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Airway smooth muscle cells respond directly to inhaled environmental factors

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Summary

A misled or overreacting immune response is assumed to be the major cause of the most prevalent chronic inflammatory lung diseases, asthma and chronic obstructive pulmonary disease (COPD). The contribution of tissue forming cells, especially of airway smooth muscle cells, to the pathologies of both diseases has only recently attracted some attention. New studies in childhood asthma and a Rhesus monkey model strongly suggest a central role of the airway smooth muscle cells on lung development, structure, function and response to environmental factors. Airway smooth muscle cells express and respond to activation of IgE receptors. In addition, airway smooth muscle cells recognise and respond to environmental factors, including allergens and dust, via mechanisms that are independent of the immune system such as PAR2 or calreticulin. Interestingly these changes occur not on the level of gene activity but on the level of protein synthesis. The reason why these temporary changes become chronic in asthma and COPD remains to be studied.

Key words: epithelial cells; airway smooth muscle cells; fibroblast; asthma; COPD

Introduction

The two commonest chronic inflammatory airway diseases are asthma and chronic obstructive pulmonary disease (COPD), which are a substantial burden for healthcare systems worldwide. Together the two diseases affect 11–19% of the world's population, with wide geographic variation. Asthma and COPD account for the majority of absences from school and work, as well as for increased morbidity and mortality [1, 2].

The healthy lung's main function – gas exchange – relies on homeostatsis of the tissue structure of the bronchi and of the alveoli, which are formed by very thin cell layers that provide a large surface between inhaled air and blood vessels [3]. Any change in this structure may reduce breathing capacity and thereby gas exchange. Fibrosis of the alveoli with increased extracellular matrix deposition hinders gas exchange. Thickening of the airway wall by tissue-forming cell types including fibroblasts and airway smooth muscle cells, as well as increased deposition of extracellular matrix increases stiffness and hyperconstriction, thereby reducing breathing capacity [1–3]. While the structure of aveoli is changed in COPD, airway wall remodelling occurs in a disease- specific fashion in the upper airways in asthma and in the smaller airways in COPD [3]. Exacerbation in asthma and COPD is caused by either infections or air pollutants. In general, air pollution has been estimated to account annually for >3.6m deaths and 62 000 hospital admissions for respiratory malfunction in Europe [4]. Air pollutants impair lung function and cause inflammation and airway remodelling in adults, while in children it may result in reduced lung growth [4].

Recent knowledge of the pathologies of both diseases suggests that a misled immune response is the major cause [2–7]. For years this view has placed the focus of research in lung-infiltrating immune cells and the array of pro-inflammatory cytokine these cells release locally. Data from animal and clinical studies suggested various hypotheses as to how an imbalance of pro-inflammatory cytokines and growth factors induce and propagate chronic inflammatory lung diseases [5–9]. The role of Th1 and Th2 cells was suggested by animal models and seemed to be confirmed in human studies [9–14], resulting in inclusion of this definition in World Health Organisation guidelines [15]. However, subsequent studies did not support this theory since in humans the suspected cytokines (IL-4, IL-5, IL-13) did not correlate with the severity of the diseases and thus put in question the role of T-cells in these pathologies [16–19].

A summary of the large amount of data now available on the role of immune cells in chronic inflammatory lung diseases affords growing evidence that initiation and progression does not necessarily need the immune system [5, 7, 20–22]. At least in childhood asthma, in humans as well as in rhesus monkeys there is evidence that airway wall remodelling occurs long before any sign of inflammation can be detected [20–22]. Furthermore, the rhesus monkey model suggests a special role for airway smooth muscle in the attraction and activation of lung infiltrating immune cells [20, 22]. This reposes the question of where it all starts?

Asthma was first described as a pathology of the airway smooth muscle since all asthma cases examined presented one unique pathology, an increased mass of airway smooth muscle bundles [23]. Today an increasing number of publications have provided evidence on both the clinical and experimental level that this tissue- and structure-forming cell type may indeed be more important than was subsequently thought. Shortly after it became possible to isolate and cultivate human airway smooth muscle cells, a number of cell-type and disease-specific pathophysiologies were described. Airway smooth muscle cells of asthma patients show a predisposition to proliferate faster [24, 25] which was linked to both reduced expression of the transcription and differentiation factor C/EBP-α [26] and to an increased number of mitochrondria which were hyperactive [25]. Interestingly, many mitochondrial genes are controlled by C/EBP, which itself is the target of mitochondrial proteins as summarised earlier [27]. In a new mouse model of maternally transmitted airway inflammation it was also shown that the airway smooth muscle cells play a pivotal directing role in lung structural development during embryogenesis, implying this role in adult life during regeneration or inflammation [28]. An overview of these functions is provided in figure 1.

However, asthma is a complex disease with a highly variable phenotype, and it would be superficial to assume that a single cell type may cause it. It is more likely that the communication network linking the different cell types of the airway wall has gone out of balance. However, the airway smooth muscle cell and the so-called myo-fibroblast may be more in the centre of the action than previously assumed [29–31]. New evidence suggests that in asthma epithelial cell differentiation may be less prominent and result in a predisposition to undergo transition to mesenchymal cells, which in turn present features of muscle-like cells [32]. Together with the altered airway smooth muscle cells and myofibroblasts, reduced airway epithelial cell function and the lung infiltrated immune cells may keep the chronically inflamed lung in a constant state of alert, thus responding faster to environmental stimuli [20, 22].

In COPD airway remodelling occurs more distally in the medium- to small-size airways, and the cytokines involved are not all the same as in asthma [33–36]. COPD was long regarded as an extreme form of asthma, followed by lung deterioration and emphysema [37, 38]. Again, immune cells were seen as the major driving force behind disease progression. Similarly to asthma, recent clinical observations and experimental data suggest a different story: evidence is accumulating that the interaction of the so-called "epithelial-mesenchymal unit" is disturbed in COPD [20, 37, 38]. The control of an organ's homeostasis and function depends on the communication between the different cell types forming it. In this case it is communication between the epithelial cells and the fibroblasts and myo-fibroblasts (fig. 2) in particular. It is now suspected that this communication is disturbed, mainly by products contained in cigarette smoke and by fine dust particles [39, 40]. The question is: How can inhaled substances so different from each other modify the function of specific lung cells persistently?

There is evidence that the airway smooth muscle initiates even the inflammatory response in asthma, especially in response to inhaled allergens and infectious microorganisms [41, 42]. However, on this view it is assumed that inhaled allergens mainly act on immune cells, causing them to adhere to airway smooth muscle cells and thereby altering their function via cell adhesion molecules (CAM). Importantly, it was also pointed out that airway smooth muscle cells release chemo-attractants and thus contribute to the further recruitment of immune cells into the lung [41, 42]. Thus, activated immune cells modify the function of airway smooth muscle cells in such a way that they call in more immune cells.

Micro-organisms such as *Chlamydia* or *Rhinovirus* are a major cause of exacerbation in asthma and COPD, and they may activate airway smooth muscle cells directly via toll-like receptors (TLR) and glycol proteins. TLR recognise bacterial and viral proteins and stimulate an inflammatory response. For airway smooth muscle cells it appears that LPS is the most important direct ligand to TLR and thus increases airway hyper-responsiveness [43] and the secretion of pro-inflammatory cytokines such as IL-6, eotaxin, or ICAM [44–46]. The observation that microorganisms modulate the activity of differentiation and inflammation regulating transcription factors such as C/EBPs, NF_KB, AP-1, and even the glucocorticoid receptor in various host cell types [47–49], requires investigation of this issue in airway smooth muscle cells in asthma and COPD. Such a mechanism could be regarded as a microorganism-induced reprogramming of the host cells' function and thereby induce a state of chronic inflammation.

Several studies have demonstrated that under defined conditions airway smooth muscle cells of asthma patients produce more pro-inflammatory cytokines than cells of non-asthmatics [50–53]. The range of pro-inflammatory factors released by asthma patients' activated airway smooth muscle cells includes those which attract immune cells into the lung [35, 41, 42, 54–56] and a differently composed extracellular matrix [50–53]. Changes of the extracellular matrix also have significant effects on the differentiation and function of neighbouring cells and of lung-infiltrating immune cells [53, 54], although more studies in this area are needed.

These findings point towards a precondition of the airway smooth muscle cell in asthma that has to be activated by environmental factors such as allergens and dust particles, leading to chronic inflammation. The inheritable component of asthma may be linked to innate immunity, since in several studies the expression and function of anaphylatoxin receptor C3a correlated with asthma symptoms in the lungs of mice and humans [57–59]. The C3a receptor is thought to mediate the interaction of airway smooth muscle cells with mast cells and induce degranulation, which contributes to inflammation [57, 59]. However, the conclusion on the role of C3a and C5a in airway smooth muscle cell function in asthma was based on indirect evidence [56] and a later study questioned whether human airway smooth muscle cells express this protein while they interact with mast cells that express C3a and C5a [57].

Studies in a non-human primate model for asthma indicated that exposure to allergens shortly after birth somehow persistently modifies the differentiation setting of airway smooth muscle cells [20, 22, 60]. The studies suggested that the airway smooth muscle cell is able to directly recognise and respond to allergens. Indeed, there are reports that airway smooth muscle cells express the IgE receptors. The FcepsilonRII (CD23) is expressed at a significantly higher level on airway smooth muscle cells of asthma patients compared to controls [61]. In our own study we found no significant differences of the IgE receptor expression comparing them on airway smooth muscle cells of asthma patients and non-asthma controls [62].

In response to IgE complex stimulation, airway smooth muscle cells produced IL-1β, a well known pro-inflammatory factor for asthma. In addition, human airway smooth muscle cells express FcepsilonRI and its activation increases intracellular calcium levels and cell contractility. FcepsilonRI activation also resulted in the production of typical asthma related cytokines including IL-4, IL-5, IL-13 and eotaxin. All these responses were counteracted by the presence of neutralising antibodies to FcepsilonRI [63]. Further, we observed that both cell types secreted asthma-relevant IL-4, IL-6, IL-8 and TNF-α upon IgE stimulation, which was inhibited by IgE-antibodies [62]. Thus, it is likely that earlier reports that sensitisation of airway smooth muscle cells by serum led to increased calcium and muscle cell contraction involved the action of IgE receptors [64, 65]. Also, airway smooth muscle cells expressed the three receptors for IgG (CD64, CD32, CD16), but with no known consequences [61, 66].

It is also possible that airway smooth muscle cells are activated by inhaled allergens or microorganisms by immune-globulin receptor-independent mechanisms which apply to both asthma and COPD. Chambers et al. reported that human airway smooth muscle cells express the protease-activated receptor-2 (PAR-2) and its activation caused muscle cell constriction [67]. This study also suggested an interaction of the IgE receptor pathways with PAR-2 since trypsin increased calcium release and proliferation in serum sensitised cells more than in non-sensitised cells. The same group reported later that PAR-2 activation in human airway smooth muscle cells led to increased secretion of PGE-2 and cyclo-oxygenase-2 [68]. Inflammation up-regulated the expression of PAR-2 by airway smooth muscle cells [69]. Importantly, most PAR-2 mediated responses of airway smooth muscle cells were not inhibited by glucocorticoids [70]. House dust mite allergens activated PAR-2 in epithelial cells [69], modulated the function of chloride channels [71] and stimulated the secretion of IL-6 and IL-8 [73, 74]. Unfortunately, animal models of PAR-2 function in airway inflammation contradicted each other and no conclusions can be drawn. A summary of the function and possible interactions of PAR-2, calreticulin and IgE receptors on the function of airway smooth muscle cells is provided in figure 3.

Importantly, house dust mite allergens disrupted the cell-cell contacts and created gaps in the epithelial cell barrier; this process involved the action of PAR-2 and may enable allergens to penetrate into sub-epithelial tissue [75]. How this process is linked to other allergen transport mechanisms across the epithelial barrier is unclear. However, there is evidence that certain splice-forms of the IgE receptor FcεRI, which is expressed by epithelial cells, binds and transports allergens into the sub-epithelial tissue [76]. There is evidence that at least FcεRI is a binding partner for allergen and transports them through epithelial cells in large quantities without changing their structure [77]. By such mechanisms allergens can cross the epithelial barrier and act in sub-epithelial tissues.

In summary, these data strongly suggest that airway smooth muscle cells take an active part in the immune response, far from being only a response to activated immune cells. Airway smooth muscle cells contribute to chronic airway inflammation by secreting pro-inflammatory, chemo-attractive cytokines, and respond to allergens via immune globulin receptors and non-immune systems. Thus they modify the lungs' response to environmental factors leading to chronic inflammation. However, the main questions (how and why such short term changes of physiology in normal cells become persistent in cells of asthma and COPD patients) remains to be investigated.

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Figure 1

Summary of cell type specific pathologies of isolated human airway smooth muscle cells obtained from patients with asthma when compared to cells isolated from either healthy controls or patients with chronic obstructive pulmonary disease. ECM: extracellular matrix,

Figure 2

Tissue homeostatsis is guaranteed by the interaction between epithelial cells and mesenchymal cells. Epithelial damage by mechanical stress or allergens or micro-organisms can disrupt this interaction and lead to chronic inflammation.

Figure 3

Known mechanisms that modify airway smooth muscle cell action and its implication for the pathogenesis of asthma. FcεR: IgE receptor; MAPK: mitogen activated protein kinase.

Figure 1

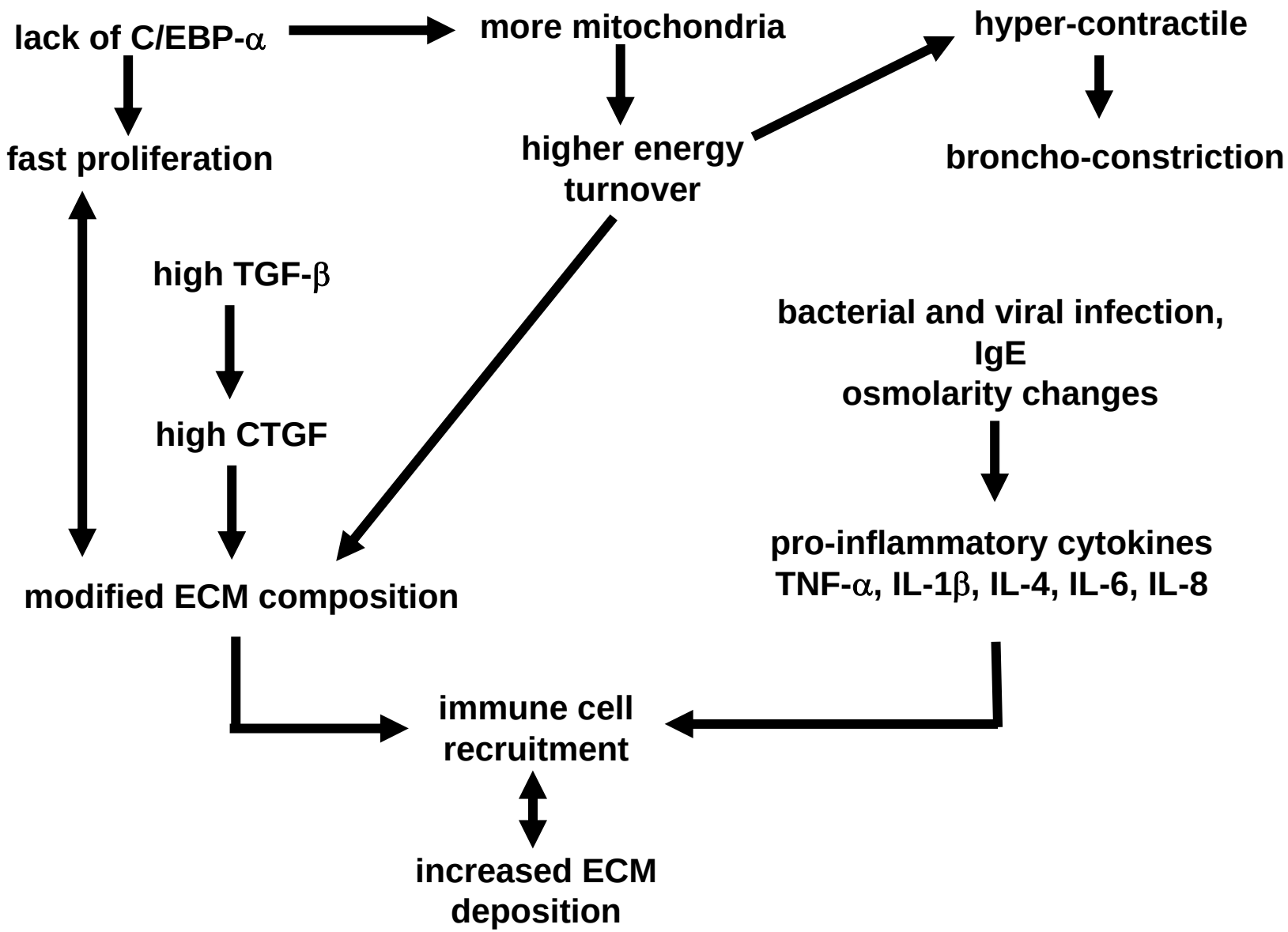

lack of C/EBP-α
more mitochondria
hyper-contractile
fast proliferation
higher energy turnover
broncho-constriction
high TGF-β
high CTGF
bacterial and viral infection,
IgE
osmolarity changes
modified ECM composition
pro-inflammatory cytokines
TNF-α, IL-1β, IL-4, IL-6, IL-8
immune cell recruitment
increased ECM deposition

Figure 2

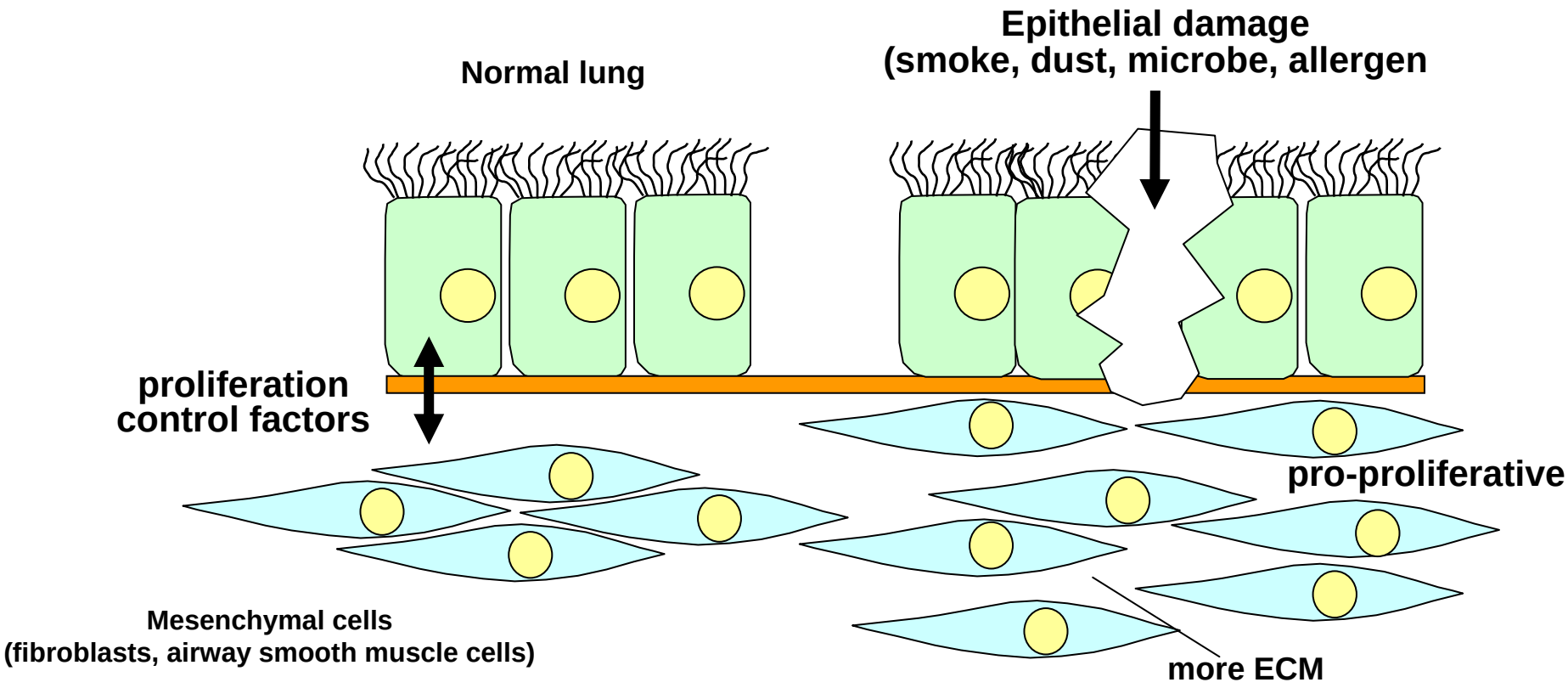
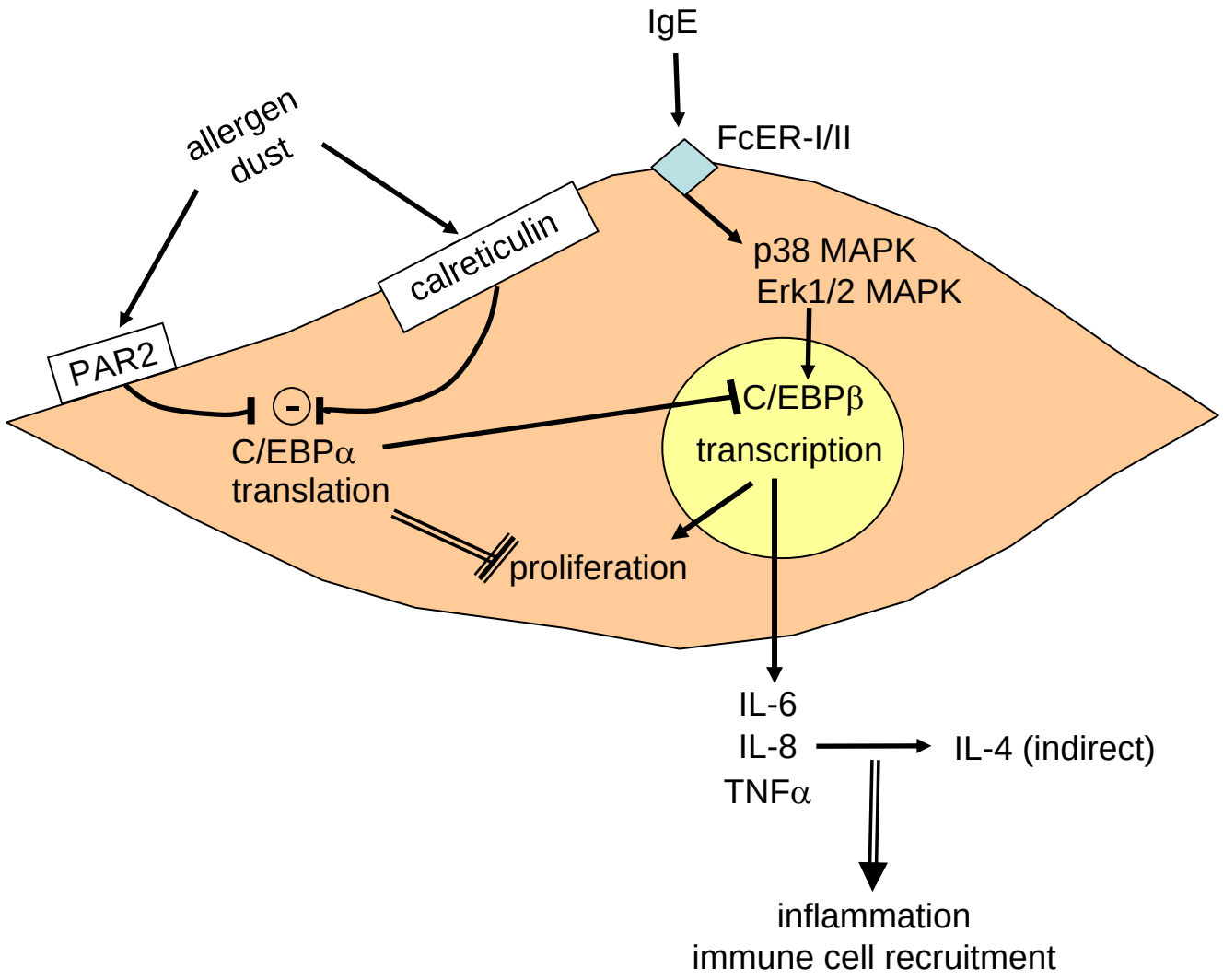

Epithelial damage
(smoke, dust, microbe, allergen
Normal lung
proliferation
control factors
pro-proliferative
Mesenchymal cells
(fibroblasts, airway smooth muscle cells)
more ECM

Figure 3


IgE
allergen
dust
FcER-I/II
calreticulin
p38 MAPK
Erk1/2 MAPK
PAR2
C/EBPβ
transcription
C/EBPα
translation
proliferation
IL-6
IL-8
TNFα
IL-4 (indirect)
inflammation
immune cell recruitment