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Lectins as Potential Adjunct Therapeutics for COPD/Emphysema?

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Chronic Obstructive Pulmonary Disease (COPD/emphysema) is a predominantly cigarette-smoke related, chronic inflammatory airways disease, which is currently incurable. Existing treatments are largely symptomatic, and there is an urgent need for identification of new therapies. Crucial for our understanding of the pathogenesis of this and other chronic lung diseases was the identification of a significant defect in the ability of pulmonary macrophages to phagocytose apoptotic airway epithelial cells (defective *efferocytosis*) [1,2], which may contribute to an excess of apoptotic material, secondary necrosis of the uncleared material and perpetuation of chronic airway inflammation [3,4]. Impaired phagocytosis of bacteria in COPD was also shown; an important finding given the contribution of infective exacerbations to airways destruction in these patients [5].

Importantly, these defects could be substantially overcome using macrophage-targeted therapies [2,5-8] including macrolide antibiotics that improved efferocytosis, and reduced airway epithelial cell apoptosis and inflammation in vivo [5,6]. Nakanishi et al. [9] further showed that administration of clarithromycin prevented the onset of emphysema in smoke-exposed mice [9]. Two important lines of reasoning indicate that the macrolides are exerting anti-inflammatory rather than anti-microbial actions to improve these facets of COPD pathogenesis. Firstly, the low doses of macrolides shown to be beneficial in COPD frequently fail to reach the MICs of respiratory pathogens. Secondly, the beneficial effects of these drugs in COPD pathogenesis are being recapitulated with non-antimicrobial macrolide congeners [10]. Nevertheless, concern regarding the selection of resistant bacteria necessitates the evaluation of immune based, non anti-microbial approaches to avoid this consequence.

Of recent interest is the use of lectins in this regard. Lectins are soluble carbohydrate-binding proteins that include C-type (lung surfactants and Mannose Binding Lectin (MBL)), S-type (galectins), L-type, heparin binding proteins and pentraxins. They contain carbohydrate recognition domains (CRD) and are traditionally recognised for their roles in recognition of Pathogen-Associated Molecular Patterns (PAMPs) and facilitation of pathogen clearance. More recently we and others have shown that lectins also have the ability to facilitate phagocytosis of apoptotic cells [8,11]. Mannose binding lectin is produced in the liver, is present in the airway [8,12] and recognizes nucleic acids including fragmented DNA on apoptotic cells and products of tissue damage (eg, heat shock proteins, cell membrane material) thus mediating its actions in clearing apoptotic debris [13]. MBL research has primarily focused on defence against pathogens, a key immune function that has relevance to the exacerbations that occur in COPD particularly its role in defences against *Streptococcus pneumoniae* [14], although these may be indirect and mediated by enhanced pentraxin binding. More recently however, decreased airway levels of MBL were shown in patients with COPD and smokers (with no changes noted in plasma) [8].

Importantly, the levels of MBL were low in the airway even in the presence of infection, and levels correlated with efferocytosis and COPD disease severity (FEV1) [8]. Nebulized administration of MBL to smoke-exposed mice reversed the dysfunction of both alveolar and lung tissue macrophages and reduced airway inflammation (evidenced by a significant reduction in WCC and macrophage numbers to near-normal levels) [8]. While the effects of the local MBL deficiency in the handling of pathogens such as *S. pneumoniae* and *H. influenzae* that colonize the airway in COPD are currently unknown, the available data do support human in vivo studies of MBL therapy in COPD.

Both plasma-derived (pdMBL) MBL and recombinant (rMBL) have been produced and studied for potential immunotherapeutic benefits. Plasma-derived MBL is superior to rMBL when comparing the key biological processes central to MBL function, including mannan binding and complement deposition in vivo. Rajagopalan et al. [15] reported that (a) pdMBL bound mannan significantly more efficiently than rMBL (b) complement deposition was reduced 5 fold in rMBL compared to pdMBL (c) the proportion of higher order oligomers (required for functional mannan binding and complement deposition) is far lower in rMBL than in pdMBL [15]. In our studies we also found that the significant improvement in macrophage function with pdMBL did not occur with rMBL. Recombinant MBL has been clinically trialled [16] however no data is available on the outcome of this study, as this and all other clinical trials of rMBL were ceased before study completion due to a failure to meet commercialisation milestones that are as yet not fully enunciated. In contrast, pdMBL has been utilised in a number of early phase clinical trials and has been shown to be safe, well tolerated, and efficacious [17-20]. Plasma-derived MBL may thus prove to be a useful adjunct therapeutic strategy for COPD and other chronic lung diseases where MBL may play a pathophysiological role, and clinical trials are warranted. In particular, the use of intra-nasal or aerosolized administration of MBL would be an attractive treatment option.

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