Immunomodulating mechanisms in the lower respiratory tract: nitric oxide mediated interactions between alveolar macrophages, epithelial cells, and T-cells

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Introduction

A number of immunomodulating mechanisms are necessary to prevent uncontrolled inflammation in the lower respiratory tract. Proliferative responses of immune cells are tightly controlled in both bronchi and alveoli in the healthy lung. In diseases such as bronchial asthma, there is not only a partial failure of these mechanisms, but also an immune-deviation with a propensity towards a Th2-cell involvement.

The role of alveolar macrophages (AM) controlling T- and B-cell activation in the lower respiratory tract is discussed by considering mainly published results. This review focuses on immunomodulating mechanisms exerted via cytokines, such as Interleukin-10 (IL-10), transforming growth factor-beta (TGF-β), and Interleukin-1 receptor-antagonist (IL-1ra), prostaglandins, such as prostaglandin E2 (PGE2), and especially nitric oxide (NO).

The Th1 and Th2 concept in asthma is introduced, being the best-described mechanism of immune-deviation in the lung. The possibility of re-inducing T-cell unresponsiveness is of particular interest. The physiological immunomodulating mechanisms used by AM are explained in detail, as they offer many possibilities for therapeutic immunomodulation. Special emphasis is put on the cGMP/phosphatase dependent, reversible mechanism of NO-mediated immunomodulation and differences in the activation of NO synthases between murine and human alveolar macrophages are mentioned.

Keywords: alveolar macrophages; bronchial epithelial cells; T-cells; immunomodulation; nitric oxide; cGMP; phosphatase; interleukin-10; transforming growth factor-β

How these T cells are regulated was poorly understood for many years, because it could not be explained how they are normally prevented from reacting to irrelevant antigens in inspired air, while maintaining their capacity to respond to pathogens. Evidence from the last few years implicates the AM in the down-regulation of local lymphoid cells under normal steady-state conditions in the alveolus [3]. Epithelial cells are the primary candidates for the control of immune cells in the bronchial compartment [4, 5]. Epithelial cells may also be involved in mechanisms leading to immune-deviation as observed in the T helper 2 (Th2) response in bronchial asthma [4].

The epithelial-lining fluid in the lower respiratory tract contains a number of different immune cells: macrophages, T-cells, B-cells, neutrophils, eosinophils, mast cells, and the occasional dendritic cell. These populations may be readily sampled by broncho-alveolar lavage (BAL), a technique originally developed for laboratory animals [1], which was later used for clinical practice and for studies in man as a relatively simple extension of fibroptic bronchoscopy.

Alveolar macrophages (AM) account for up to 95% of cells recovered by BAL in all species tested. Among the immunocompetent lymphocytes, approximately 65% are CD4+ T cells, which are predominantly of the activated/memory phenotype [2].
The respiratory tract: an immune-privileged site?

As the respiratory tract is continuously exposed to organisms or particles of the environment, there is a need for appropriate defense mechanisms to prevent injurious and infectious processes. Most of the clearance of small inhaled particles and microorganisms reaching the periphery of the lung relies on the phagocytic system [6]. Macrophages are the primary phagocytes in the healthy lung. They reside in the interstitial spaces of the bronchi and alveoli, in the vascular compartment, and in the alveolus. Through the release of numerous secretory products and the expression of several surface receptors the macrophages interact with other cells and molecules [7].

Alveolar macrophages as potent modulators of the immune response

In vitro immunomodulating function of alveolar macrophages

Many in vitro studies examined the role of AMs in pulmonary immunity, and in particular their capacity to support T- and B-cell activation. Though interspecies differences were observed, these studies consistently indicate that AMs are inefficient in providing accessory cell activity in vitro compared to macrophages derived from other sources or monocytes [8]. In fact, AM have been shown to be efficient suppressors of T-cell activation and in antibody production by B cells [9]. This is especially the case at a high AM/T-cell ratio. Therefore, AM are incompetent in presentation of antigens to T-cells.

On the other hand, dendritic cells (DC) in the bronchial and alveolar walls are potent antigen-presenting cells [10]. At low AM/T-cell ratios some stimulatory effect may be present owing to the presence of DCs which can not be completely excluded in an AM preparation [10]. Electron microscopic examination of normal lung fixed by intravascular perfusion in the inflated state revealed that the majority of AM are localised in recesses at the alveolar septal junctions. In this position, AM are in intimate association with the alveolar epithelial surface, and are effectively separated by as little as 0.2 µm from underlying interstitial spaces which contain the periperal lung DC population. A similar juxtaposition of airway intraepithelial DCs was demonstrated with underlying submucosal tissue macrophages [11]. This potent downmodulation of antigen-presenting capacities of DCs in the bronchial and alveolar environment by the respective macrophage population was shown to be reversible by cytokines [12]. Thus, a potential mechanism for the upregulation of local T-cell responsiveness during acute inflammation is the secretion of cytokines such as GM-CSF, IL-4, TGF-β, and TNF-α by mesenchymal cells and/or macrophages.

Therefore, not only T-cells, but also DCs are maintained in a downmodulated state in the airways, tightly controlled by high numbers of nearby macrophages.

Effect of in vivo depletion of alveolar macrophages on the pulmonary immune response

- By limiting dilution analysis, pulmonary T cells isolated by bronchoalveolar lavage, exhibit a markedly reduced capacity to proliferate compared to peripheral blood T cells. However, intratracheal inoculation of liposomes containing dichloro-methylene-diphosphonate (DMDP) at a dosage shown to eliminate the majority of resident AM rapidly restores the immune competence of these lung T-cell populations [9].
- When antigen is delivered in normal animals as a bolus via the intratracheal route, virtually no response is elicited. When the same amount of antigen is identically administered to animals that were previously depleted of AM, local antibody production in pre-primed animals exposed to antigen aerosols is markedly increased [9].
- After in vivo depletion of AM by the methods described above, the antigen presenting capacity of lung dendritic cells is enhanced more than fourfold. This was shown to be a function of time post DMDP-liposome administration, with the maximal effects of AM elimination occurring within 24 h [11].

Nature of the immunomodulating mechanisms exerted by alveolar macrophages

The factors involved in T-cell and DC downmodulation by AM are partly known: In mice, nitric oxide (NO) produced by AM is the major source of this immunomodulation [3]. Several other immunomodulating factors produced by AM have been isolated, the most important being prostaglandins and cytokines.

Prostaglandin E2 (PGE2) was the first macrophage-derived immunomodulator to be described. Increased production of PGE2 by monocytes appears to be a pivotal mechanism in post-trauma immunomodulation [13]. PGE2 enhances peripheral blood lymphocyte IL-10 transcription and protein production [14] which per se offers possibilities for potent immunomodulation (see below). Finally, PGE2 has been described as deactivating AM and T-cells, and it is produced by AM [15].

An IL-1 inhibitor that competitively blocks
the IL-1 binding on its receptor was found to be the IL-1 receptor antagonist (IL-1ra) [16]. However, IL-1ra does not inhibit human T-cell proliferation induced by mitogens, soluble antigens or allogeneic determinants [17]. IL-4 and IL-10 have been shown to reduce the production of metalloproteinases by human alveolar macrophages [18, 19], but there is no evidence that IL-4 is produced by alveolar macrophages to suppress T-cells functions; conversely, PGE2 production by AM is inhibited by Th2 cytokines such as IL-4 [20].

TGF-β and IL-10 have been shown to inhibit the secretion of pro-inflammatory cytokines and possibly the proliferation of T-cells [21, 22]. Another possible immunomodulating mechanism for both cytokines is a reduced rate of apoptosis in human AM, thus indirectly enhancing AM-mediated inhibition of T-cell proliferation: Alveolar macrophages from normal human volunteers undergo apoptosis after a life span of up to 100 days [23]. Upon activation with bacterial products there is a considerable increase in this basal rate of apoptosis [24]. Apoptosis is regulated by the presence of cytokines in particular, IFN-γ increases the rate of apoptosis, IL-10 and TGF-β decrease it [24]. Because AM are pivotal regulators of local immunological homeostasis, AM population density (which is regulated by lifespan and therefore the rate of apoptosis), is accordingly decisive for many immune-processes in the lungs. The reduced incidence of sarcoidosis in smokers may be one example of the potential consequences of an increased number of AM.

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Molecular mechanisms of immunomodulation: involvement of nitric oxide

No or low output NO secretion by AM in humans?

Although many researchers have noted high level activation of rodent mononuclear phagocytes for nitric oxide synthetase type 2 (NOS2) expression and NO production with a variety of agents such as interferon (IFN-γ) and endotoxin, it has been difficult to demonstrate activation of NOS2 in human mononuclear phagocytes [25]. Two explanations for the hyporesponsiveness of the human iNOS (inducible nitric oxide synthetase) promoter to LPS ± IFN-γ were postulated: (1) multiple inactivating nucleotide substitutions in the human counterpart of the enhancer element that has been shown to regulate LPS/IFN-γ-induced expression of the mouse NOS2 gene [26]; and (2) absence of a nuclear factor in human macrophages (eg, an LPS-inducible nuclear factor-kappa B/Rel complex), that is required for maximal expression of the gene [26]. However, treatment of mononuclear cells in vitro with IFN-α was found to cause a dose-dependent increase in NOS2 activity and NO production, and increased expression of NOS2 protein and mRNA expression [27]. In addition, IL-4 seems to induce an increased secretion of nitrite by human monocytes potentiated by IFN-γ and inhibited by the competitive NOS2 inhibitor, mono-methyl-arginine (MMA) [28]. Taken together, these and other data suggest that the expression of NOS2 is at least much more tightly controlled in human as compared to murine mononuclear phagocytes.

NOS2 expression in human bronchial epithelial cells

Evidence supporting an important role for the increased levels of NO in asthmatic airways is substantial, although the cellular and molecular mechanisms leading to increased NO are not known in detail. NOS2 expression in human bronchial epithelial cells was demonstrated by different groups. A recent publication stated that NOS2 up-regulated by cytokines could be part of an autoregulatory feedback loop (i.e., allergen challenge stimulates inflammatory cytokine production, which in turn stimulates NO production, and NO down-regulates cytokine production) [29]. Furthermore, asthmatic bronchial epithelial cells show increased NOS2 mRNA and protein due to transcriptional regulation via constitutive activation of STAT1 [5]. NOS2 mRNA expression decreases in asthmatic patients treated with inhaled corticosteroids. Post-translational mechanisms, such as an increase in the NOS2 substrate (L-arginine) in bronchial epithelial cells of asthmatic individuals may even enhance the local output of NO. Finally, nitration of proteins in airway epithelium provides evidence of functional consequences of increased NO [5].

Mechanisms of NO-induced immunomodulation

Which functional consequences of increased NO production are known in cells of the immune system?

- Nitric oxide inhibits the GM-CSF-mediated maturation of rat lung dendritic cells [11], and also the TNF-α-mediated maturation of human dendritic cells, via cyclic GMP-dependent mechanisms [30]. NO might therefore prolong the ability of human DCs to internalise antigens at the site of inflammation and thus modulate the initial steps leading to antigen-specific immune responses. This could indicate that antigen-presentation is not possible as long as NO is present, which is a novel form of immunomodulation in the lung.
- Nitric oxide inhibits secretion of pro-inflammatory cytokines such as TNF-α by alveolar
macrophages and in-vitro matured monocytes. For each cell population, the responses of asthmatics and healthy controls are comparable. The effect is not cytokine specific since similar results were obtained with GM-CSF [31]. Conversely, NO dose-dependently enhances IL-4 secretion by human PBMC [32] and Th2 cell clones [33]. A preferential inhibition of Th1-associated cytokines was not observed in another study [34].

- Nitric oxide suppresses T-cell proliferation in murine spleen cells, lymph-node cells in the rat [35] as well as polyclonal and monoclonal human T-cells [36].

**Bronchial epithelial cells as modulators of the immune response**

While it has long been recognised that the epithelium is disrupted in severe asthma, evidence was just recently gathered that the epithelium could be the origin of asthmatic inflammation. The predisposition to generate IgE to common environmental allergens (“atopy”) is one of the strongest risk factors in asthma. However, while up to 50% of the population may be atopic, only 7–10% of the adult population have diagnosed asthma. Since allergen sensitisation most likely occurs via the inhaled route, the discrepancy between atopy and asthma deserves explanation. Local “tissue structure cell factors” are likely to play an important role in this regard [37].

Among the structural cells in the lower respiratory tract, the bronchial epithelium provides the physical barrier between the external environment and the internal tissue milieu – unlike bronchial smooth muscle cells and fibroblasts (that have deliberately been omitted from this review) – and would therefore be ideally placed for participating in the initiation, maintenance, and progression of asthma [38] [39]. Expression of IL-11 results in sub-basement membrane collagen deposition, myofibroblast proliferation, increased bronchial smooth muscle cell growth, and bronchial hyper-responsiveness similar to the remodelled airway in asthma but in the absence of eosinophilia [40]. These findings suggest that the bronchial epithelium may be capable of orchestrating much of the observed immunopathology of asthma.

**Structural changes in the asthmatic bronchial epithelium**

Evidence to support the view that the epithelium is abnormal in asthma is provided by overexpression of the epidermal growth factor receptor EGFR [41] and the epithelial isoform of the adhesion molecule CD44 in up to 80% of the airway epithelium [42]. Bronchial biopsy studies in atopic non-asthmatic subjects have revealed low levels of mast cell activation and eosinophil infiltration, suggesting that the lower airway Th2 response is “capped” in these subjects.
The Th1 and Th2 paradigm

The description of two subtypes of T-helper cells based on cytokine profiles by Mosmann and Coffman [45] was a major step forward in thinking about control of immune responses. They described murine T-cell clones that could be divided into either Th1 (producing IFN-γ and IL-2, but not IL-4 and IL-5) or Th2 (producing IL-4 and IL-5, but not IFN-γ). The potential relevance of Th2 responses to atopic disease is rapidly apparent since IL-4 and IL-5 could explain both IgE and eosinophilic inflammation: IL-4 unopposed by IFN-γ is essential in switching B cells to IgE synthesis [46] and IL-5 is involved in eosinophil development and survival [47].

The Th1 and Th2 concept in asthma

Assessment of mRNA expression in BAL cells from atopic asthmatics showed a predominant Th2 pattern [48], and numbers of cells expressing both IL-4 and IL-5 mRNA were correlated with measures of disease severity such as bronchial responsiveness or forced expiratory volume in 1s. In addition, IL-4 and IL-5 but not INF-γ protein levels were increased in BAL fluid from atopic asthmatics when compared to controls [49], and allergen-specific Th2 type clones could be isolated from the respiratory mucosa of atopic subjects [50]. In addition, by combining immunohistochemical staining to identify cell phenotype with in situ hybridisation for cytokine mRNA, IL-4 and IL-5 mRNA were predominantly localised to CD4+ cells in the airway mucosa from asthmatics, with lesser contributions from CD8+ cells, mast cells, and eosinophils [51]. Taken together, T helper-cell balance is skewed in favour of a Th2 response in asthma [52]. The factors that drive this Th2 response in initiating the allergic diathesis are yet to be identified in detail, and may act even in utero [53].

Involvement of NO

Asthmatic patients show an increased expression of inducible nitric oxide synthetase (iNOS) in airway epithelial cells [54] and an increased level of nitric oxide (NO) in exhaled air. It was also shown that treatment with inhaled corticosteroids reduces the amount of NO produced in the lungs [55]. Levels of exhaled NO in infants are even dependent on the atopy status of their parents, irrespective of the presence of asthma [56].

NO as a potent downmodulator of eosinophil apoptosis

It has been shown that Fas ligand-Fas receptor interactions are involved in the regulation of eosinophil apoptosis and that dysfunctions in this system could contribute to the accumulation of these cells in allergic and asthmatic diseases. NO was shown to be involved in Fas receptor resistance that might contribute to the eosinophilia associated with asthma. Therefore, it can be hypothesised that glucocorticoids, which are known to suppress NO concentrations in asthmatic patients, decrease eosinophil numbers by sensitisation of the Fas receptor to apoptosis [57].

Factors influencing T helper-cell balance

Not only disease, but also factors such as surgical stress [58], mercury and lead intoxication [59] as well as pregnancy [60] have an influence on a Th2 skew in the pattern of cytokine secretion, possibly a consequence of an increased rate of apoptosis of Th1 cells [61]. Th1/Th2 cytokine balance is also affected by antigen dose, affinity, and time of differentiation based on the strength of signalling and the length of the response [62].

Hormones such as corticosteroids [63], second messengers such as cGMP [34] – though with conflicting results [64] – prostaglandin E2 as well as NO [33] have been described as influencing T helper-cell balance. NO is known to inhibit the secretion of IFN-γ by Th1 cells [65, 64] but seems to lack capacity for inhibition of the production of IL-4 by Th2 cells [33]. Furthermore, Th1 response in mice lacking inducible nitric oxide synthetase (NOS2 knock-out mice) is massively enhanced [66]. The most potent regulators of the cytokine balance are notably cytokines. However, the extremely high redundancy and the mutual influences in the cytokine network will make it very difficult to find the primary culprit of a T helper cell dysregulation.
The mechanism of NO-mediated immunomodulation: the final answer to “immune stimulation, -suppression or -deviation”?

T-cells activated in the presence of alveolar macrophages are unable to proliferate despite expression of IL-2R and secretion of IL-2. This process is reproduced by the NO generator S-nitroso-N-acetylpenicillamine (SNAP) and is inhibitable by the NO synthetase inhibitor monomethyl-arginine (MMA). Analysis of T-cell lysates by immunoprecipitation with specific antibodies and subsequent immunoblotting indicated marked reduction of tyrosine phosphorylation of Jak3 and STAT5 mediated by NO. Further studies indicated that NO-mediated T-cell suppression was reversible by the guanylate cyclase inhibitors methylene blue and LY-83583 and was reproduced by a cell-permeable analogue of cyclic GMP, implicating guanylate cyclase activation as a key step in the inhibition of T cell activation by NO [35].

Further studies showed the involvement of a yet unknown phosphatase causing dephosphorylation of nuclear STAT5 dimers after continuous exposure to NO for 4 to 16 hours. Interestingly, there was spontaneous re-phosphorylation of STAT5 if the continuous NO exposure was stopped within 20 hours [36].

Reversible T-cell “anergy”:
Th2 clones unaffected?

All Th2 clones examined show a similar, NO-concentration dependent growth arrest as compared to their Th1 counterparts [36].

As Th2 cells do not appear to be resistant to growth arrest induced by NO via cGMP activated phosphatases, it seems that NO is not involved in the immune-deviation hypothesised by Barnes and Liew [4]. Conversely, NO produced by human bronchial epithelial cells inhibits T-cell proliferation irrespective of the cytokine pattern secreted by the respective clones. This is demonstrated in figure 1, where T-cell clones were stimulated with IL-2 in the presence of IFN-γ activated (and therefore NO producing) human bronchial epithelial cells [67]. As STAT5 dephosphorylation is involved in NO-induced inhibition of T-cell proliferation, and a partial reconstitution of STAT5 activity is shown in the presence of MMA, it can be concluded that growth arrest can be achieved similarly in Th1 and Th2 cells by epithelial derived NO.

Figure 1
Electro-mobility-shift assay (EMSA)of human T-cell lysates: After 24 h of culture, the T-cells were lysed and nuclear protein extracts were analysed for STAT5 activity.
- : T-cell clones deprived of IL-2 show little STAT5 activity as assessed by EMSA using radiolabelled casein-promotor as the binding site for nuclear STAT5; + : T-cells restimulated with IL-2 for 30 minutes show an enhanced STAT5 activity; A: T-cells restimulated with IL-2 for 30 minutes in the presence of human bronchial epithelial cells show the same amount of STAT5 activity as the positive control (100% of +); B: T-cells restimulated with IL-2 for 30 minutes in the presence of human bronchial epithelial cells that were previously activated with IFN-γ show reduced STAT5 activity (36% of +) and proliferation (not shown) due to NOS2 activation and high NO production by epithelial cells; C: T-cells restimulated with IL-2 for 30 minutes in the presence of human bronchial epithelial cells that were previously activated with IFN-γ in the presence of the NO-inhibitor monomethyl-arginine (MMA) show a partial reconstitution of STAT5 activity.

Conclusion

Interactions between alveolar macrophages and T-cells in the healthy lung have been studied for the past 20 years. The immunomodulating properties of alveolar macrophages have been demonstrated in particular in the mouse and rat, but also in the human, where some of the mechanisms have not been elucidated yet. More recent evidence showed that the bronchial epithelial cell seems to possess immunomodulating properties as well. For the understanding of the pathophysiology of asthma, the immunomodulating properties of the bronchial epithelial cell are of prime interest. Among the plethora of immunomodulating mechanisms in the lung (table 1), NO is one of the best described factors. Patients with bronchial asthma show an increased level of NO in exhaled air. NO was claimed to inhibit the proliferation of Th1, but not Th2 cells, and it was therefore attractive to hypothesise that increased amounts of NO could contribute to a preferential Th2 response in allergic disease of the respiratory tract. It was concluded that specific NOS2 inhibitors could represent a novel therapeutic approach for asthma[4]. However, our own results [35–37] suggest that reversible growth arrest induced by NO is not restricted to Th1 cells. Therefore, manipu-
Table 1

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<tr>
<th>Effector cell</th>
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<th>target cell function</th>
<th>effector cell mechanism</th>
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<td>T-cell</td>
<td>IL-10 secretion</td>
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Summary of the immunomodulatory cell-cell interactions described in this review.

*IFN-γ secretion by Th1 cells is not a directly immunomodulatory interaction between Th1 cells and macrophages. This mechanism has been included for its pivotal role activating NOS2 transcription via STAT1 in macrophages and epithelial cells.

In the lower respiratory tract, immune modulation is critical for maintaining respiratory health. NO plays a significant role in this modulation, influencing processes such as bronchodilation, where it acts as a potent bronchodilator. NO inhibitors have the potential to adversely affect the physiological immunomodulation in the lower respiratory tract. However, selective phosphodiesterase inhibitors may become an attractive tool for the control of bronchial asthma, as an elevation of intracellular cGMP not only causes bronchodilation, but also contributes to a reversible growth arrest of bronchial T-cells [67].

Thus, the further elucidation of the physiological mechanisms of immunomodulation in the lower respiratory tract will lead to the discovery of better therapies for chronic lung disease.

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