This is exemplified by the ADAR-1 interaction with the RNA binding protein HuR, which promotes HuR binding to the target transcript, increasing its stability [49].

3. miRNAs

Several RNA-based mechanisms evolved in eukaryotes to modulate gene expression or sup-press invading material. In animals, the small non-coding RNAs (18–30 nucleotides) are sub-divided into three major classes, namely microRNA (miRNA), small interfering RNA (siRNA) and PIWI-interacting RNA (piRNA). The main purpose of piRNAs are suggested to be silenc-ing of transposable elements in germline cells [45], siRNAs and miRNAs seem to have evolved

from an antiviral defense system into an ubiquitous gene expression modulation mechanism [46, 47]. Originally identified in *Caenorhabditis elegans* [48], miRNAs are the dominating class of small RNAs in most somatic tissues, being highly conserved and repressing the expression of target genes by inhibiting mRNAs translation and/or stability [49, 50]. The latest update of the human miRNA database lists 2588 mature miRNAs, processed out of 1881 precursors [51]. miRNA genes are originally transcribed by RNA polymerase II (Pol II) as a long (typically over 1 kb) primary transcript (pri-miRNA) bearing hairpins, in which miRNA sequences are embedded [52]. Hairpins are cropped by the Drosha nuclear RNase III liberating the stem-loop shaped ~65 nucleotide long precursor miRNA (pre-miRNA) [53]. Upon exporting to the cytoplasm through Exportin 5 (EXP5), pre-miRNAs are cleaved by DICER near the terminal loop, liberating a small RNA duplex [54]. This duplex is subsequently loaded onto RNA-induced silencing complex (RISC), RNP effector complexes containing Argonaut (AGO) proteins. Finally, unwinding of the RNA duplex allows the final single-stranded miRNA to act as a guide for the effector complex [55]. Specific targeting is accomplished by base pairing between mRNA and miRNA, as miRNAs usually guide RISC to 3′UTR regions in target protein-coding transcripts [56], recruiting proteins that lead to target RNA degradation, deadenylation or decay [53]. However, miRNAs may also interact with 5′UTR and coding sequence (CDS) regions, culminating in a range of effects, from translational activation to repression.

More than 60% of human protein-coding genes contain at least one conserved miRNA-binding site [57], encompassing every major cellular functional pathway. Therefore, miRNAs biogenesis needs to be under tight temporal and spatial control, and their deregulation is evidently associated with a wide range of human diseases, including cancer [58]. The first instance of the direct involvement of a miRNA in cancer was uncovered in 2002. A critical region at chromosome 13q14, frequently deleted in chronic lymphocytic leukemia (CLL), was shown to harbor miRNA genes miR-15a and miR-16-1. About 70% of CLL cases have null or reduced expression of these miRNAs, which normally control apoptosis by targeting BCL-2 [59, 60]. The following years revealed a remarkable number of additional examples, establishing the association of miRNAs and cancer to be the norm, rather than the exception. Currently, hundreds of human miRNAs are associated to the onset and progression of several malignancies, including lymphomas, colorectal carcinoma, breast cancer, lung cancer, thyroid cancer and hepatocellular carcinomas [61].

Several miRNAs may be differentially expressed in cancer patients, when compared to normal samples, acting either as oncogenes or tumor suppressors [62] (**Table 1**). Most often, miRNAs are detected as tumor suppressors, with reduced expression in tumors when compared to normal tissues [63, 64]. These miRNAs have commonly been shown to negatively regulate protein-coding oncogenes. Thus, HER2 and HER3, two oncogenes which are significantly correlated with decreased disease-specific survival in breast cancer patients [65], are suppressed by miR-125a or miR-125b [66]. Additionally, the let-7 family of miRNAs targets several genes associated with cell cycle and cell division, including the RAS oncogene [67]. Inhibition of epidermal growth factor receptor by miR-128b in non-small cell lung cancer (NSCLC) [68] and miR-7 in glioma [69] are additional pertinent examples of miRNAs acting as tumor suppressors. However, several miRNAs have also been found to be overexpressed in cancer, being classified as oncomiRs, often repressing known tumor suppressors. Thus, overexpression of miR-155 and miR-21 is sufficient to induce lymphomagenesis in mice [70, 71].

miRNA	Cancer phenotype	Target mRNA	Cancer association	References
miR-15a	Tumor suppressor	BCL2	Chronic lymphocytic leukemia	[59, 60]
miR-16-1	Tumor suppressor	BCL2	Chronic lymphocytic leukemia	[59, 60]
miR-125a	Tumor suppressor	HER2/HER3	Breast cancer	[66]
miR-125b	Tumor suppressor	HER2/HER3	Breast cancer	[66]
let-7	Tumor suppressor	RAS	Lung tumor	[67]
miR128-b	Tumor suppressor	EGFR	Non-small lung cancer	[68]
miR128-b	Tumor suppressor	EGFR	Acute lymphoblastic leukemia	[77]
miR-7	Tumor suppressor	EGFR	Glioma	[69]
miR-155	Oncogenic	BIC	Lymphoma	[70, 71]
miR-21	Oncogenic	NA	Lymphoma	[70, 71]
miR-127	Tumor suppressor	BCL6	Prostate cancer	[75, 76]
miR-372/373	Oncogenic	RAS, p53	Testicular germ cell tumor	[170]
miR-17	Tumor suppressor	c-MYC	Large B-cell lymphoma	[72, 171]
miR-34	Tumor suppressor	P53	Ovarian cancer	[73]
miR-210	Tumor suppressor	DIMT1	Multiple myeloma	[172]
miR-10b	Tumor suppressor	TIAM1	Gastric cancer	[173]
miR-126	Tumor suppressor	ADAM9	Breast cancer	[174]
miR-335	Tumor suppressor	BRCA1	Breast cancer	[175]

Table 1. List of miRNAs involved in cancer and their respective mRNA targets.

Mapping efforts have revealed that many miRNAs are located in fragile regions of the genome, which are deleted, amplified or translocated in cancer, directly altering miRNAs genes expression, hence leading to aberrant expression of downstream target mRNAs [59]. In addition to genomic alterations, miRNA expression is also modulated by tumor suppressor or oncogenic factors, which function as transcriptional activators or repressors to control pre-miRNA transcription. One of the first examples of this interaction is the transcriptional upregulation of the miR-17/92 cluster by the c-*myc* oncogene product, counterbalancing the apoptotic activity of E2F1 and allowing c-Myc mediated-proliferation [72]. Likewise, p53 stimulates transcription of the miR-34 family, inducing apoptosis and senescence. Loss of p53 function induces downregulation of the miR-34 family in a very high percentage of ovarian cancer patients with a p53 mutation [73]. The expression of miRNA genes may also be indirectly modulated. Aberrant epigenetic changes, such as DNA hypermethylation of tumor suppressor genes, extensive genomic DNA hypomethylation and alteration of histone modification patterns, are a well-known feature of cancer cells. In fact, epigenetic modifications represent another common mechanism related to the alteration of miRNA expression in cancer. Tumor-suppressing miRNAs are usually found to be hypermethylated in cancer,

which, in turn, allows overexpression of their oncogenic targets [74]. Thus, epigenetic repression of the tumor-suppressor miR-127 in primary prostate cancer [75] and bladder tumor causes upregulation of its target transcripts, including that of the proto-oncogene BCL6 [76]. A cancer-driving alteration may arise early in the biogenesis of miRNAs, during transcription of the pri-miRNA. For example, a point mutation in miR-128b gene blocks processing of pri-miR-128b and reduces the levels of mature miR-128b, thus leading to glucocorticoid resistance in acute lymphoblastic leukemia (ALL) [77]. Another mechanism which can lead to an aberrant expression of miRNAs and, thus, to cancer, is the altered expression and/or function of the enzymes involved in the biogenesis of microRNAs, such as DROSHA and DICER. Aberrant expression of these proteins affects the biogenesis of all miRNAs in the cell, influencing the regulation of a multitude of genes. Thus, the first heterozygous germline mutations in DICER1 were identified as causing pleuropulmonary blastoma (PPB), a rare pediatric lung tumor that arises during fetal lung development [78]. Likewise, decreased expression of DROSHA and DICER has been found in 39% of ovarian cancer patients [79]. miRNA biogenesis may also be modulated during nuclear translocation by exportin 5 (XPO5). XPO5 mutations in some tumors generate pre-miRNA accumulation in the nucleus, reducing miRNA maturation and availability in the cytoplasm [80]. miRNA processing is orchestrated by a large number of proteins assisting the basic machinery. Several of these modulatory proteins, such as DDX5 and DDX17, were shown to be either directly mutated or to serve as targets for oncoproteins or tumor suppressors, modulating miRNA biogenesis [81].

The functional outcomes of miRNAs deregulation coincide with the hallmarks of malignant cells, namely: (1) self-sufficiency in growth signals (let-7 family), (2) insensitivity to anti-growth signals (miR-17-92 cluster), (3) apoptosis evasion (miR-34a), (4) limitless replicative potential (miR-372/373 cluster), (5) angiogenesis (miR-210) and (6) invasion and metastases (miR-10b). miRNAs have also been shown to regulate the generation of cancer stem cells (CSCs) [82, 83] and epithelial-mesenchymal transition (EMT), paramount for the metastatic process [84]. Thus, as breast cancer cells metastasize, expression of miR-126 and miR-335 is lost. Overexpressing these miRNAs in cancer cells decreases lung and bone metastasis in vivo [85].

The high number of human miRNAs, regulating a wide range of cancer-related processes, renders these small non-coding RNAs an ideal profiling tool. miRNA expression profiles can distinguish not only between normal and cancerous tissue, but also help to discriminate different subtypes of a particular cancer, or even specific oncogenic abnormalities [86], increasing the accuracy of tumor classification. These expression profiles were able to classify tumors according to their tissue of origin with accuracy higher than 90%. miRNAs regulation of cancer progression also allows these molecules to serve as efficient predictors of prognosis, tumor metastasis and therapy selection. Specific miRNA signatures have recently been shown to correlate to metastatic breast and colon tumors, arising as potent biomarkers to predict metastatic outcome. miRNA profiles may also be applied to select for more personalized and efficient therapies and to adjust the therapeutic scheme during treatment to achieve a better outcome. Noteworthy, in ovarian cancer, miRNA signatures are able to predict chemoresistant tumors, while a polymorphism (SNP34091), which creates a new binding site for miR-191, was suggested as a modulator of tumor chemosensitivity [75].

miRNAs are highly stable molecules present in body fluids including plasma, blood, serum, urine, saliva and milk, being potential cancer biomarkers which may be found in different phases of the tumoral process [87, 88]. Although understanding of how miRNAs are selectively released from cells and how circulating miRNAs are related to disease remains largely unclear, circulating miRNAs may serve as novel diagnostic and prognostic biomarkers for human diseases, including cancer [89].

4. Long non-coding RNAs

Recent studies based on the Encyclopedia of DNA elements (ENCODE) project indicate that more than 80% of the human genome contains functional DNA that includes protein coding genes, non-protein coding regulatory DNA elements and non-coding RNAs (ncRNAs) [90]. Non-coding RNAs is a class of genetic regulators, containing short (<200 nucleotides) and long (>200 nucleotides) transcripts with novel abilities to be used as biomarkers due to their role in disease development and their implications for genomic organization [91, 92]. Short ncRNAs include ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), small nuclear RNAs (snRNAs) and small nucleolar RNAs (snoRNAs). Regulatory long non-coding RNAs (lncRNAs) have been found in a large variety of organisms, ranging from yeasts to mammals, including mice and humans [93]. lncRNAs have emerged as a fundamental molecular class whose members play critical roles in genome regulation and in tissue development and maintenance [92]. Based on their positions relative to the protein coding genes in the genome, lncRNAs can be classified into natural antisense transcripts (NATs), long intronic ncRNAs and long intergenic ncRNAs (lincRNAs) [93].

Recent transcriptional profiling of multiple human tissues, including both normal and tumor samples, has led to the assumption that misregulation of lncRNAs could disrupt these delicate processes and lead to tumorigenesis [94–97]. These studies have validated the tissue-specific expression of lncRNAs in normal tissues, and have identified large sets of lncRNAs which are aberrantly expressed in either a specific cancer or multiple types of cancer, suggesting these RNAs act as master regulators of gene expression [98, 99]. Differential expression of lncRNAs is increasingly recognized as a hallmark feature in cancer [100]. lncRNAs are a novel class of mRNA-like transcripts, which contribute to cancer development and progression, accelerating cancer cells proliferation, apoptosis, invasion and metastasis [101] (**Table 2**).

General mechanisms of lncRNA function implicated in cancer progression are associated with a wide-repertoire of biological processes. Among the main biological pathways, lncRNAs may be involved in epigenetic silencing, splicing regulation, translational control, regulation of apoptosis and cell cycle control [102]. Like protein-coding genes, lncRNAs can function as oncogenes or tumor suppressors. Many lncRNAs shuttle between the nucleus and the cytoplasm, suggesting that they may have dual functions, while others are restricted to the nucleus [103]. In the nucleus, lncRNAs are often part of the nuclear architecture and, in some cases, are critical for maintenance of sub-nuclear structures [104].

LncRNA	Cancer phenotype	Molecular mechanism	Cancer association	References
HOTAIR	Oncogenic, promotes metastasis and invasion	Interacts with PRC2 and LSD1 complex, promotes silencing of HOX genes in *trans* epigenetically	Overexpressed in liver, breast, lung and pancreatic tumors	[109, 176, 177]
GAS5	Tumor suppressor, induces growth arrest and sensitizes cells to apoptosis	Inhibits and binds glucocorticoid receptor (GR) from activating target genes	Downregulated in breast cancer	[178, 179]
H19	Oncogenic, promotes cell proliferation and tumor growth	Unknown	Breast cancer	[180]
MALAT1	Oncogenic, promotes cell proliferation and metastasis	Related to alternative splicing and active transcription, regulation of gene expression	Overexpressed in lung, breast, pancreatic, colon, prostate and hepatocellular carcinomas	[117, 181, 182]
MEG3	Tumor suppressor, inhibits cell proliferation and induces apoptosis	Enhancing p53's transcriptional activity on its target genes. Controls expression of gene loci through recruitment of PRC2	Downregulated in multiple tumor types	[183, 184]
PTENP1	Tumor suppressor; Inhibits cell proliferation, migration, invasion and tumor growth	Binds and inhibits miRNAs from targeting and repressing *PTEN*	Locus lost in prostate cancer, colon cancer and melanoma	[185–187]
ZFas1	Tumor suppressor and inhibits proliferation	Unknown	Breast cancer and dysregulated in many types of tumors	[128, 188]

Table 2. List of lncRNAs involved in cancer with their proposed functions.

lncRNAs bind to and target chromatin regulators allowing connection between RNA and chromatin, acting on the control of gene expression at the transcriptional level [105]. Moreover, several lncRNAs mechanistic themes have emerged, both at the transcriptional and post-transcriptional levels, such as decoys, scaffolds and guides [106]. Examples of the mechanisms of action of some lncRNAs on the control of gene expression and mammalian cells regulation are described below.

HOTAIR (Hox transcript antisense intergenic RNA) is expressed from the HOXC locus and was the first lncRNA shown to be acting in *trans*. *HOTAIR* binds to and targets the PRC2 complex to the HOXD locus [107], functioning as an RNA scaffold containing two main functional domains. The 5′ domain of *HOTAIR* binds PRC2, whereas a 3′ domain binds the LSD1/ CoREST/REST H3K4 demethylase complex [108], thus bridging two repressive complexes in order to coordinate their functions in gene silencing. Ectopic *HOTAIR* expression in epithelial cancer cells induces genome-wide retargeting of PRC2, leading to widespread changes in

repressive (H3K27me3) and active (H3K4me3) chromatin markers, resembling those found in embryonic fibroblasts. This results in more invasive and metastatic cells and *HOTAIR* expression is predictive of cancer survival [109].

lncRNAs can also participate in global cellular behavior by controlling cell growth. The growth-arrest-specific 5 (*GAS5*) lncRNA sensitizes the cell to apoptosis by regulating the activity of glucocorticoids in response to nutrient starvation [110]. *GAS5* binds to the DNA-binding domain (DBD) of the glucocorticoid receptor (GR), where it acts as a decoy, preventing GR interaction with cognate glucocorticoid response elements (GRE). Under normal conditions, GR target genes are involved in apoptosis suppression, such as cellular inhibitor of apoptosis 2 (cIAP2) and inhibit the cell-death executioners caspases 3, 7 and 9 [111]. However, upon growth arrest, *GAS5* activation compromises GR ability to bind to the cIAP2 GRE, reducing cIAP2 expression levels, thereby removing its suppressive effect on caspases [110]. *GAS5* has also been associated with breast cancer because its transcript levels are significantly reduced, when compared to unaffected normal breast epithelium [110]. Therefore, *GAS5* could act as a tumor suppressor if reduced levels of this lncRNA are unable to maintain sufficient caspase activity to activate an appropriate apoptotic response in disease-compromised cells.

H19 is an imprinted gene expressed exclusively from the maternal allele, which maintains silencing of IGF2. *H19* is highly expressed in a wide variety of solid tumors. The majority of cancers express high levels of *H19* when compared to normal tissues. *H19* is generally overexpressed in stromal cells, rarely in tumor epithelial cells and has been found to be associated with the presence of estrogen receptor (ER) and progesterone receptor (PR) [112]. Data indicating both oncogenic and tumor suppressive roles for *H19* in different cancers are available [113]. In cancer cell lines, *H19* RNA expression is directly regulated by E2F1, promoting cell cycle progression [114].

The lncRNA *MALAT1* (metastasis associated in lung adenocarcinoma transcript) was identified in an attempt to characterize transcripts associated with early stage non-small cell lung cancer (NSCLC) [115]. Some studies found that *MALAT1* regulates alternative splicing through its interaction with the serine/arginine-rich (SR) family of nuclear phosphoproteins, which are involved in the splicing machinery [116, 117]. Because the SR family of proteins affects the alternative splicing patterns of many pre-mRNAs, its activity must be tightly regulated. Small changes in SR protein concentration or phosphorylation status can upset the fragile balance that controls mRNA variability among different cells and tissue types [118]. Therefore, the lncRNA *MALAT1* has been suggested to serve as a fine-tuning mechanism to modulate the activity of SR proteins.

The maternally expressed gene 3 (*MEG3*) is an imprinted lncRNA located on chromosome 14q32 is expressed exclusively from the maternal allele. *MEG3* has been shown to activate p53 and facilitate p53 signaling, including enhancement of p53 binding to target genes [119]. Furthermore, *MEG3* regulates genes of the TGF-β pathway through formation of RNA-DNA triplex structures [120]. *MEG3* overexpression in meningioma, hepatocellular carcinoma and breast cancer cell lines leads to suppression of cell proliferation [121–123].

The *PTEN* (phosphatase and tensin homolog) gene encodes a tumor suppressor that functions by negatively regulating the AKT/PKB signaling pathway [124, 125]. Mutations of this gene

constitute a step into the development of many cancers and it is one of the most commonly lost tumor suppressors in human cancer [126]. A highly homologous processed of *PTENP1* (phosphatase and tensin Homolog pseudogene 1) is a pseudogene which is associated with the lncRNA class found on chromosome 9, regulating *PTEN* by both sense and antisense RNAs. This long non-coding RNA acts as a decoy for *PTEN*, targeting microRNAs and exerting a tumor suppressive activity [125, 127].

The lncRNA *Zfas1* (Znfx1 antisense 1) is a transcript antisense to the 5′ end of the protein-coding gene Znfx1, which has functions in epithelial cells and was identified in large-scale studies aimed at isolating differentially expressed genes during mammary development [128]. *Zfas1* intronically hosts three C/D box snoRNAs (*Snord12*, *Snord12b* and *Snord12c*) [128] and recently has been associated with ribosomes cancer cells [129].

The highly specific lncRNA expression signatures render them as attractive markers for accurate disease diagnosis and patients prognosis. In addition, advancement of RNA-based therapeutics opens new avenues for lncRNAs as new targets for cancer therapy.

5. mRNA decay

mRNA degradation is an important mechanism for post-transcriptional control of gene expression, controlling both the quality and the abundance of cellular mRNAs. Deadenylation of the mRNA is the default process, often representing a rate-limiting step in cytoplasmic mRNA decay, in which the poly(A) tail of the transcript is degraded through recruitment of deadenylase complexes [130–132]. In the literature, different deadenylases or poly(A)-specific ribonucleases have been described, namely PARN (poly(A)-specific ribonuclease), Pan2/Pan3 (poly(A) nuclease 2/3) complex and CCR4–NOT (carbon catabolite repression 4) complex [131, 133]. The PARN deadenylase is involved in destabilization of different transcripts related to cell cycle progression and cell proliferation [133, 134], as well as in degradation of oncogenic miRNAs, such as miR-21 [135]. In addition, its expression is altered in different tumors, such as gastric tumors [136] and acute leukemias [137].

Different proteins are able to interact with each other and promote the recruitment of deadenylases to the mRNA poly(A) tail. Members of BTG/Tob family, associated with anti-proliferative activities [138], are able to associate with both Caf1a and Caf1b (enzymatic subunits of the CCR4-NOT complex) [139], and, also, with PABPC1 (cytoplasmic poly(A)-binding protein) [139, 140], promoting mRNA poly(A) tail removal and cytoplasmic mRNA decay. Expression of the BTG/Tob proteins is classically associated with inhibition of cell cycle progression [138]. The Tob/Caf1 complex is also involved in the negative regulation of c-*myc* proto-oncogene expression by accelerating deadenylation and decay of its mRNA [141]. In addition, BTG2 has been characterized as a p53 transcriptional-target, being an essential component for suppression of Ras-induced transformation by p53 [142]. In agreement, reduced expression of BTG2 and TOB proteins are observed in human samples derived from different types of tumor [143–146]. On the other hand, interaction of Tob1 with Caf1a (but not with Caf1b) was recently associated with the metastatic phenotype in mouse mammary

carcinoma model and the deadenylase activity of Caf1a was shown to be required for promotion of metastatic disease [147]. Using a human breast cancer model, it has also been shown that high expression of either TOB1 or CNOT1 (the scaffold subunit of the CCR4-NOT complex) correlated with poor survival [147] and was associated with poor distant metastasis free survival in breast cancer patients [148]. Interestingly, PABPC1 has also been described as an oncogenic protein in gastric carcinoma. Zhu and collaborators showed that PABPC1 is upregulated in gastric carcinoma tissues, predicting poor survival and inhibits apoptosis by targeting miR-34c [149]. Following shortening of the poly(A) tail, mRNA can either be degraded through the 3' pathway, by the eukaryotic exosome complex, or, alternatively, by removal of the cap by Dcp2 and exonuclease decay through the 5' pathway, promoted by exonuclease Xrn1 [130, 131].

AU-rich elements (ARE) are critical *cis*-acting elements in the 3'-UTRs of a variety of short-lived transcripts. Tristetraprolin (TTP) and human antigen R (HuR) are two important RNA-binding proteins which can bind to AREs in their target mRNAs. TTP promotes deadenylation and degradation of target mRNAs, whereas HuR, as already mentioned, is involved in stabilization of target mRNAs. It has been extensively described that TTP expression is significantly decreased in different types of tumors [150] and that it is involved in cell cycle control, angiogenesis and tumor metastasis [151]. Recently, it has been reported that TTP inhibits the epithelial-mesenchymal transition (EMT) of cancer cells through mRNA degradation of the EMT inducers, specifically, Twist1 and Snail1, and inhibits cell proliferation through down-regulation of c-*fos*, CDC34 and VEGF [152]. Interestingly, TTP appears to bind to AREs and interact with proteins involved in mRNA decay, such as the PM-scl75 exosome component, Xrn1 5'–3' exonuclease, CCR4deadenylase and Dcp1 decapping enzyme [153], supporting a model in which TTP promotes mRNA decay through the ability to recruit components of the cellular mRNA decay machinery to the target mRNAs. In recent publications, high expression levels of HuR have been correlated with tumor progression and aggressiveness by affecting cell cycle progression, migration, invasion, metastasis and apoptosis in different tumor models [154–157]. HuR enhances the stability of the human epidermal growth factor receptor 2 (ERBB2/HER-2) mRNA, modulating the estrogen receptor-alpha-positive (ER+) breast cancer cells responsiveness to tamoxifen [158].

In addition, deadenylase complexes could be recruited to the mRNA poly(A) tail through the action of miRNAs. GW182 proteins, which participate of the miRNA-induced silencing complex (miRISC), directly interact with PAN3 and NOT1 subunits, leading to recruitment of the PAN2-PAN3 and CCR4-CAF1-NOT deadenylase complexes to the 3'-UTR of target mRNAs [159]. Also, it has been described that PARN deadenylase binds to the 3' UTR of p53 mRNA through recruitment mediated by miR-125b-loaded miRISC, promoting p53 mRNA decay [134]. Interestingly, this effect can be reverted by HuR proteins, which bind to the p53 AREs and increase p53 mRNA stability [134].

The deadenylation machinery is also an important target for antitumor agents and anticancer therapy. Cantharidin (an inhibitor of protein phosphatase 2A) inhibits the invasive ability of pancreatic cancer cells, with concomitant deadenylation-dependent degradation of MMP2 mRNA [20]. Resveratrol (3,5,4'-trihydroxystilbene), a naturally occurring compound, induces

TPP expression in U87MG human glioma cells and leads to the decay of urokinase plasminogen activator (uPA) and urokinase plasminogen activator receptor (uPAR) mRNAs, promoting suppression of cell growth and inducing apoptosis [160].

Additionally, several mature mRNAs surveillance mechanisms guarantee quality and fidelity to encode a functional protein in a translation-dependent manner. The nonsense-mediated decay (NMD) pathway is the best understood surveillance mechanism; detecting and degrading transcripts which contain premature termination codons (PTCs), avoiding the expression of semi-functional and truncated proteins [161]. The UPF-1 (up-frameshift1) protein, a key component of the NMD mechanism, interacts with both Dcp2 and PARP, linking NMD with the decapping and deadenylation processes [162]. Low expression levels of UPF-1 protein as well as inactivation of UPF-1 function were described in several types of human cancer, suggesting that NMD downregulation is related to tumorigenesis. Decreased levels of UPF-1 were detected in lung adenocarcinoma in comparison to normal tissues, and its downregulation was correlated to poor prognosis and higher histological grade [163]. The pancreatic adenosquamous carcinoma (ASC) is an aggressive tumor which is associated with high metastatic potential and poor prognosis. In these tumors, a mutation that promotes *UPF-1* alternative splicing and results in a non-functional UPF-1 protein, has been observed. Inactivation of the NMD pathway promotes selective accumulation of a p53 isoform, which acts in a dominant-negative manner, contributing to tumorigenesis [164].

NMD can also be inhibited by a wide variety of cellular stresses, some of which are associated to the tumoral context [165]. In response to stress events, phosphorylation of the alpha-subunit of the eukaryotic initiation factor 2 (eIF2α) is able to inhibit NMD. It has been described that phospho-eIF2α is necessary for oncogene c-*myc*-mediated NMD inhibition [106]. Inhibition of NMD by cellular stress promotes stabilization of the SLC7A11 mRNA, which encodes a subunit of the cystine/glutamate aminoacid transport system, leading to increased intracellular levels of cysteine, accelerating the production of glutathione. SLC7A11 is upregulated in hypoxic cells, promotes tumorigenesis and chemotherapy resistance, suggesting that it could be an adaptive response that protects tumor cells against oxidative stress [166]. It has recently been described that NMD regulates the epithelial-mesenchymal transition (EMT) in the lung adenocarcinoma model, by targeting the TGF-β signaling pathway [163]. In addition, the NMD mechanism controls the expression of a novel human E-cadherin variant mRNA produced by alternative splicing. Overexpression of this alternatively spliced E-cadherin variant in MCF-7, breast cancer cells was able to induce EMT by promoting higher expression levels of Twist, Snail, Zeb1 and Slug, with a concomitant decrease in the wild type E-cadherin mRNA levels [167].

Several promising NMD targets mRNAs for cancer therapy have been proposed. The MDM4 protein, which is undetectable in normal tissues, is frequently upregulated in cancer cells, acting by inhibiting the p53 tumor-suppressor function [168]. The abundance of the MDM4 protein is controlled, at least in part, by alternative splicing mechanisms and the NMD pathway. In most normal adult tissues, the lack of exon 6 in the Mdm4-spliced variant leads to the production of an unstable transcript (Mdm4-S), which contains a PTC and is targeted to NMD [168]. On the other hand, the oncogenic splicing-factor SRSF3 supports exon 6 inclusion

in the Mdm4 mRNA transcript (full-length Mdm4 variant), which is not efficiently degraded by NMD. Therapeutic strategies which lead to antisense oligonucleotide-mediated (ASO-mediated) Mdm4 exon 6 skipping efficiently decreases MDM4 abundance and inhibits tumor cell growth in melanoma and diffuse large B cell lymphoma models, as well as increases sensitivity to MAPK-targeting therapies [169].

6. Final considerations

Different post-transcriptional mechanisms have been associated with gene expression control, leading to complex transcriptional signatures in cancer. The mechanisms presented in this chapter constitute fine regulators of gene expression which influence multiple and highly relevant pathways in cancer development (summarized in **Figure 1**). Several splicing
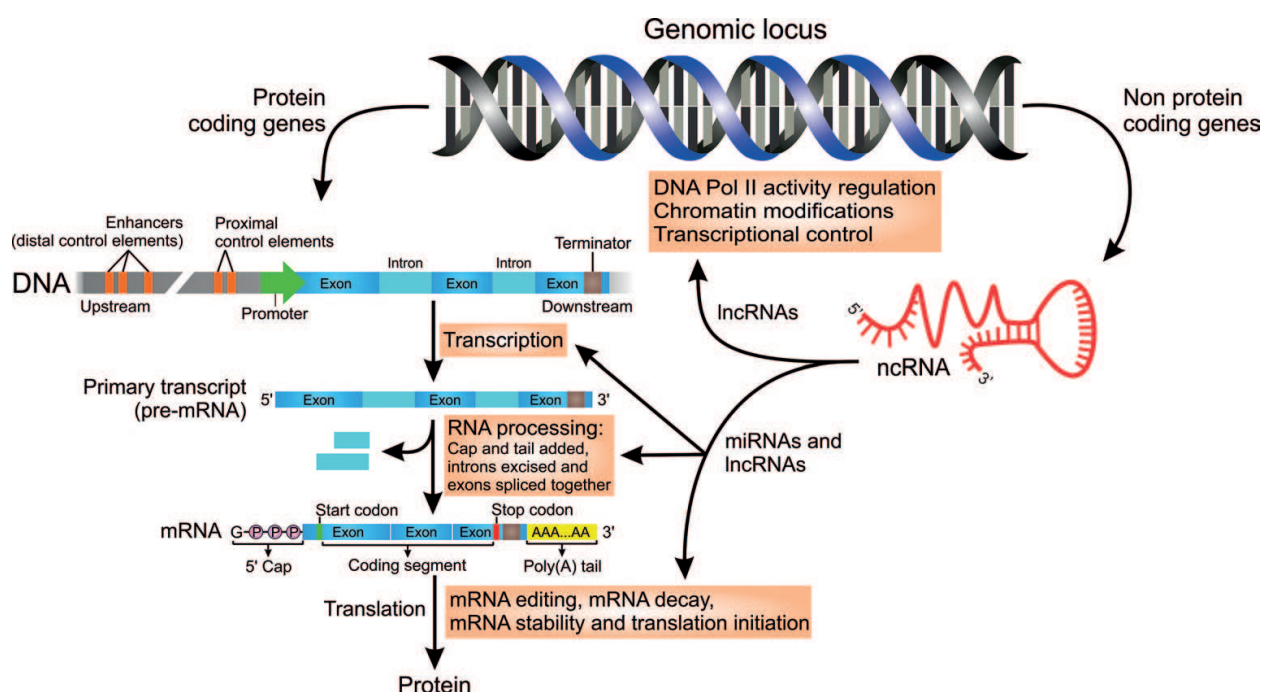

Figure 1. Schematic representation and key roles of different RNA species in the control of gene expression in mammalian cells. This scheme represents a genomic locus and the main molecular mechanisms associated with the control of gene expression pattern. Proximal control elements are located close to the promoter, while distal elements (called enhancers) may be far away from a gene or even located in an intron. Alternative splicing (AS) generates transcriptome diversity. During AS, *cis*-acting regulatory elements, present in the pre-mRNA sequence, determine which exons are retained and which exons are spliced out. For an individual pre-mRNA, several alternative exons show different types of alternative-splicing patterns. Addition of 5′ Cap and Poly(A) tail are controlled events which are extremely important for the stability of the mRNA and its transport from the cytoplasm to the nucleus. Non-coding RNAs (ncRNAs) with regulatory functions can act in multiple pathways during the transcription process by controlling specific events which culminate in synthesis of different proteins. Long non-coding RNAs (lncRNAs) target protein complexes to specific genomic loci affecting transcription patterns (transcriptional interference), leading to chromatin modifications (interplay between epigenetic marks, such as DNA methylation and histone acetylation) and DNA polymerase II activity. Advances in transcriptomics have resulted in the discovery of large numbers of ncRNAs (miRNAs e lncRNAs), many of which display the capacity to regulate gene expression at the levels of transcription (control of AS), post-transcription (mRNA editing, mRNA decay and mRNA stability) and translation (translation initiation).

variants, miRNAs and lncRNAs, have been shown to act as possible oncoRNAs or as tumor suppressors. The functional roles of these RNAs are only beginning to be elucidated providing an uncharted resource for the development of diagnostic methods and novel cancer therapies.

Abbreviations

ADAR	Adenosine deaminases acting on RNA
AGO	Argonaut
Akt/PKB	Protein kinase B
Apaf-1	Apoptotic protease activating factor 1
APOBEC	Apolipoprotein B Mrna editing enzyme, catalytic polypeptide-like
ARE	AU-rich elements
AS	Alternative splicing
ASC	Pancreatic adenosquamous carcinoma
ASO	Antisense oligonucleotide
AZIN1	Antizyme inhibitor 1
BCL	B cell lymphoma gene family
BrdU	Bromodeoxyuridine (5-bromo-2'-deoxyuridine)
BTG	BTG anti-proliferation factor
Caf1	Chromatin assembly factor-1 complex
Casp	Caspase
CCR4	C-C motif chemokine receptor 4
CCR4–NOT	Carbon catabolite repression 4 complex
CD44	CD44 molecule (Indian blood group)
CD6	Cluster of differentiation 6
CDC34	Cell division cycle 34
CDS	Coding DNA sequence
c-fos	Proto-oncogene c-Fos
cIAP2	Cellular inhibitor of apoptosis 2

CLL	Chronic lymphocytic leukemia
c-Myc	Myc proto-oncogene
CNOT1	CCR4-NOT transcription complex subunit 1
CoREST	REST corepressor 1
CSCs	Cancer stem cells
DBD	DNA-binding domain
Dcp1	Decapping protein 1
DDX	DEAD-box helixases
DICER	Dicer 1, ribonuclease III
DROSHA	Drosha ribonuclease III
E2F1	E2F transcription factor 1
eIF2α	Eukaryotic initiation factor 2
EMT	Epithelial-mesenchymal transition
ENCODE	Encyclopedia of DNA elements
ER	Estrogen receptor
ER$^+$	Estrogen receptor-alpha-positive
ERBB2/HER	Human epidermal growth factor receptor 2
EXP5	Exportin 5
GAS5	Growth-arrest-specific 5
GR	Glucocorticoid receptor
GRE	Glucocorticoid response elements
H19	H19, imprinted maternally expressed transcript
H3K4	Histone H3 lysine 4
hnRNP	Heterologous nuclear ribonuclear particle
HOTAIR	Hox transcript antisense intergenic RNA
HOXC	Homeobox C cluster
HuR	Human antigen R
IGF2	Insulin-like growth factor 2
lincRNAs	Long intergenic ncRNAs

lncRNAs	long non-coding RNAs
LSD1	Lysine-specific histone demethylase 1
MALAT1	Metastasis associated in lung adenocarcinoma transcript
MAPK	mitogen-activated kinase-like protein
MDM4	MDM4, p53 regulator
MEG3	Maternally expressed gene 3
miRISC	miRNA-induced silencing complex
miRNA/miR	microRNA
MMP2	Matrix metalloproteinase 2
NATs	Natural antisense transcripts
ncRNAs	Non-coding RNAs
NMD	Nonsense-mediated decay
NSCLC	Non-small cell lung cancer
ODC	Ornithine decarboxylase
p53	Tumor protein p53
PABPC1	Cytoplasmic poly(A)-binding protein
PABPC1	Poly(A) binding protein cytoplasmic 1
Pan2/Pan3	Poly(A) nuclease 2/3 complex
PARN	Poly(A)-specific ribonuclease
piRNA	PIWI-interacting RNA
Pol II	RNA polymerase II
PPB	Pleuropulmonary blastoma
PR	Progesterone receptor
PRC2	Polycomb repressive complex 2
Pri-miRNA	miRNA primary transcript
PTCs	Premature termination codons
PTEN	Phosphatase and tensin homolog
PTENP1	Phosphatase and tensin homolog pseudogene 1
Ras	HRas proto-oncogene, GTPase

REST   RE1-silencing transcription factor

RISC   RNA-induced silencing complex

rRNAs   Ribosomal RNAs

siRNA   Small interfering RNA

SLC7A11   Solute carrier family 7 member 11

Slug   Snail family transcriptional repressor 2

Snail1   Snail family transcriptional repressor 1

snoRNAs   Small nucleolar RNAs

SNPs   Single-nucleotide polymorphisms

snRNAs   Small nuclear RNAs

snRNP   Small nuclear ribonucleoprotein particles

SRP   Serine-rich protein

SRSF1   Serine and arginine-rich splicing factor 1

TGF-β   Transforming growth factor beta 1

Tob   Transducer of ERBB2

tRNAs   Transfer RNAs

TTP   Tristetraprolin

Twist1   Twist family BHLH transcription factor 1

uPA   Urokinase plasminogen activator

uPAR   Urokinase plasminogen activator receptor

UPF-1   Up-frameshift1 protein

UTR   Untranslated region

VEGF   Vascular endothelial growth factor

XPO5   Exportin 5

Xrn1   5′–3′ exoribonuclease 1

Zeb1   Zinc finger E-box binding homeobox 1

Zfas1   Znfx1 sntisense 1

Znfx1   Zinc finger NFX1-type containing 1

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