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The Role of Mnk-1, Eukaryotic Translation Initiation Factors and Translation Control in the Pathogenesis of Asthma

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Commentary

Asthma is the most common chronic inflammatory disease of the lung and is characterised by inflammation and airway wall remodelling. Chronic inflammation can be controlled by inhaled anti-inflammatory drugs, while airway wall remodelling can only be limited by bronchial thermoplasty. The mechanism that leads to airway wall remodelling is not well understood and recent studies suggested that epigenetics play a major role in asthma pathogenesis. Epigenetics describe mechanisms that modify the expression of genes without changing the genetic code. Epigenetic events can be triggered by environmental factors and even be inherited over several generations. In asthma, there is evidence suggesting that epigenetic events lead to faulty translation control of specific proteins. Mitogen activated protein kinase interacting serine/threonine-protein kinase 1 (Mnk-1) and eukaryotic translation initiation factor (eIF4E) are two major controllers for the initiation of mRNA translation into proteins. Mnk-1 controls mRNA stability, its export from the nucleus and the initiation of translation through eIF4E. In asthma, the expression of several pro-inflammatory cytokines and factors that contribute to remodelling have been linked to deregulated action of the translation initiating protein eIF4E or its ligand eIF4E binding protein. The expression and action of eIF4E is regulated by Mnk-1 and mTOR, both have been recently associated with asthma pathologies. The best studied proteins that are regulated *via* translation control in asthma are: Nox4, C/EBP-α, p38, calveolin-1, CXCL10 and eotaxin. The aim of this review is to establish a hypothesis where deregulated translation control is driving the pathogenesis of asthma.

Introduction

The concept of airway wall remodelling in asthma has significantly changed over the past decade. Earlier it was thought that airway wall remodelling results from term chronic inflammation in asthma or COPD [1-4]. Recent clinical studies indicated that airway wall remodelling occurs before or without inflammation [1,5,6]. Asthma relevant cytokines such as IL-3, IL-4, IL-5, TGF-β, TNF-α and IgE, contribute to airway wall remodelling, but their inhibition did not significantly reduce the pathology [7]. Thus, there must be other mechanism that control airway wall remodelling or reduce the threshold for mesenchymal cells to response to these remodelling driving stimuli.

In 2011, Grainge et al. conducted a study where volunteers inhaled either a cholinergic stimulus or house dust mite antigens three times over five days, with bronchus biopsies obtained before and inhalation and three days after the last inhalation [6]. Shown in tissue biopsies, airway wall remodelling was induced by both stimuli and prevented in patients who inhaled a short acting β2-agonist. Remodelling was indicated by epithelium derangement, increased gland cell numbers and thickening of the sub-epithelial basal membrane [6]. Unfortunately, this study did not investigate the modification of sub-epithelial mesenchymal cells. Furthermore, hypertrophy of sub-epithelial fibroblasts and airway smooth muscle cells in the absence of inflammation was reported in childhood asthma and preterm born children [8-10]. Data in cohorts of preterm born people suggest that such a condition during embryogenesis pre-sets the lung to develop asthma or COPD later in life [11,12]. This correlation had been described earlier in rhesus monkeys exposed to ozone or allergens enriched air during pregnancy, which led to permanent rearrangement of airway smooth muscle cells and asthma like symptoms after birth [13-15]. These animal studies provided first evidence that exposure to asthma triggers during embryogenesis start a process that alters lung maturation lastingly and which stays active even after the stimulus was removed for long term, suggesting epigenetic events.

Epigenetics, Translation and Remodelling

The term "epigenetics" was introduced by Waddington in 1942 [16] does not describe a specific mechanism but describes changes of gene expression without any alteration of the genetic code. In 2001, epigenetics was redefined as changes of gene function which can be inherited but do not entail changes in the DNA sequence [17]. Approximately, 147 base pairs of DNA are wrapped around 8 histones (2x histone2A. histone 2B, histone 3, histone 4) in non-transcriptional conditions. When DNA is transcribed into RNA, it is unwound from histones to give space for transcription factors and other proteins [18]. The rate by which DNA is transcribed into RNA can be regulated by the density of the DNA-histone packaging and this is susceptible to chemical modification by various enzymes and presents the first of many epigenetic events [19]. DNA and histones can be methylated, and thereby modify the rate of gene transcription and have been associated with the pathogenesis of asthma [20,21]. DNA methylation patterns in lung cells were associated with endotype and genetic risk of asthma [22].

It is indicated that histone 3 is a preferential target for epigenetic modification by either methylation or acetylation [23]. The mechanism by which histone 3 contributes to the pathogenesis of asthma may occur in a cell type specific pattern and in epithelial cells involves the action of Erk1/2, C/EBP-β, p300 and NFκB [24]. In airway smooth muscle cells, histone 3 methylation correlated with the secretion of vascular endothelial growth factor (VEGF) which was directly dependent by the action of methyl transferase G9a [25,26]. In asthma, airway smooth muscle cells are deficient of G9a and therefore the hypomethylation of specific promoters, including that of VEGF gene had been described [27].

Histone methylation is also regulated by protein arginine methyl transferase (PRMT), and arginine methylation was controlling the action of acetyl transferase p300 [28]. Constitutive expression of PRMT1 had been described in human airway mesenchymal cells and was linked to increased remodelling properties [29]. Interestingly, PRMT1 expression was regulated through another epigenetic event, microRNA expression. MicroRNAs are regulatory units which target mRNA and thereby increase their degradation and block their translation into proteins. In regard to asthma, it has been reviewed that microRNAs are coming into focus for the pathogenesis of several respiratory diseases [30,31]. Studies assessing the heritability of asthma suggested that epigenetic modification of gene regulation is a central pathology which can be handed down over at least over three generations [32-35]. Recent studies indicated that asthma is caused by an inheritable epigenetic event which modifies protein expression [11,34]; thus, post-transcriptional control became focus of interest. Reflecting these new data on epigenetic events and airway wall remodelling in asthma, the American Thoracic Society stated that unless airway wall remodelling is understood, there will be no cure for asthma [4]. Thus, the search for new therapeutic targets in asthma has to be promoted.

In regard to the pathogenesis of asthma, several translation regulators have been described as relevant, including mitogen activated protein kinase interacting serine/threonine-protein kinase 1 (Mnk-1) and eukaryotic translation initiation factor (eIF4E). Both factors interact or interfere with each other on the level of signal transduction. Translation of mRNA into protein depends on binding of eIFs which is essential for cell proliferation [36]. Nutrition and growth factors activate phosphatdylinositol-3-kinase (PI3k) which stimulates mTOR and thereby phosphorylates 4EBP, which is an inhibitor of eIF4E [37,38]. Freed eIF4E then forms a complex with other eIFs which initiates translation of most cell cycle driving proteins including cyclin-B1, -D1, -E, cyclin dependent kinase (cdk) and p21Waf1/Cip1. Interestingly, the blockade of either mTOR or eIF4E was sufficient to reduce proliferation of stem cells and smooth muscle cells on the level of translation control; while mRNA levels of the above named cell cycle proteins was not altered [37]. Importantly for chronic inflammatory lung diseases, radical oxygen species scavengers achieve a similar effect on translation [39]. In smooth muscle cells of other organs, the role of eIF4E, 4EBP, p70S6 kinase and Akt in the control of proliferation has been studied in more detail; thus, it is likely that translation control is similar important in airway smooth muscle cells. In vascular smooth muscle cells, arachidonic acid stimulated proliferation was signalled through COX by phosphorylation of Akt, p70S6 kinase, 4EBP and eIF4E [40]. In the same cell type, Mnk-1 was necessary for the phosphorylation of eIF4E involving Erk1/2 but not p38 mitogen activated protein kinase (MAPK), which resulted in smooth muscle hypertrophy [41]. In our study on human airway smooth muscle cells, inhibition of MNK-1 and subsequent eIF4E phosphorylation resulted in reduced cell proliferation and an inhibition of chemokine secretion [42]. The same signalling pathway was activated by angiotensin-II in regard to smooth muscle cell hypertrophy in angiogenesis [43,44], which could be inhibited by PPAR-γ and 4EBP activation [45]. Insulin and amino acid also activated smooth muscle cell proliferation through p70S6 kinase and eIF4E [46].

Smooth Muscle Cell Function and Translation Control

In airway smooth muscle cells, oxidative stress induced Mnk-1 and eIF4E activity through both Erk1/2 and p38 MAPK suggesting that in different organs, translation is controlled through distinct signalling pathways [47]. The expression of contractile proteins in airway smooth muscle cells by TGF-β1 was also regulated on the translational level through hyper-phosphorylation of e4BP and therefore by eIF4E [48]. In addition, TGF-β induced hypertrophy of airway smooth muscle cells was also regulated through translation control by eIF4E [49,50].

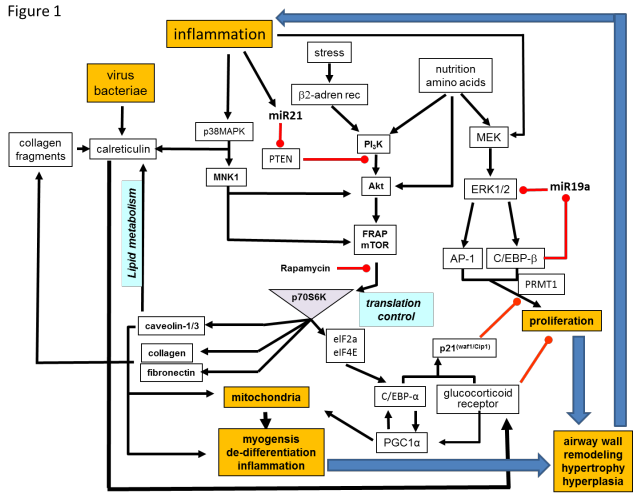

Figure 1: Interaction of intra-cellular signalling cascades involving MNK-1 with IP3K-Akt-mTOR and airway wall remodelling. Akt: Serine/Threonine kinase; AP-1: Activating Protein-1; β2-adren rec: β2 adrenergic receptor; C/EBP: CCAAT enhancer binding protein; eIF4E: Eukaryotic translation Initiation Factor 4E; ERK: extracellular signal-regulated kinases; FRAP/mTOR: mechanistic Target of Rapamycin; MEK: MAPK Erk-kinase; miR: microRNA; MNK: mitogen activated kinase interacting kinase; PGC1α: PPARG co-activator-α; PI3K: Phosphoinositol-3 kinase; PRMT1: Protein Arginine Methyl Transferase; PTEN: Phosphatase and TENsin homolog; p21waf1/ciop1: Cyclin dependent kinase inhibitor p21; p38: mitogen activated protein kinase 14; p70S6K: Ribosomal protein S6 Kinase.

However, other eIFs are involved in airway smooth muscle hypertrophy including eIF2B [51]. Chronic stress in an animal model activated the signalling cascade PI3 kinase/Akt/GSK3β, which hyper-phosphorylated 4EBP and up-regulated calcium sensing channel in smooth muscle cells which interfere with the muscle relaxing long acting β2-agonists [52]. TGF-β induced epithelial mesenchymal transition was also sensitive to the blockade of eIF4E and involved the translation of Snail1 [53]. In regard to asthma eIF4E has been linked with hypertrophy of airway smooth muscle cells [50] which could be induced by TGF-β1 treatment [54].

Airway smooth muscle cells differentiation was linked to the activation of eIF4E by TGF-β induced expression of caveolin-1 [55]. Furthermore, the activation of eIF4E was also reported in response to virulence protein C of human parainfluenza virus type 3 in three different immortalized human epithelial cell lines [56], suggesting that viral induced asthma exacerbations may be linked to modified translation. In conclusion, these results support the idea that airway wall remodelling and airway smooth muscle hypertrophy is mainly controlled through translation, rather than by transcription. The details of this post-transcriptional regulation of airway wall

remodelling are not well studied. Thus, better understanding of the process and its modification in chronic inflammatory airway diseases may leads to new therapeutic options which go beyond symptom control.

Faulty translation as a cause of pathologic airway smooth muscle cell function in asthma had been linked to uncontrollable proliferation leading to hypertrophy [57], and this pathology can be induced by allergens or cigarette smoke on different post-transcriptional levels [58,59]. The reduced translation of the smooth muscle cell differentiation factor C/EBP-α was the result of low levels of eIF4E and increased expression of calreticulin, the later has been reported to bind directly to the mRNA of C/EBP-α through a CUG nucleotide sequence [57,59,60]. An overview of the regulatory intracellular signalling pathways that have been proven for tissue forming cells in asthma associated airway wall remodelling is provided in Figure 1.

Epigenetic Programming of Cell Function on the Level of Translation Control

The rhesus monkey presents the best model to study lung development, structure and function in the context of the pathogenesis of chronic inflammatory lung diseases [15]. These studies provided first evidence that lung maturation is lastingly altered when mothers were exposed risk factors for asthma or COPD. Importantly, the tissue structure changing effect of inhaled allergens or gases has now been confirmed in human [61]. Both study groups provided evidence that the airway smooth muscle not only the mass of airway smooth muscle is increased in asthma, but also its arrangement in the airway wall forming a spiral like structure. Such a spiral forming smooth muscle bundle will constrict the airway much more than smooth muscle bundle which are arranged in no specific pattern. Referring to the studies performed by the research team of Prof. Plopper in rhesus monkeys, it is indicated that this structuring of smooth muscle bundles occurs during the late embryogenesis and is not controlled on the level of transcription. However, the mechanism by which this rearrangement of muscle bundle in asthma is controlled remains unclear and needs further investigation.

Oxygen plays a central role to initiate the maturation of the developing lung after birth by surfactant protein activation through C/EBP-α and hypoxia inducible factor 1α [62-64]. In mice, the interaction of C/EBP-α and cAMP Response Element Binding protein (CREB) affected the development of the embryonal lung [65]. In this context, earlier studies indicated direct interference of C/EBP-α with CREB should be taken into consideration [66,67].

A central role of C/EBP-α in the development and maturation of the embryonic lung has been reported by others [68-70]. C/EBP-α is also important for the response to the most frequently prescribed anti-inflammatory asthma drugs–steroids. The glucocorticoid receptor forms a complex with C/EBP-α and most probably with other C/EBP-isoforms which directs the action of the transcription factors [71-74]. In airway smooth muscle cells of asthma patients, the expression of C/EBP-α was controlled through translation involving the action of calreticulin which directly binds to C/EBP-α mRNA [57] and this mechanism was triggered by house dust mite antigens as well as cigarette smoke in human lung cells [58,59]. However, the question if the constitutive low expression of C/EBP-α in asthmatic airway smooth muscle cells [75] is due to the overexpression of calreticulin or involves other translation regulators such as the eukaryotic translation initiation factor 4E (eIF4E) or its binding protein (4E-BP) has to be further investigated.

The pathogenesis of asthma was also linked to other eukaryotic translation initiation factors. In asthma, eIF2B was linked to muscle hypertrophy in ovalbumin challenged mice, which was independent of TGF-β but sensitive to glycogen synthase kinase-3β and lithium chloride (LiCl) [51]. LiCl is known to regulate C/EBP-α expression [76], and thereby links the action of eIF2B to the lack of C/EBP-α in asthma patients described earlier [75]. Signalling *via* eIF2 was indicated to be affected by viral infection of the respiratory duct in children based on transcriptomic assessment [77]. Such a signalling pathway is supported by an animal model of allergen induced asthma in mice [78].

Other Epigenetic Mechanisms that Affect Protein Translation and their Roles in Predisposition to Asthma

DNA methylation can be induced by cigarette smoking across the human genome which lasts even years after smoking cessation [79]. Three recent publications reported that prenatal smoking of mothers induces DNA methylation which seems to be irreversible during the life time of the child [80-82]. Comparing the effect of cigarette smoking of mothers during pregnancy in 65 children with asthma to that of 462 children also with asthma born to mothers who did not smoke during pregnancy, significant CpG methylation was observed in 2 genes (FRMD4A, Cllorf52) and a lower increase of methylation in 4 additional genes (XPNPEP1, PPEF2, SMPD3, CRYGN) [81]. The function of these genes is either unknown or affects protein phosphorylation; not much is known on the function of these proteins by cigarette smoke beside this study. The study suffers from the lack of healthy control groups, which would consist of healthy children from mothers who smoked and did not smoke during pregnancy. A second study supported the effect of tobacco smoke during pregnancy on DNA methylation in 572 children. Smoking of mothers during pregnancy reveal increase DNA methylation of the children at school age and the analysis of 26 CpG loci indicated a gene specific methylation pattern including the AHRR and CYP, which are both related to inflammation innate immunity and DNA accessibility [82]. Most of the other loci which were methylated by prenatal smoking have no known function, therefore, their impact on lung function and development has to be further investigated.

DNA methylation and histone modification are two of the best studied epigenetic regulatory mechanisms that are associated with organ function efficiencies [83,84]. Interestingly, DNA methylation induced by cigarette smoking affected α-1 anti-trypsin deficiency, which may be linked to the development of emphysema [85]. In this study, CpG methylation occurred mainly in genes that regulate signal transduction proteins inducible by TGF-β. Cigarette smoke also inhibits intra-cellular signalling of Erk1/2 in human lung fibroblasts [86], which also regulate mucus secretion in a rat model [87].

Another mechanism that regulates DNA accessibility is the acetylation of histones, which has been suggested to play an important role in CILD [88,89]. Pro-inflammatory signalling such as NFκB and its inhibitors IκB were linked to histone acetylation in animal models [90,91]. Other modification of histones include phosphorylation and sumoylation [92,93]. However, the question why DNA methylation or histone acetylation induced by cigarette smoke seems to be restricted to certain genes is not understood.

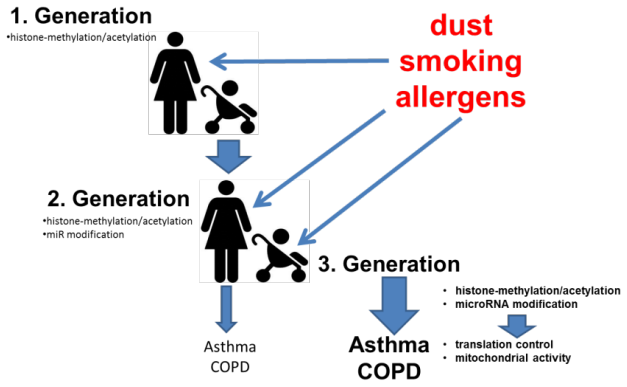

Figure 2: Cross generation transfer of environmentally-initiated epigenetic events that can lead to asthma or chronic obstructive pulmonary diseases (COPD).

Recently reported novel post translational modification factors are Protein Arginine Methyl Transferases (PRMT) [94]. The function of PRMT had been linked to histone methylation and thus could affect DNA accessibility indirectly [95,96]. In an animal model, the cell type specific expression of PRMT1 was described [97]. In this model, PRMT1 was induced in the bronchial and alveolar epithelium after allergen inhalation. Furthermore, it was shown that IL-4 was the major mediator of the allergen effect on PRMT1 expression [97,98]. In the second study of the same group, it was reported that PRMT1 expression is cell specific with being up-regulated in acute inflammation after allergen exposure in the epithelium, while in animals with chronic allergen exposure, it is up-regulated in fibroblasts [99]. In fibroblasts, PRMT1 correlated with the expression of COX-2 and VEGF and function as a mediator of TGF-β stimulation. Finally we provided evidence that PRMT1 is constitutively up-regulated by an epigenetic event which diminishes the expression of the Erk1/2 MAPK inhibitor microRNA-19a in human airway smooth muscle cells of asthma patients and increases airway smooth muscle cell proliferation, migration and inflammation [29]. Furthermore, we show that PRMT1 affects the activity of mitochondria, thus cell activity and energy consumption through up-regulated PGC-1α expression, which is an epigenetic mechanism by itself. In Figure 2 we present a summary of the known epigenetic events that can be handed down over at least three generations and which pre-dispose the lung to develop asthma or COPD later in life.

Conclusion

There is increasing evidence that translation control through eIFs plays a role in the pathogenesis of asthma. The regulation of eIFs involves the action of Mnk-1 and mTOR signalling; however, the details have to be further evaluated. It remains to be elucidated by which mechanism these epigenetic events become constitutive and can even be inherited.

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