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TOPIC HIGHLIGHT

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Regulation of the mRNA half-life in breast cancer

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Abstract

The control of the half-life of mRNA plays a central role in normal development and in disease progression. Several pathological conditions, such as breast cancer, correlate with deregulation of the half-life of mRNA encoding growth factors, oncogenes, cell cycle regulators and inflammatory cytokines that participate in cancer. Substantial stability means that a mRNA will be available for translation for a longer time, resulting in high levels of protein gene products, which may lead to prolonged responses that subsequently result in over-production of cellular mediators that participate in cancer. The stability of these mRNA is regulated at the 3'UTR level by different mechanisms involving mRNA binding proteins, micro-RNA, long non-coding RNA and alternative polyadenylation. All these events are tightly interconnected to each other and lead to steady state levels of target mRNAs. Compelling evidence also suggests that both mRNA binding proteins and regulatory RNAs which participate to mRNA half-life regulation may be useful prognostic markers in breast cancers, pointing to a potential therapeutic approach to treatment of patients with these tumors. In this review, we summarize the main mechanisms involved in the regulation of mRNA decay and discuss the possibility of its implication in breast cancer aggressiveness and the efficacy of targeted therapy.

Key words: mRNA stability; Breast cancer; RNA binding proteins; MicroRNA; Alternative polyadenylation

Core tip: This review article is dedicated to the understanding of the mechanisms involved in the regulation of mRNA half-life. mRNA relative stability is an important way to rapidly increase or decrease the level of a given gene. This process is a much more rapid mechanism compare to transcriptional regulation. Since many genes implicated in cancerous processes are regulated at the level of their half-life, the proteins and/or small non coding RNA implicated in this regulation may serve as relevant prognosis markers or predictive markers of the efficacy of chemotherapeutic agents.

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GENERAL INTRODUCTION TO mRNA STABILITY

In the last few decades, our knowledge of the complexity of the regulation of gene expression in eukaryotes has expanded considerably. Control of regulation is exerted through several mechanisms that take place in

the nucleus or in the cytoplasm. In the past, the majority of studies focused on transcription, but modulation of post-transcriptional events has gaining a lot of interest and represents a rapid and plastic way of regulating gene expression. In particular, regulation of mRNA stability determines the spatial and temporal expression of many genes and plays a fundamental role in determining the outcome of gene expression[1,2].

Most mRNA regulatory elements involved in this process are situated within the 5' and 3'untranslated regions (UTRs), where they act as platforms for the assembly of protein complexes and other regulatory factors. Whereas the 5'UTR is primarily involved in controlling mRNA translation[3], the 3'UTR regulates multiple aspects of mRNA metabolism, including nuclear export, cytoplasmic localization, translational efficiency and mRNA stability[4].

Tight regulation of mRNA stability is essential for cells to perform their normal functions. Substantial stability means that a mRNA will be available for translation for a longer time, resulting in high levels of protein gene products. The lengths and structures of the 3'UTR vary substantially and more than half of the mammalian genes produced by alternative splicing and alternative polyadenylation (APA) multiple the number of mRNA isoforms that differ in their 3' UTRs and therefore in regulatory sequences within their 3' UTRs[5-7].

Modulation of the mRNA half-life plays a central role in inflammatory diseases and various cancers[8-17]. Aberrant stabilization of mRNAs may lead to prolonged responses that subsequently result in undesirable states, including over-production of growth factors, oncogenes and other mediators that participate in cancer. The steady state levels of mRNA-binding proteins and regulatory RNAs are often associated with invasion and aggressiveness[18,19].

We are only beginning to define the mechanisms coordinating the mRNA half-life and to understand its involvement in tumorigenesis. The fate of a transcript is determined by the complex interplay of *cis*-acting sequences within the 3'UTR of the mRNA and *trans*-acting factors, such as RNA binding proteins (RBPs) and regulatory RNAs (microRNA (miRNA) and long non coding RNA (lncRNA)) that bind directly or indirectly to the *cis*-acting elements and promote the deadenylation and degradation of the mRNA.

In this review we will discuss the role played by all these factors on mRNA stability, focusing on breast cancer and the recent advances made in evaluating cancer aggressiveness and the efficacy of targeted therapy. We will focus on the effect of these key factors on only the mRNA half-life and not on the efficiency of protein translation (for more comprehensive studies see[20-22]). We will also briefly discuss new topics such as shortening of 3' UTR by alternative polyadenylation.

A BRIEF OVERVIEW OF THE MECHANISMS INVOLVED IN THE REGULATION OF THE mRNA HALF-LIFE

The stability of common RNAs is regulated by a variety of signals acting on specific sequences within the RNA, which are recognized by *trans*-acting factors such as mRNA binding proteins, miRNA and lncRNA. All these factors are post-transcriptional gene regulators that bind mRNA and can regulate both mRNA stability and translation.

AU-rich sequences and mRNA binding proteins

The most conspicuous among the different cis-acting destabilizing elements identified so far are the AU-rich elements (AREs), located in the 3'UTR of a variety of short-lived mRNAs such as those for cytokines and proto-oncogenes[23,24]. Estimated to represent approximately 7% of all transcripts, ARE-mRNAs (see public database at: http://rna.tbi.univie.ac.at/AREsite) encode a functionally diverse group of proteins involved in the inflammatory and immune response, transcription, cell proliferation, RNA metabolism, development, and signaling[25,26]. This functional enrichment of ARE-genes correlates with the observed rapid patterns of mRNA decay, particularly of those involved in transcription and signaling[27]. These elements are recognized by trans-acting factors, such as mRNA-binding proteins that bind directly or indirectly to the cis-acting elements and promote the deadenylation and degradation of the mRNA. These proteins may have opposite effects on mRNA stability. Some of them, such as AU-rich element RNA-binding protein 1 (AUF1), tristetraprolin (TTP) and KH-type splicing regulatory protein (KSRP), promote mRNA degradation, while others such as embryonic lethal abnormal vision (ELAV)-like protein 1 (HuR) and polyadenylate-binding protein-interacting protein 2 (PAIP2) act as mRNA stabilizing proteins[10,28,29].

Briefly, AUF1 binds with high affinity to RNA that contain ARE sequences such as *MYC*, *FOS* and *GM-CSF* mRNAs. In contrast, it does not bind with high affinity to RNA sequences that lack a ARE[30]. Over-expression of AUF1 correlates with rapid degradation of ARE-containing mRNAs[31-33].

TTP (also named *ZFP36)* is characterized by two tandem repeat zinc finger motifs through which it binds to AREs and mediates mRNA decay[34,35]. Some of the well-established targets of TTP include TNF alpha mRNA[36], granulocyte/macrophage colony-stimulating factor (GM-CSF)[37], cyclooxygenase 2[38], vascular endothelial growth factor (VEGF)[39], interleukin-1[40], interleukin-8[41,42] and the hypoxia-inducible factor-1 (HIF-1)[43]. HuR is a member of the ELAV family of proteins found in mammalian cells. HuR selectively binds and stabilizes ARE-containing mRNAs of proto-oncogenes, cell cycle regulators, cytokines and other early-response genes[44,45]. For a more

comprehensive review and detailed description of RNA binding proteins see[10,28,30,46,47].

Regulatory non-coding RNA

RNAs have long been considered as an intermediate between DNA sequences and proteins that execute cellular functions. However, recent genome-wide analyses suggest that protein-coding genes represent only 2% of the human genome while there are at least thousands of non-coding RNAs (ncRNAs) transcribed from mammalian genomes. For many of them, a clear role in regulation of gene expression has been demonstrated[48,49].

There are two major classes of ncRNAs; the small ncRNA, such as miRNAs and lncRNAs. miRNA act by pairing to the mRNAs of protein-coding genes to direct their repression, while lncRNAs show different mechanism of action, varying from chromatin remodeling, transcriptional responses and RNA processing[50,51].

miRNAs, a small class of ncRNAs approximately 18-25 nucleotides in length, are able to regulate gene expression at the post-transcriptional level, by binding to partially homologous sequences to the 3'UTR of target mRNAs, and thereby causing a block in translation and/or mRNA degradation[52]. Although miRNAs were first identified in the early 1990s, it is only during the past decade that their potential has been more widely explored. Several studies have demonstrated that miRNAs are highly specific for developmental stages and that they play important roles in essential processes, such as differentiation, cell proliferation, stress response and cell death[53,54]. Gene regulation by miRNAs is important for the onset and progression of several human cancers[55-57].

Recent profiling studies have identified miRNAs that are aberrantly expressed in human cancers and miRNAs are now widely believed to play an essential role in many malignancies, acting as either tumor suppressors or oncogenes. This classification is based on repression of their target genes, which means that certain miRNA will be tumor suppressive if its target gene is an oncogene or a tumor suppressor[58,59]. miRNA usually act by pairing to complementary sequences in their 3'UTR and promoting mRNA deadenylation or a translational block[20,60].

LncRNA are a new class of ncRNA, with a length ranging from 200 bp to 100 kbp, which have recently caught a lot of attention. The latest GENCODE project has annotated 14880 lncRNAs from 9277 loci[61], but only a few of them have been characterized. Studies demonstrated that lncRNAs play major biological roles in embryonic stem cell biology and cellular development and show developmental and tissue specific expression patterns[62-65]. LncRNA are involved in numerous biological roles such as imprinting[66,67], epigenetic regulation[68], apoptosis and cell cycle control[69], transcription[49] and post-transcriptional regulation, splicing[70] and aging[71].

Therefore, aberrant lncRNA expression can cause various human diseases including cancer[69,72]. Currently, dozens of lncRNAs have been identified to play critical roles in the development and progression of cancer, acting as potential onco- or tumor-suppressor RNAs[73,74]. The mechanisms of action of lncRNAs are varied and include the creation of secondary RNA structures, binding to DNA and RNA binding proteins, or hybridization with complementary sequences of RNAs[75,76].

Accumulating evidence of deregulated lncRNA expression in numerous cancer types suggests that this type of regulation may open new avenues to identification of therapeutic targets for cancer[73,77]. For more a detail discussion on short and long RNA see also[59,78-80].

Alternative polyadenylation

Alternative polyadenylation (APA) is emerging as a widespread mechanism used to control gene expression but the mechanisms/steps governing both global and gene-specific APA are only starting to be deciphered.

APA consist of two steps, cleavage and polyadenylation of RNAs, which are maturation events that cut and add an oligo(dA) tail to the 3' end of the nascent transcript. This processing protects mRNAs from degradation and increases their stability. The specific cleavage position and the efficiency of the process depend on the interaction between *trans*-acting polyadenylation factors and *cis*-elements present in the pre-mRNAs, such as the central sequence motif AAUAAA, identified in the mid 1970s and subsequently shown to require flanking, auxiliary elements for both 3'cleavage and polyadenylation pre-mRNA[2,81-83]. Previous studies have indicated that more than half of the human genes possess multiple polyadenylation sites[84], called APA, which may produce mRNA isoforms with different protein-coding regions or 3'UTRs of variable length (when APA occurs in the last exon). The differential recognition of polyadenylation signals leads to long or short 3'UTR of the transcripts. Usage of alternative poly(A) sites influences the fate of mRNAs in several ways, for example, by altering the availability of RNA binding protein sites and miRNA binding sites. Usage of APA and alterations in polyadenylation are beginning to be discovered and studied in human diseases[85,86] and it is now clear that APA has several functional consequences in cancerogenesis.

INTERACTIONS BETWEEN THESE MECHANISMS

Our knowledge of the complexity of post-transcriptional regulation has expanded continuously and it is now clear that there is a strict connection between all the mechanisms involved in determining mRNA half-life. Evidence collected so far show a growing number of connections between miRNAs and RNA-binding proteins, underlying a new level of complexity of regulation of gene expression[87,88]. As described above, miRNAs and RBPs are post-transcriptional gene regulators that bind mRNA and can regulate both mRNA stability and translation.

Bioinformatic analyses showed that ARE motifs, normally recognized by RBPs, are over-represented in

miRNA target sites of transcripts and might antagonize or cooperate with miRNA-dependent gene regulation[89]. This *in silico* analysis provides support for other studies in which close interactions between ARE-BPs and miRNAs were found[88,90]. In fact, recent studies demonstrated co-operative interactions between miRNA and ARE-BPs in the modulation of gene expression. TTP and miR16, a miRNA containing a UAAAUAUU sequence that is complementary to the ARE sequence, were shown to depend on each other to efficiently suppress the mRNA of TNF alpha[88]. In other cases, ARE-BPs and miRNA compete for a binding site on the mRNA, thereby counteracting the functions of each other. The binding of HuR to the 3'UTR of the cationic amino acid transporter 1 (CAT1) mRNA prevents miR122-mediated repression of CAT-1 expression, thereby resulting in enhanced expression of the CAT-1 gene[91]. Other studies revealed that HuR sites are enriched near predicted miRNA sites in mRNAs and frequently overlap with them[92,93].

There are also other examples, miRNAs can regulate the expression of RBPs, or the converse, where an RNA-binding protein specifically regulates the expression of a specific miRNA, and some of them have been described in detail in a recent review[94].

Recently an interaction between the two major classes of regulatory RNAs has been demonstrated: miRNA and lncRNA. It has long been assumed that miRNAs can only target protein-coding mRNAs in the cytoplasm. However, recent studies have revealed that miRNAs are also transported from the cytoplasm to the nucleus, where they function in a non-canonical manner to regulate lncRNAs[95]. These results suggest that certain miRNAs might affect the expression level of many genes through modulating the biogenesis and function of lncRNAs[96]. Recently, a dynamic interplay between alternative polyadenylation and miRNA regulation has also been reported. Since APA often results in mRNA isoforms with different 3'UTRs lengths, these isoforms of an mRNA are differentially regulated by miRNAs[97].

The connection between all the mechanisms involved in determining mRNA half-life underlies the great potential of fine-tuning post-transcriptional control of gene expression. A careful revision of the literature has made us realize that alterations and dysfunction in all these mechanisms may be involved in breast cancer.

BREAST CANCER

Breast cancer is the leading cause of cancer-related deaths among women and its incidence is increasing worldwide. This neoplasia is a multi-factorial disease in which several factors contribute to initiation of the disease such as a genetic predisposition, chronic inflammation, exposure to toxic compounds, abundant stress factors, and others. The cumulative effects lead to a high incidence of breast cancer in populations worldwide[98]. In the last few years post-transcriptional regulation has been demonstrated to play a major role in breast cancer. Below, we will provide an overview and update of the dysfunction or alteration involved in the control of the mRNA half-life. Therefore, a better understanding of these mechanisms may help exploit the full potential of mRNA stability with respect to cancer diagnosis, treatment, and therapeutics.

RBPS IN BREAST CANCER

Modulation of the mRNA half-life plays a central role in breast cancer. Evidence collected so far has demonstrated the important role for RNA binding proteins in regulation of the mRNA half-life of several genes involved in cancer progression such as oncogenes, cytokines, and growth factors that are often involved in tumorigenesis[10,99,100]. In particular, TTP and HuR have often been shown to be deregulated in breast cancer and can be proposed as prognostic markers.

Several studies performed on breast cancer cell lines showed that TTP is deficient in breast cancer cells when compared with normal cell types, suggesting the involvement of TTP as a tumor suppressor in breast cancer[101,102]. Similar results were confirmed by analysis of samples from breast cancer patients.

In 2009, a gene array data set of 251 breast tumors, showed a negative correlation between TTP mRNA levels and tumor grade, with more advanced tumors typically showing the weakest TTP expression[103]. Moreover, patients with intermediate or low tumor TTP mRNA levels were 2- to 3-fold more likely to die from recurrent breast cancer than patients whose tumors strongly expressed TTP, suggesting that suppressed TTP expression may represent a negative prognostic indicator in breast cancer. The same findings were confirmed by other studies, which also found that TTP expression is higher in normal breast tissue and benign lesions than in infiltrating carcinomas. Moreover a strong positive association of TTP expression and mammary differentiation was identified in normal and tumor cells, with mammary differentiation inducing expression of TTP[104]. Loss of TTP also enhances infiltration of monocytes/macrophages into the tumors, which is typically associated with poor prognosis in breast cancer[105]. Recently, TTP has been showed to be involved in mammary differentiation both in normal and tumor cells, suggesting that this protein might play specific and relevant roles in the normal physiology of the gland[104]. Regarding HuR, a lot of evidence showed a direct role in breast carcinogenesis. HuR seems to enhance breast cancer cell growth and invasion[106], even though the same group showed that breast cancer patients expressing high levels of HuR had a favorable prognosis[107]. This finding contradicts two recent studies showing that cytoplasmic HuR expression is elevated in ductal *in situ* carcinomas, when associated with a high tumor grade[108], and a negative prognostic indicator for survival in patients with breast cancer[109]. Moreover, in breast cancer cell lines HuR specifically regulates the Forkhead box O (FoxO) transcription factor FOXO1, an important tumor suppressor involved in apoptosis,

the cell cycle, DNA damage repair and oxidative stress. Recently, it was demonstrated that cytoplasmic HuR is associated with reduced survival in invasive breast cancer and can be used as an independent prognostic marker in breast cancer patients undergoing chemotherapy[110].

REGULATORY RNA IN BREAST CANCER

As described above, regulatory RNAs include miRNAs and lncRNA that play important gene-regulatory roles. While lncRNAs show different mechanisms of action, miRNA act by pairing to the mRNAs of protein-coding genes to direct their repression. In this way, they can decrease the translational efficiency and/or decreased mRNA levels of gene targets[50]. Even though most of miRNA act by lowering mRNA levels[20], after reviewing the vast amount of literature on miRNAs, we found that most of the published articles do not investigate the mechanisms by which the miRNA act. Most of them reported the binding of the miRNA to the 3'UTR of the gene or the effect obtained with a luciferase assay, without clarifying if the miRNA affect the mRNA stability or efficiency of translation of the target gene. Since the effect on the efficiency of translation goes beyond this review, we will focus here on miRNA that affect the mRNA half-life and not the global number of miRNA involved in breast cancer. This topic has been extensively covered by other reviews[111-114]. We will briefly discuss some examples of miRNA demonstrated to directly affect mRNA stability. By acting on mRNA stability, miR125a and mir125b decrease the expression of HER2 and HER3, two genes crucial in breast carcinogenesis and c-RAF, another gene that plays a crucial role in cancer[115-117]. Another important miRNA is miR206, which targets ER alpha and represses both ER alpha mRNA and protein expression[118,119]. miR200 regulates epithelial-mesenchymal transition (EMT) targeting Zfhx1b mRNA probably by mRNA deadenylation and destabilization[120] while miR506 is always involved in EMT by increasing the levels of E-cadherin (CDH1)[121]. miR34 suppresses invasion and metastatic potential of breast cancer cells by directly targeting Fos related antigen 1 (Fra1) by reducing both the mRNA and protein level[122]. miR31 decreases the mRNA levels of many genes involved in breast cancer metastasis[123], while miR203 plays a crucial role in triple negative breast cancer by targeting baculoviral IAP repeat-containing protein 5 (BIRC5) and Lim and SH3 domain protein 1 (LASP1) at the RNA level[124]. miR21 is another miRNA that affects mRNA stability and is involved in decreasing mRNA levels of Programmed cell death 4 (PDCD4)[125], while miR26b decreases *Prostaglandin-endoperoxide synthase-2 (PTGS2)* levels in breast cancer[126] and miR124 affects the cd151 mRNA level[127].

It is interesting to note that some miRNA affect the mRNA half-life of target genes by perturbing the levels of RNA binding proteins. In 2009, miR29a was reported to suppress TTP in cancer cell lines[128]. The same miRNA is abundant in invasive breast cancer cells, where it increases stabilization and subsequent over-expression of HuR. In this way the TTP: HuR ratio was perturbed and associated with cancer invasion[129]. Moreover, other miRNAs bind to AREs and, thus, interact with ARE-binding proteins (ARE-BPs) to regulate transcript levels. miR3134 mediates an up to 4-8-fold increase in the levels of SOX9, VEGFA, and EGFR, which contain ARE in their 3'UTR, and are also regulated by HuR. Both miR3134 and HuR act together in a general mechanism of regulation of gene expression, which enhances transcript stability[130].

Another example of interactions is the one between miR125 and HuR. Guo *et al*[115] observed that the expression of miR125a inversely correlated with HuR in several different breast carcinoma cell lines. They demonstrated that HuR was translationally repressed by miR125a. This result suggested that miR125a may function as a tumor suppressor for breast cancer, with HuR as a direct and functional target.

To date, the emerging literature on lncRNA includes only one example of regulatory RNA that effect mRNA stability in breast cancer. Two studies reported the effect of a lncRNA on the half-life of the HIF-1 mRNA. HIF-1 is a heterodimeric transcription factor that regulates the expression of genes associated with adaptation to reduced oxygen pressure. HIF-1 is considered to be a reliable prognostic and diagnostic marker for an increasing number of cancers from various origins, including breast cancer[131]. A natural antisense of HIF-1 transcript (aHIF) that is complementary to the 3'untranslated region of the HIF-1 mRNA has been described in breast and renal carcinoma. The mechanism of action is not clear but it seems that aHIF could expose AU rich elements present in the 3' untranslated region of the HIF-1 mRNA and thus increase the rate of degradation of the HIF-1 mRNA[132]. aHIF has been proposed as a marker of poor prognosis[133], but further studies are clearly necessary.

ALTERNATIVE POLYADENYLATION IN BREAST CANCER

APA gives rise to mRNA isoforms with 3'UTR of variable length. There are few examples of the usage of alternative poly(A) in breast cancer in control of gene expression. One of the best examples is the shortening of the 3'UTR, which has been reported by Lembo *et al*[134] to correlate with poor prognosis. These authors showed that shorter 3'UTR can contain less regulatory elements that are normally involved in mRNA decay, such as miRNA binding sites or ARE sequences. In this way, miRNA and RBPs may increase the degradation rate of long isoforms of the gene, altering the ratio between the long and short isoforms and causing a shift from the normal to cancerous state[134,135]. Recently, it has been reported that estrogens, which play a major role in breast cancer initiation and progression, can induce APA

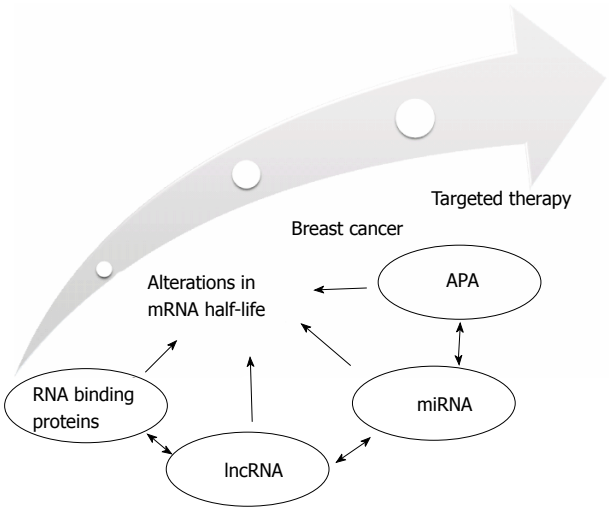

Figure 1 The regulation of the mRNA half-life and targeted therapy in breast cancer. Modulation of mRNA half-life depends on the interaction and balance between RNA binding proteins, regulatory RNAs (miRNA and lncRNA) and alternative polyadenylation in the 3'UTR of genes.

in breast cancer cells. In particular, estradiol up-regulates the 3'UTR shortening of CDC6, an essential regulator of DNA replication[136]. Further investigations are necessary to establish if the expression ratio of alternative 3'UTR can be a predictor of survival in breast cancer patients.

PROGNOSTIC FACTORS AND TARGETED THERAPEUTICS

In the last few years several studies have proposed evaluating post-transcriptional regulation as a prognostic factor for breast cancer aggressiveness and for development of targeted therapy.

Regarding miRNA, Iorio and coauthors identified several miRNA associated with breast cancer, which points to their role in the development of this neoplasia and to the impact on putative innovative therapeutic approaches[113]. Among the miRNA that have a direct impact on mRNA half-life of genes involved in breast cancer, miR206 and miR125a and 125b are surely of great interest. These miRNA are involved in specific networks, such as in the HER family-driven or ER-mediated signaling, and could likely influence the response to chemotherapy or to targeted therapies, such as trastuzumab, the monoclonal antibody directed against HER2, or antiestrogens, such as tamoxifen. Recently Hong L and coauthors investigated the role of miR210 in predicting survival. A total of 511 cases of breast cancer were examine in a global meta-analysis that showed that high expression levels of miR210 predicted poor survival in patients with breast cancer[137], confirming previous results obtained with miR210[138].

Several miRNA involved in the regulation of the mRNA half-life in breast cancer, such as miR200, miR26b miR21 miR34a are also modulated by estradiol[139], which plays a major role in a hormone-dependent cancers such as breast cancer.

Regarding RBPs, it is now generally assumed that loss of TTP and gain of HuR expression represent useful negative prognostic indicators in breast cancer. Monitoring mRNA or protein levels of these RBPs is being discussed, but it seems that at least for TTP, monitoring protein levels would provide a better negative correlation with breast cancer invasiveness than quantifying transcript levels[101,104]. Recently, it has been suggested that the ratio between TTP and HuR be evaluated, since it is perturbed in invasive breast cancer patients, and to correlate it with cancer invasion[108,109,129,140,141]. Due to the pivotal role played by TTP and HuR in stabilizing mRNA of key factors and cytokines involved in carcinogenesis and subsequent cancer progression, their clinical implication and therapeutic potential in cancer have been thoroughly investigated and recently reviewed by Ross *et al*[46], Eberhardt *et al*[142], Srikantan *et al*[47] and Abdelmohsen *et al*[143].

Recently, Wang *et al*[110] investigated the predictive and prognostic value of HuR expression in women with breast cancer who underwent neo-adjuvant chemotherapy followed by surgical resection. They evaluated the relationship between the HuR expression level and pathologic complete response (pCR), and found that cytoplasmic expression of HuR was an independent prognostic marker in breast cancer patients undergoing chemotherapy[110].

Promising data have been obtained from the study of regulatory lncRNA or alternative polyadenylation, but need further investigation and large-scale studies on cohorts of breast cancer patients.

It is of interest to point out the genetic polymorphisms in TTP and HuR, which may represent prognostic factors for breast cancer. Since the two RBPs play a central role in post-transcriptional control of genes involved in breast cancer, some studies analyzed the frequency of germline polymorphisms in breast cancer patients compared to healthy controls. A synonymous polymorphism in the TTP gene showed a statistically significant association with a lack of response to Herceptin/trastuzumab in HER2-positive breast cancer patients[101]. This polymorphism was associated with a decrease in translational efficiency. Moreover, another genetic variation in the promoter of the gene drastically reduced the amount of TTP mRNA and was significantly associated with poor prognosis. No association between polymorphisms of the HuR gene and breast cancer have been found[144].

Several polymorphisms in miRNA have been described but meta-analysis has shown that they can be used for prediction of breast cancer risk in healthy population but not as prognostic markers in breast cancer patients[145-148].

FINAL REMARKS

In recent years the importance of post-transcriptional control in breast cancer has become recognized. This process involves several steps including mRNA degrada-

Table 1 mRNA half-life modulators in breast cancer

mRNA half-life modulators	Main target	Prognostic factor	Ref.
RBPs			
TTP	GM-CSF, cox2, VEGF, IL8, HIF1a, TNF-α	Yes	Griseri and Pagès
HuR	GM-CSF, cox2, VEGF, IL8, TGFB, TNF-α	Yes	Griseri and Pagès
microRNA			
miR125a, miR125b	HER2, HER3, cRAF, HuR	Possible	[115-117]
miR206	ER	Unknown	[118,119]
miR200	Zfhx1b	Yes	[120,137,138]
miR506	cdh1	Unknown	[121]
miR34	Fra1	Unknown	[122]
miR31	Fzd3, ITGA5, MMP16, RDX, RhoA	Unknown	[123]
miR203	BIRC5, LASP1	Unknown	[124]
miR21	PDC4	Unknown	[125]
miR26b	PTGS2	Unknown	[126]
miR124	cd151	Unknown	[127]
miR29a	TTP	Unknown	[128]
miR3134	SOX9, VEGFA, EGFR	Unknown	[130]
miR125	HuR	Unknown	[115]
lncRNA			
aHIF		Possible	[132,133]

tion and translation. Here we have focused on the regulation of the RNA half-life in breast cancer, focusing on several mechanisms that control this process, all involving the 3'UTR of genes: mRNA binding proteins, regulatory RNA such as short and long RNAs, alternative polyadenylation. All these mechanisms lead to a broad range of rates in gene decay. A diagram summarizing the involvement of different proteins in regulating the balance between stabilization and degradation of mRNA is given in Figure 1. In this review, we have discussed how alteration of mRNA stability mediated by all these mechanisms can contribute to the development of breast cancer. The goal is to elucidate the molecular mechanisms involved in breast cancer and to identify molecules that are useful as bio-markers of diagnosis or prognosis.

Full knowledge of this process may help to develop potential diagnostic and therapeutic strategies against tumor progression. The available data strongly suggest the use of RBPs or miRNAs as markers of diagnosis and prognosis, and eventually as new targets or tools in specific therapy. Table 1 shows the key players involved in control of mRNA half-life in breast cancer as discussed in this review, documenting the functional importance in defining the aggressiveness of breast cancer cells. A better understanding of the pathways they modulate and how this dictates pathological processes will surely help to obtain a better understanding of the pathogenesis of breast cancer and will in the future open doors for better classification, prognosis and direct treatment.

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