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Role of RNA-binding proteins in both COPD and lung cancer

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Abstract

Chronic obstructive pulmonary disease (COPD) is an independent risk factor for the development of lung cancer. Several pathogenic pathways such as oxidative stress and chronic inflammation of the lower airways are shared by these two diseases. The RNA-binding proteins (RBPs) can modulate the post-transcriptional expression of genes involved in several biological processes, such as cell cycle, cell proliferation and injury/stress responses. The bonding between RBPs and targeted transcripts regulates mRNA turnover, subcellular localization, splicing and translation, through the formation of ribonucleoproteins (RNPs) complexes. Several pro-inflammatory mediators, that induce and maintain chronic lung inflammation and carcinogenesis, are modulate by RBPs.

RBPs can have a key role in lung cancer onset in COPD patients, sharing several common pathogenic processes, including oxidative stress, inflammation of lower airways, DNA damage and impaired DNA-repair mechanisms.

Further studies are mandatory to clarify the application of RBPs as novel biomarkers and potential therapeutic targets. This review will investigate recent evidences showing the role of RBPs in the pathogenic mechanisms sharing by lung cancer and COPD.

KeyWords: chronic airway inflammation, COPD, lung cancer, post-transcriptional regulation, RNA-binding proteins

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Introduction

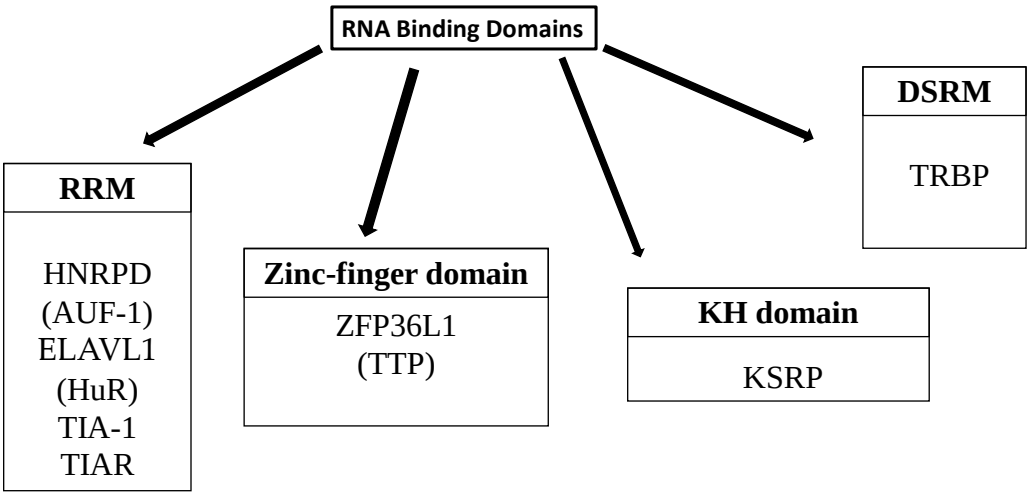
Chronic obstructive pulmonary disease (COPD) and lung cancer share several common features, such as genetic background, risk factors and pathophysiological mechanisms (1,2).

The complex pathogenic mechanisms shared by these diseases have been studied with the aim to explain the epidemiological and clinical association of the two diseases. In particular, oxidative stress mediates in COPD lower airways chronic inflammation through aberrant signalling pathways, transcriptional regulation and epigenetic mechanisms (3-6). In this review we will discuss the most recent data showing the role of RNA-binding proteins (RBPs) in the pathogenic mechanisms shared by lung cancer and COPD, emphasizing the potential role of RBPs both as disease biomarker and therapeutic target.

RBPs structure and activity

RBPs and noncoding RNAs (ncRNA), mainly represented by microRNAs (miRNAs), are the major players of post-transcriptional gene regulation (PTGR), modulating messenger ribonucleic acid (mRNA) metabolism and protein translation rates. RBPs represent a family of proteins that modulate stability, maturation, transport and degradation of cellular mRNAs (7). RBPs mediate their activity through their binding and interactions with mRNAs and other proteins; these form the dynamic complexes termed ribonucleoproteins (RNPs). The interaction with targeted transcripts occurs by binding conserved sequences mainly located in the untranslated regions (UTRs) (8). The functional activity of RBPs is correlated to their modular structure, characterized by the repeated multiple domains. Most of RBPs are composed by one or more RNA-binding domains (RBDs) that modulate the sequence-specific binding between RBPs and their related target mRNAs (9). Several RBPs are classified as canonical RBDs, including RNA recognition motif (RRM), K homology (KH) domain, double-stranded RNA-binding motif (DSRM) or zinc-finger domain (8,10) (**Figure 1**). Another RBPs are classified as non-canonical RBDs, that specifically bind with the intrinsically disordered regions (IDRs), characterized by repeated sequences rich in lysine, glycine and arginine (11).

Fig. 1. RBPs containing canonical RNA-binding domains (RBDs). The most common canonical RBDs are the RNA recognition motif (RRM), K homology (KH) domain, double-stranded RNA-binding motif (DSRM) and zinc-finger domain.



RBPs expression and function can change through intracellular and extracellular environmental stimuli modulating their subcellular localization and conformational state.

Alternative splicing of genes coding for RBPs mediates expression of several protein isoforms characterize by specific functions. The alternative splicing of the heterogeneous nuclear ribonucleoprotein (HNRNP)-D coding-gene, also termed as AU-rich element binding factor 1 (AUF-1),

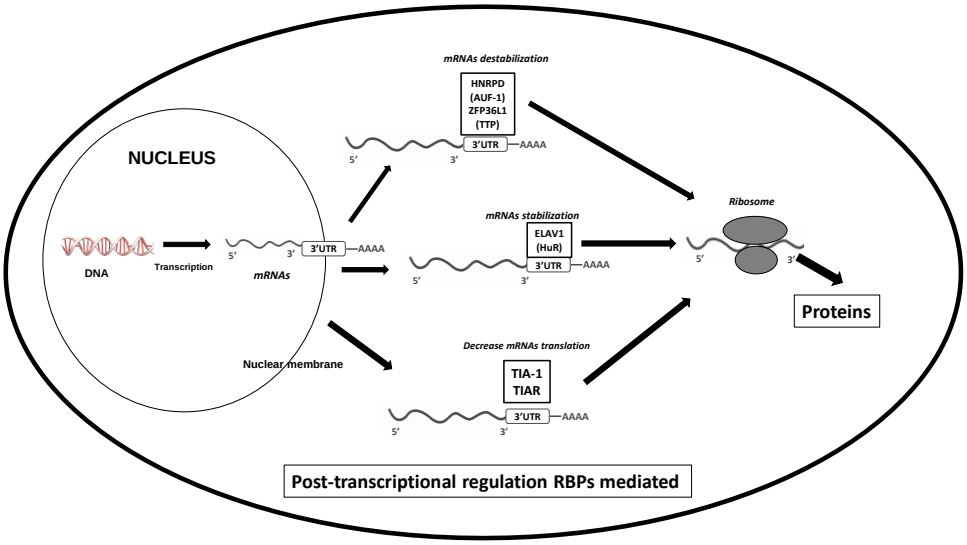
can mediate the expression of four different isoforms correlating also their differential sub cellular localization and binding capacity (12).

Post-translational modifications that characterized RBPs include methylation, acetylation, ubiquitination, isomerization and in particular the phosphorylation that is the most investigated. The RBP ZFP36 ring finger protein (ZFP36) also termed tristetraprolin (TTP) is characterized by several phosphorylation sites showing *in vivo* increased phosphorylation levels, mediated by kinase pathways activation (13,14).

Both mRNAs stability and translation are regulated by RBPs interacting with specific sequences present in the 3'UTRs and 5'UTRs and also in the coding sequence of the transcripts.

The most well-characterized RBP binding sequence is represented by the adenosine/uridine-rich elements, also termed AU-rich elements (AREs). Many RBPs correlating with ARE sequences of the gene transcripts can mediate mRNA destabilization, such as TTP, AUF-1 and KH-type splicing regulatory protein (KSRP), whereas others, such as embryonic lethal abnormal vision (ELAV) also termed human antigen R (HuR) show stabilizing effects (15-17). In addition, others ARE-binding proteins, such as T-cell-restricted intracellular antigen-1 (TIA-1) and T-cell internal antigen-1 related protein (TIAR), can mediate silencing of targeted transcripts (18) (**Figure 2**). Moreover, reversible biochemical modifications present on the mRNAs, collectively known as epitranscriptome, modulate the mRNAs metabolism during both physiological and pathological processes, through the modulation of the RBPs accessibility to mRNAs. In particular, the methylation of adenosine in RNA molecules (N6-adenosine methylation or m^6A) is the most known post-transcriptional mRNA modification process (19). Several RNPs are able to specifically interact with m^6A install, modulating mRNA stability and translation, splicing, miRNA biogenesis in homeostatic and disease conditions (20,21).

Fig. 2. RBPs activity on mRNAs. RBPs specifically can bind target mRNAs through conserved region in the 3'UTR region. AUF-1, TTP and BRF-1 are correlated to mRNA destabilization, HuR shows stabilizing effect, whereas TIA-1 and TIAR can mediated silencing of targeted transcripts.



RBPs in COPD pathogenesis: modulation of lower airways inflammation and drugs response

Role of RBPs have been evaluated in both homeostatic and pathogenic conditions, such as lung cancer and COPD, based on several pre-clinical data that correlate them in oxidative stress responses and chronic inflammation. RBPs have a key role in the post-transcriptional regulation of genes encoding for pro-inflammatory mediators (22), including interleukin (IL)-1β, IL-6, tumour necrosis factor (TNF)-α, interferon (IFN)-γ, transforming growth factor (TGF)-β, vascular endothelial growth factor (VEGF), C-X-C motif ligand (CXCL)-1, CXCL5, CXCL8, C-C motif ligand (CCL)-1, CCL2. Decreased levels of AUF-1, but not of HuR and TTP, were found in bronchiolar epithelium sampled from stable COPD patients compared to smokers with normal lung function. Similar results were shown in human bronchial epithelial cells upon inflammatory stimulation and, additionally, increased levels of pro-inflammatory mediators AUF-1-mediated were found in condition of AUF-$1^{-/-}$ (23). Furthermore, *in vitro* study of bronchiolar epithelial cell transcriptome of stable COPD patients showed a global downregulation of RBPs expression when compared to both smokers with normal lung function and non-smoker subjects; moreover, several molecules acting as co-regulated RBPs were found, showing the potential for RBPs interplay and shared post-transcriptional modulation of biological pathways involved in the pathogenesis of COPD (24).

The RBP heterogeneous nuclear ribonucleoprotein C (HNRNPC)1/2, that share the same protein family with AUF-1, was increased in both lung tissue of COPD patients and in mouse model of COPD cigarette smoke-induced (25). The RBP zinc finger protein 36-like 1 (ZFP36L1), also termed as Tis11b or butyrate response factor (BRF-1), included in the TTP zinc finger RBP family, can inhibit its binding with several targeted transcripts, including CXCL-8, IL-1β, matrix metalloproteinases (MMP)-3, MMP-10 and $p21^{WAP/CIP1}$ mRNAs when is phosphorylated (26).

Several studied have shown that RBPs have a key role also in drugs response and efficacy in treatment of COPD patients. Indeed, the RBP heterogeneous nuclear ribonucleoprotein U (HNRNPU) can bind the glucocorticoid receptor (GR) forming a complex that is localized into the nucleus (27). Interestingly, GR can act as an RBP by association with a specific subset of mRNAs carrying a guanine-cytosine motif in their 5'UTR, including those correlated to CCL2 and CCL7 expression, and mediating their increased decay (28). Post-transcriptional control plays a key role also in the β_2-adrenergic receptor (β2-AR) expression. The 3'UTR of β2-AR is composed by conserved ARE region binding the RBPs TIAR and HuR, inducing decreased expression of the receptor (29,30). Moreover, the 3'UTR of β_1-AR is correlated with AUF-1, HNRNPA1 and HuR (31,32).

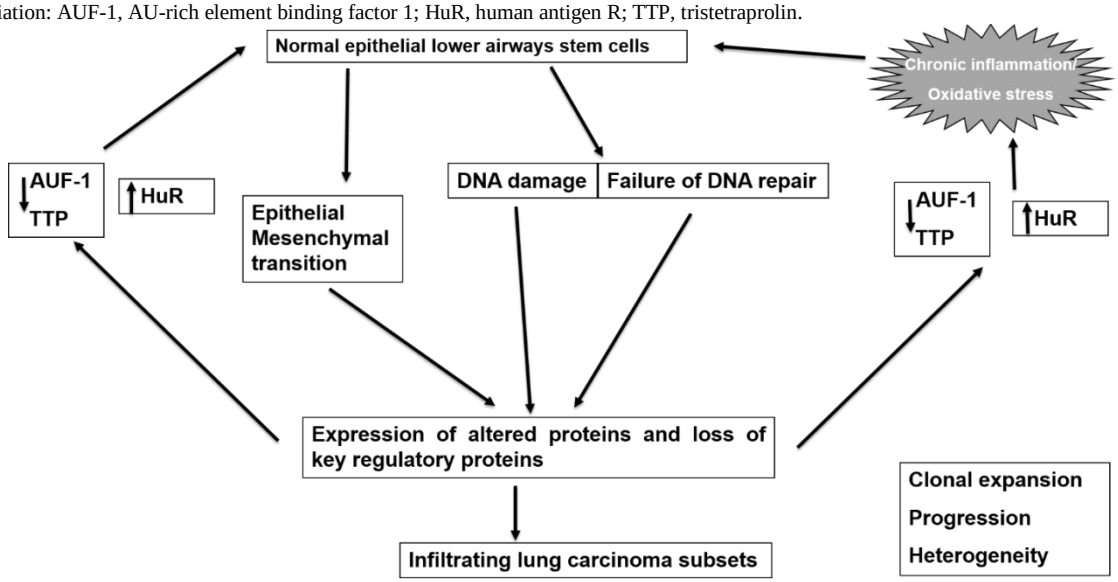
Role of the RBPs in the pathogenesis of lung cancer

Impaired RBPs expression and intracellular localization have been found also in several cancers, including lung cancer **(Figure 3)**. RBPs can regulate the mRNAs of several factors that have a key

role in several cell processes such as cell cycle, apoptosis, angiogenesis and epithelial–mesenchymal transition (EMT), they may also have a key role in the increased proliferation and invasiveness of the tumour cells.

HuR, a mRNA-stabilizer, is found into cytoplasm of cancer cells and can increase the stability and expression of several mediators inducing neoplastic transformation, such as the cationic amino acid transporter 1 (CAT1) and cyclooxygenase (COX)-2, through the inhibition of the miRNA binding (33,34). Whereas, TTP can modulate several pro-inflammatory and stress response transcripts, also regulated by HuR, through the decrease of their stability (35). The ratio between these RBPs has a key role in the pathogenesis of cancers. Indeed, decreasing of TTP is correlated to enhanced expression and activation of HuR, increasing mRNAs stabilization characterized in carcinogenesis (36,37).

Fig. 3. Molecular role of RBPs in lung carcinogenesis in COPD. Chronic airway inflammation and increased oxidative stress induce in normal epithelial lower airways stem cells DNA damage/impaired DNA repair mechanisms and epithelial mesenchymal transition. These are correlated to expression of altered proteins and loss of key regulatory proteins including increased HuR levels and decreased AUF-1 and TTP levels. These have a key role in maintaining of chronic inflammation and increased oxidative stress and in mediating lung carcinoma development. Abbreviation: AUF-1, AU-rich element binding factor 1; HuR, human antigen R; TTP, tristetraprolin.



Several RBPs have been associated with lung squamous cell carcinoma. In particular, the increased RBPs were mainly correlated to the modification and degradation of RNAs, whereas the decreased RBPs were mainly correlated in mediating of translation, TGF-β and Toll-like receptors (TLRs) signalling pathways (38). Furthermore, in patients with lung squamous cell carcinoma, nine RBP-coding genes were found differentially correlated with their prognosis (38). Enhanced expression of HNRNPK was found positively correlated with advanced tumour stage and negatively correlated with patients prognosis in non-small cell lung cancer (NSCLC). In addition, HNRNPK can have a key role in the TGF-β1-induced EMT in lung cancer cells mediated by a specific correlation with several cytoskeletal protein such as microtubule-associated protein 1B (MAP1B) (39).

NSCLC patients showed increased tumour lung tissue cytoplasmic levels of HuR that positively correlated with poor patient outcomes, advanced clinical stage and lymph node metastasis (40). In addition, cytoplasmic HuR levels were associated with enhanced VEGF-C expression, that is a

member of the VEGF family involved in tumour-induced lymphangiogenesis, suggesting that HuR can have an important role in the development of lymph node metastasis of NSCLC (41).

The phosphorylation of TTP has a key role in the lung carcinogenesis. In normal cells the active form of TTP, characterized by decreased phosphorylation status, can bind the 3'UTR of programmed death-ligand 1 (PD-L1) transcript, inducing both its mRNA degradation and consequently its decreasing expression. The oncogenic RAS pathway when activated in tumour cells, including lung cancer cells, mediates increased TTP phosphorylation inducing its decreased function, enhanced PD-L1 expression and onset of tumour immune resistance (42). The regulator of mRNA translation Musashi 2 is increased in NSCLC tissues compared to normal controls, driving metastasis through the TGFβ signalling pathway activation (43).

The nuclear RBP RNA-binding motif protein 10 (RBM10) is found decreased in the tissues of some patients with lung adenocarcinoma (44), whereas increased RBM10 levels are correlated with inhibited cell growth and both increased apoptosis and overall survival of the patients (45). HuR is the most expressed RBP in small cell-lung cancer (SCLC) (46). Increased HNRNP (AUF-1) mRNA levels were found in SCLC cell compared to NSCLC cells (47). Decreased expression of RBM5 has also described in SCLC cells, blocking cell cycle and mediating apoptosis (48).

The role of RBPs in shared pathways of COPD and lung cancer

Both COPD and lung cancer pathogenesis is characterized by risk factors that underlie complex interactions between genetic and environmental factors, mainly including chronic cigarette smoke exposure. The increase of both pro-inflammatory mediators and oxidative stress mediate enhanced DNA damage, decreased and impaired DNA repair mechanisms increasing cellular proliferation, showing that COPD is an independent risk factor and a potent driver for lung cancer development (49,50). In addition, lower airways inflammation, can also mediate the neoplastic transformation. Particularly, proteases release mediated both extracellular matrix and tissue structure remodelling, inducing tumour cell invasion and metastasis (51). Pro-inflammatory mediators modulate recruitment and activation of several immune cells, including T cells, macrophages and natural killer (NK) cells, that inhibits tumorigenesis (51). As reported previously, the mRNAs that regulate inflammatory factors expression are regulated by RBPs (**Table 1**).

The chronic inflammation in the lower airways, that characterize COPD, induces change of the epithelial cells towards EMT, mediating the invasiveness of cells. Active EMT has been found in both squamous cell and adenocarcinoma NCLC-subsets, but also in the bronchial epithelial basal cells of stable COPD patients (52,53). The EMT-associated proteins β-catenin, SNAIL family transcriptional repressor (SNAIL)1 and also family BHLH transcription factor (TWIST) are increased in the lower airways of both smokers with normal lung function and COPD patients (52).

SNAIL-1 mRNA is a target of the RBP HuR, mediating a stabilizing effect that is decreased during enhanced oxidative stress conditions (54). In contrast to its main activity, AUF-1 can also show a stabilizer activity of the mRNAs of SNAIL1 and TWIST1 (55) (**Table 1**).

Table 1. RBPs role in the pathogenic mechanisms shared by COPD and lung cancer.

Functional effect of RBPs	**RBPs**	**Mediators**	**Biological mechanism**
mRNA decay	AUF1, ZFP36L1, TTP	$p21^{WAP/CIP1}$, $p16^{INK}$, cyclin D1, COX-2,IL-1β, IL-6, IL-8, TNF-α, CCL2, MMP3, MMP8, MMP10, VEGF, PAI, ZEB2	Oxidative stress and inflammation, epithelial-mesenchymal transition
mRNA stabilization	HuR, AUF-1	$p21^{WAP/CIP1}$, $p16^{INK}$, cyclin D1, COX-2, IL-6, TNF-α, IL-1α, CCL2, CCL8, CXCL1, CXCL2, CXCL8, MMP1, MMP9,p53, TGF-β, PAI, SNAIL, TWIST, ZEB1	Oxidative stress and inflammation, DNA damage/repair, epithelial-mesenchymal transition
Translation decrease	TIA-1/TIAR, CIRBP	TNF-α, COX-2, RPA2, ATR	Oxidative stress and inflammation, DNA damage/repair

Obtained from data 18, 26, 38, 54, 55,61-78
Abbreviation: ATR: ATR serine/threonine kinase; AUF1: au-rich element RNA-binding protein 1; CCL: chemokine ligand; CIRBP: cold-inducible RNA-binding protein; COX: cyclooxygenase; HuR: HU-antigen R; IL: interleukin; MMP: matrix metalloproteinase; p: protein; PAI: plasminogen activator inhibitor; RBPs: RNA-binding proteins; RPA2: replication protein A2; SNAIL: snail family transcriptional repressor; TGF: transforming growth factor; TNF: tumor necrosis factor; VEGF: vascular endothelial growth factor; TIA-1: TIA1 cytotoxic granule-associated RNA-binding protein; TTP: tristetraprolin protein; TWIST: twist family BHLH transcription factor; ZEB: zinc finger e box-binding homeobox; ZFP36L1: zinc finger protein 36-like.

Increasing evidences show that the lung microenvironment is correlated to homeostatic and pathological tissue responses through the extracellular vesicles (EVs), that are a heterogeneous group of membraned vesicles of different size and origin (56), that can act as mediators of many fundamental biological processes, including pro-inflammatory conditions and tumour development (57). EVs sampled from the bronchoalveolar lavage (BAL) of stable COPD patients were characterized by the presence of enhanced levels of both miR-451a and miR-663a compared to the EVs from healthy subjects (58). Similarly, increased levels of miR-27a-3p and miR-106b-3p are present in EVs sampled from lung cancer patients when compared to EVs from stable COPD patients (59).

In addition, RBPs have also the function of transporters of the cellular RNAs into EVs produced by both immune and structural cells (60). The production of EVs composed by RBPs may represent a mechanism for spreading inflammation and enhancing aging cells, through the transfer of RNAs with a key role in these biological processes or through action on transcripts into the recipient cell.

Conclusions

COPD represents an independent risk factor for the development of lung cancer, although the

complex intracellular pathways network is not fully understood. However, RBPs can have a key role, through their rapid response to both homeostatic and pathologic cell conditions, and the capacity to modulate several sets of genes correlated in chronic inflammation development and carcinogenesis. RBPs can drive chronic inflammation development and neoplastic transformation and for these reasons may be considered as potential novel therapeutic targets both when lung cancer is established and during the neoplastic promotion from COPD status. RBPs regulatory role could be a potential specific target in therapeutic strategies against accelerated, stress-induced cellular senescence. Moreover, RBPs composing EVs may also be a new target for new therapeutic strategies (e.g. drug delivery) or as biomarkers for disease progression.

Conflicts of Interest. The Authors declare no conflict of interest

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