Inhaled corticosteroids in chronic obstructive pulmonary disease a two-edged sword

Riesbeck, Kristian

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Inhaled corticosteroids in COPD – a two-edged sword

The field of immunology is constantly expanding, and although focus has slightly turned from T cell- to more B cell-oriented research, new knowledge on unconventional T cells is still garnered. One example of this is the relatively recently discovered MR1-restricted T cells designated ”mucosal associated invariant T” (MAIT) cells (1). Intriguingly, MAIT cells comprise 5-10 % of the total pool of $CD3^+$ T cells in peripheral blood. As a result of development of monoclonal antibodies, the $CD161^+$ MAIT cell subset has been defined as having an invariant T cell receptor designated TCR Vα7.2 that recognizes the MR1 molecule on antigen-presenting cells, for example, B cells.

MR1 is attached to β2 microglobulin, and therefore is designated as ”MHC (HLA) class I-like”. The MR1 molecule is non-polymorphic, which is in bright contrast to the classical MHC molecules. This means that there are only a few compunds/ molecules that actually are loaded on MR1 and consequently presented for the MAIT cell subset. Importantly, it is now known based upon refolding experiments and crystallization that it is mainly riboflavin (vitamin B2) derivatives that are bound to MR1 (2).

The human host does not produce riboflavin itself but here bacteria come into the picture (3). Upon a bacterial infection and consequently increased densities of MR1 on antigen presenting cells, MAIT cells become important players. They then can promote inflammation by inducing a mixture of T helper (Th) cytokines, and interferon (IFN)-γ, reflecting a Th1 profile, has been shown to be produced by MAIT cells originating from the lung (4). MAIT cells have also the capacity to directly kill epithelial cells that are infected with bacteria by using granzymes. Hence MAIT cells can be attributed to the innate immune system despite they do not sense infections by all microbes (5); viruses and a few Gram-positive bacteria, amongst others, group A streptococci are exceptions, and are not under attack since they cannot produce riboflavin metabolites.

In parallel to other Gram-negative bacteria, the coccobacillus *Haemophilus influenzae* possesses a riboflavin synthesis pathway (6), which indirectly (via MR1) may trigger MAIT cells. The bacterium also resides intracellularly in bronchial epithelial cells (7), which further would be a suitable target for the cytotoxic MAIT cells. Since the introduction of a vaccine against encapsulated *H. influenzae* type b (Hib), the incidence of invasive disease including meningitis and sepsis by *Haemophilus* has significantly decreased. Non-typeable, that is, non-encapsulated *H. influenzae* (NTHi) has in parts occupied the niche of Hib´s, and might even break more ground after introduction of pneumococcal vaccines in child immunization programmes recent years. Despite NTHi is a commensal in pre-school children, it is one of the major causes of mucosal infections in the airways. The pathogen is associated with acute otitis media in pre-school children, sinusitis in adults, and finally exacerbations in patients with chronic obstructive pulmonary disease (COPD) (8). In fact, COPD patients are particularly vulnerable since NTHi maintains a chronic inflammation in this group of patients also during stable disease (9). Moreover, NTHi is overrepresented in patients with poorly controlled asthma (10).

The current opinion is that COPD patients administered inhaled corticosteroids (ICS) have an elevated risk of pneumonia albeit there is a reduced incidence of acute exacerbations and no increased risk of mortality (11). In the present issue of the *Journal* (pp. XX-YY), Hinks and collaborators reveal the mechanisms behind those clinical observations in COPD patients (GOLD stage 2) with emphasis on ICS-dependent effects on the peripheral and bronchial MAIT cell populations. The authors also shed light upon the importance of MAIT

cells with respect to the commonly found bacterial species NTHi. Interestingly, when peripheral blood T cells ($CD3^+$) were analysed, a decreased percentage of MAIT cells was found in COPD patients on ICS as compared to healthy control individuals not receiving any ICS. In parallel, bronchial biopsies from COPD patients also revealed less MAIT cells in the lung tissue. Analyses of bronchalveolar lavage (BAL) and sputum did not, however, confirm the findings with peripheral blood and lung tissue, a phenomenon the authors suggest to be related to differences in MAIT phenotypes in various anatomical compartments.

The capacity of NTHi to activate either lung macophages or blood monocyte derived macrophages was also determined. Here, NTHi significantly increased MR1 and HLA-DR (class II) density on the cell surface, whereas no effect was seen with HLA-ABC (class I). There was not any *de novo* production of MR1 mRNA but only a presumed NTHi-dependent post-transcriptional effect. In contrast to whole cell NTHi, pro-inflammatory cytokines or purfied LPS in addition to influenza virus did not increase MR1 expression. The authors next harvested monocyte-derived macrophages ($MR1^+$) that had been pre-stimulated with NTHi, and added these cells to MAIT cells, $CD4^+$or $CD8^+$ T cells followed by flow cytometry analysis after intracellular staining of IFN-γ. In these experiments, all T cell subsets responded with a Th1 profile albeit only MAIT cells were actiaved via MR1 as proven with a neutralizing monoclonal antibody. Finally, to translate their observations on NTHi-dependent upregulation of MR1 that in turn triggered MAIT cells, Hinks and collaborators investigated the effect of fluticasone and budesonide on MR1 expression and IFN-γ-secreting MAIT cells. The effectiveness of both steroids was verified, that is, the antigen-presenting MR1 and pro-inflammatory cytokine release was efficiently inhibited in these experiments.

In this study, there are as expected large variations in cellular responses between subjects implying confounding factors. The genotypes of patients´ are most likely highly heterogenous explaining differences in immune responses mounted, and further research on and stratification of COPD is thus requiered (12). If we evaluate individual patients in a clinical setting, another factor is that the lung microbiome may differ, a research field that has attracted much interest lately (13). Moreover, polymicrobial infections are common, an aspect that will further complicate the picture. It is indisputable, however, that NTHi is a key player in promoting inflammation in COPD patients, and due to the highly variable genome, NTHi may induce various responses. As yet it has, however, been difficult to find precise disease-causing patterns in this highly heterogenous species (14).

Parallels that can be drawn between COPD and asthma patients on ICS therapy are striking despite the latter group seems to carry more different T cell phenotypes (1). Patients with severe asthma, presumably receiving more corticosteroids have markedly decreased levels of MAIT cells in peripheral blood as well as in bronchial biopsies. This may be one explanation as to why particularly patients with severe asthma also run an increased risk of pneumonia and sepsis (15).

In conclusion, although this highly interesting study is mainly based upon experiments done *ex vivo* it paves the way for further investigations on the innate T cell defense directed against bacteria such as NTHi that dwell in the lower respiratory tract. A customized therapy based upon a combination of patient genetics with focus on innate immune parameters, the microbiome status, and finally GOLD stage will be a future challenge in the era of personalized medicine.

Kristian Riesbeck, M.D., Ph.D.

Clinical Microbiology
Dept. of Translational Medicine
Lund University
Malmö, Sweden

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Figure 1. Non-typeable *Haemophilus influenzae* in the lung from a COPD patient. Courtesy of Dr. Matthias Mörgelin (Lund University, Sweden).