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# Basic mechanisms of lung inflammation: executive summary of the first Lung Science Meeting of the European Respiratory Society at Taormina, Italy in 2003

H.J. Hoffmann

The contribution of structural changes and the biology of lung cells to pulmonary disease was emphasised and contrasted with the inflammatory response at the first Lung Science Conference held at Taormina, Italy 26–28 March 2003 (table 1). Here the basic mechanisms of inflammation and their relevance to lung diseases are discussed. For more information on the intracellular events discussed, look at and listen to individual talks on the European Respiratory Society web page at http://www.ersnet.org/taormina.

Table 1. – Central messages from Taormina

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| Structural and functional changes in the lung play an important role in the development of lung diseases |
| Differentiation and division of lung cells during wound healing (or other responses to insult), and consequent influx and division of immune cells control the number of cells in the lung together with apoptosis, luminal clearance and necrosis |
| Transforming growth factor-β appears to play a major role in lung development, and in healing |
| Metalloproteases modify soluble effector proteins and cellular responses |

## Extrinsic and intrinsic factors determine the development of lung diseases

Both the environment ("the air we breathe and the food we eat") and the genetic potential (correct gene products expressed at the right place at the right time) contribute to homeostasis in the lung as well as to pathological deviation. Examples of environmental factors that contribute to the development of pulmonary disease were cigarette smoke condensate [1], lipopolysaccharide [2] and diesel exhaust particles. The redox potential of the lungs [3] is critical to the response to environmental insults and the subsequent expression of lung diseases [4]. Genetic contributions to risk factors were discussed for sarcoidosis [5] and idiopathic fibrosis in surfactant protein (SP)-D variants [6].

## Wound repair is similar to early developmental processes

A wound inflicted upon the pulmonary epithelium will attempt to heal. Concurrently, the immune system will respond with an inflammatory response to protect against imminent infection. Among the stimulating talks on repair, growth and differentiation of structural cells, the description of how embryos heal wounds [7, 8] was most fascinating. Using green fluorescent protein-labelled actin in drosophila and zebra fish, video sequences of differentiating embryos and wounded embryos showed how the epithelial cells stretch and pull toward each other in an attempt to close a wound. At the ends of the wound, lamellipodia of cells meet and interdigitate to reform the intact epithelium. If the drosophila homologue transforming growth factor (TGF)-β PUK is deleted, healing occurs at a much slower rate. Similar results were found in zebra fish and mice. As shown by LI *et al.* [9], the repair response of epithelial cells in murine tracheal sections, which attempt to cover the edge of the section, was similar to that seen in drosophila. In matrix metalloproteinase (MMP)-7-knockout animals, the capacity of epithelial sheets to interdigitate before migrating across a wound was severely attenuated. Inflammatory responses can contribute to the healing process as neutrophil defensins, in addition to protecting against bacteria, accelerate wound closure [10]. Wounding may be due to extrinsic factors like cigarette smoke, diesel exhaust particles, bacteria or their exotoxins. Alternatively, it may be the consequence of intrinsic factors like a genetic defect (for example, mutations in the SP-D gene [6], leading to an inappropriate response or a combination of both. During repair, regulated growth of basal stem cells differentiating into epithelium, fibroblasts and specialised cells like Clara cells, type-I and type-II cells, as well as appropriate apoptosis of these cells is required, and defects in either growth or (induction of) apoptosis of these cells [11] may lead to disease [12]. In the development of asthma, deregulation of the epithelial mesenchymal trophic unit coined by S. Holgate describes a new approach to understanding how disease develops in the lung [13].

TGF-β and prostaglandin $(PG)E_2$ were shown to have significant profibrotic effects on structural cells, in addition to their documented effects on the immune system. It appears as though a lack of TGF-β promotes fibrosis [14]. In a murine model system of fibrosis, T-cell-derived proinflammatory cytokines interleukin (IL)-1β, tumour necrosis factor (TNF) or interferon, supported growth of fibroblasts, whereas eosinophil-derived cytokines IL-4, IL-13 and TGF-β promoted differentiation into smooth muscle cells [15]. Novel profibrotic modulators in the lung were thrombin and factor Xa that activate fibroblasts through protease-activated receptors [16], angiotensin [17] and C5a [18].

## Metalloproteases modulate signalling molecules and alter tissue to enhance inflammatory cell motility

MMPs are thought to open up tissue to allow access for the migration of cells of the immune system [19]. Description of

Correspondence: H.J. Hoffmann, Dept of Respiratory Medicine - Building 2b, Aarhus University Hospital - Nørrebrogade 44, Aarhus, Denmark. Fax: 45 89492110. E-mail: hansjuergen.hoffmann@get2net.dk

phenotypes of knockout mice deleted for various MMPs and elegant experiments with tissue segments demonstrated that a key function of these molecules is the modulation of other protein factors by processing (cleaving them at specific sites to change their activity), in addition to clearing the way for lymphocytes through tissue. The effects of MMPs, like those of TGF-β and $PGE_2$, are exerted on both structural and immune cells, making the assessment of the vital function of a given molecule in a given scenario a complex issue.

One of the key functions of MMP-7 is recruitment of neutrophils into the pulmonary lumen [9], another is the regulation of wound closure. Similarly, MMP-9 has been shown to activate IL-8 to accelerate recruitment of neutrophils into the lung. MMP-12 is required for migration of macrophages into the lung. A hydroxamate-based inhibitor (RS-132908) of MMPs attenuates development of emphysema in mice [20]. The MMP profile represents a differentiation marker of macrophages; lung tissue macrophages have a different spectrum than alveolar macrophages [21]. ADAM33, a distant relative of MMPs, is associated with bronchial hyperresponsiveness, independent of atopy [22–24].

## Old and new drugs to modulate pulmonary disease

The inflammatory response of the immune system must be carefully coordinated with the repair process; indeed improvement in the coordination of these two responses may be a mechanism by which corticosteroids act, and may be the aim of future strategies in treatment of lung disease. In the inflammatory and immune responses, it is the influx of cells as well as local cell division, and apoptosis and luminal clearance that have to be controlled to maintain an appropriate response [25].

Steroids are amongst the major regulators of immune (and local cell) activity. Forty years after their first use in treatment of pulmonary disease, the function of steroids is still not entirely understood, although it appears certain now that the complex of steroid and glucocorticoid receptor-α (GRα) inhibits transcription of inflammatory genes by interfering with nuclear factor-κB and the basal transcription machinery [26, 27]. At the level of chromatin remodelling, interaction with transcription factors is important. There are candidate drugs that could reduce the requirement for steroids by a factor of two logs. In mast cells, the GRα-steroid complex inhibits transcription of the FceRI gene, and the extracellular signal-regulated kinase (phosphatase) pathway through activation of the mitogen-activated protein kinase phosphatase MKP-1 [28, 29]. Steroids bound to GRβ could counteract the effect of GRα. Steroids also have effects on fibroblasts, where they may regulate myoblast differentiation through upregulation of the pathway in which inhibitor of DNA binding-1 ID-1 is found [30].

A number of antibodies and soluble receptors have been advocated as candidate drugs in recent years. Data were presented in support of a role for the TNF antagonist omanizulab in acute asthma where symptom scores and methacholine responsiveness were significantly reduced in an open trial, and for anti-IL-5 in eosinophilia, where symptoms, blood and skin eosinophil counts were significantly reduced by treatment with anti-IL-5 [31]. Anti-IL-5 was shown to affect both bone marrow, blood and bronchoalveolar lavage eosinophils in mice challenged with a relevant allergen [32].

## Immune responses in the airways and lung

Understanding of neutrophil recruitment has progressed significantly, including demonstration of the roles of MMP-7 and MMP-9 [19], and demonstration of the expression of toll-like receptors (TLRs) on neutrophils regulating expression of IL-8 receptors [2, 33]. Ligation of TLR4 has been shown to be antiapoptotic and induces upregulation of adhesion molecules, whereas ligation of TLR2 induces shedding of CXCR1 and 2. Removal of neutrophils from the lung occurs primarily by apoptosis [31]. This is exacerbated by the exotoxin phenazine of *Pseudomonas aerigunosa* [34].

The T-cell macrophage interaction is interesting because by the time the patient presents, the priming effect on T-cells by antigen-presenting cells is history [35]. T-helper type-1 and -2 cell phenotypes can be measured by IL-1 and IL-1Ra production in the human acute monocytic leukemia cell line THP-1. Understanding the immune response requires that dendritic cell flux and function are considered, as demonstrated by the fact that type-II epithelial cells recruit immature dendritic cells to the lung [36].

## Conclusion

Among extrinsic factors contributing to development of pulmonary disease the redox potential remains the most evasive. It is possible to count cigarettes smoked, quantitate viral, bacterial, pollen and pollution load, but at present there is no direct measure for the redox potential in the lung (J.D. Crapo, Dept of Medicine, National Jewish Medical and Research Center, Denver, CO, USA; personal communication). This meeting highlighted the significance of the question "How important is the inflammatory response in recovery from lung injury in man today?" New treatment strategies may continue to address modulation of inflammatory and immune responses, and combinations of treatments may reduce the amount of medicine required, and, by proxy, the side-effects. "Good" inflammatory and immune responses such as the right amount of transforming growth factor-β or matrix metalloproteinase may contribute significantly or even crucially to recovery after injury.

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