WHAT BRINGS TOGETHER CELIAC DISEASE AND CHRONIC OBSTRUCTIVE PULMONARY DISEASES: PHARMACOLOGICAL IMPACT?

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Abstract

Celiac disease is characterized by destruction of the intestinal epithelium, mucus excess, cell infiltrate of cytotoxic CD8 T cells and remodelling of the intestinal mucosa due to increased type 1 immune response triggered by gluten and/or infectious agents. Recently excess activation of CD8 T cells was correlated to high levels of IL-15 produced by macrophages and epithelial cells.

Chronic obstructive pulmonary diseases also are characterized by type 1 CD8 T cell infiltrate and destruction of the respiratory epithelium, excess of mucus and lung remodelling and viruses are the common cause of exacerbations.

We were interested to find out if, similar to celiac disease, in chronic obstructive pulmonary diseases there is also an increased production of IL-15 and consequently excess stimulatory molecules on respiratory epithelial cells and subsequently increased activation of cytotoxic T cells. We started by determining in vitro how RSV infection modulates IL-15 production and surface molecules in respiratory epithelial cells.

Similar pathogenesis to celiac disease, would suggest that targeting IL-15 could be a successful therapy in chronic obstructive pulmonary diseases.

Keywords: celiac disease, COPD.

Introduction

Celiac disease (CD) develops in genetically susceptible individuals, and is strongly associated with MHC class II molecules HLA-DQ2 and HLA-DQ8. Because the patients develop gluten-specific CD4 T cells and autoantibodies specific for the enzyme transglutaminase 2 (TG2) [1] which modifies the antigenicity of gluten celiac disease is considered an organ-specific autoimmune disease [2]. TG2 is inactive in the intestinal mucosa in the resting state but is activated following treatment of the animals with polyinosinic–polycytidylic acid (polyI:C; a ligand of TLR3) [3] suggesting that infection with double-stranded RNA viruses (such rotavirus infections) might be involved *in vivo* through the provision of ligands for TLR3 [4].

Also pro-inflammatory cytokine IFN-γ is produced at high levels in celiac lesions [5] and there is an excess of IL-15 production [6,7,8-10]. IL-15 contributes to enhanced survival and subsequent accumulation of nontransformed intraepithelial lymphocytes (IELs) in celiac disease [11]. IEL accumulation is not caused by local proliferation, but rather results from an antiapoptotic signal delivered by IL-15 overexpressed in the gut epithelium [12]. Because IL-15Rα is unregulated in epithelium and lamina propria of celiac disease patients [13], it was speculated that IL-15/IL-15Rα complexes selectively stimulate Bcl-xL expression [12]. Since IL-15 is upregulated in response to infections, IL-15–induced upregulation of Bcl-xL may help effector lymphocytes to escape activation-induced cell death in infected tissues and thereby help eliminate the causative pathogen. However, prolonged production of IL-15 might result in accumulation of proinflammatory and/or autoreactive lymphocytes sustaining chronic inflammation and autoimmunity [10].

Increased IL-2/IL-15Rβγc receptor levels on IELs in celiac disease compared with residual normal IELs could enable them to respond to lower concentrations of IL-15, providing them with a selective advantage that could

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explain their progressive accumulation and the simultaneous disappearance of normal IELs.

Interestingly, gluten increases IL-15 production by lamina propria macrophages and dendritic cells [6,14,10] and some effects of gluten reported in literature are similar with the effects of IL-15: induction of epithelial cell apoptosis and destruction [14-16] and upregulation of expression of the stress-inducible MHC class I polypeptide-related molecules (MICs) [17,18,19] ligands of the NKG2D receptor. IL-15-treatment up-regulated MICA/B and a neutralizing IL-15 antibody blocked the glutted-induced MIC in celiac disease biopsies [17,20].

In addition, IL-15, has recently been shown to induce signalling in cytotoxic T cells and can alter their function, in particular by upregulating the expression of NKG2D and co-stimulating the NKG2D cytotoxic signalling pathway [18,21,22]. MIC molecules and their receptor NKG2D are up-regulated in active celiac disease mucosa [17,19].

Interestingly, innate cytokine IFN-α production by plasmacytoid dendritic cells was reported increased in celiac disease [23,24] and increased production of IFN-α will increase gluten-induced IFN-γ production by T cells [25]. Also IFN-α treatment of viral chronic hepatitis was found to precipitate the induction of inflammatory anti-gluten responses and the generation of TG2-specific antibodies [26].

Also there is a predominant type 1 immune response, earlier studies have linked celiac disease with a number of infections, including invasive pneumococcal disease [27], sepsis [28], and tuberculosis [29].

In a recent study of >29,000 individuals with biopsy-verified celiac disease, Marild et al found a twofold relative risk of incident influenza virus infection [30]. Interestingly, smoking is negatively associated [31] or not associated at all [32] with celiac disease but positively associated with influenza [33]. A role for virus infection was proposed also when sequence homology was found between A-gliadin and the E16 protein from the human adenovirus type 12 [34]. More recently epidemiologic observations on the seasonal pattern of incidence of celiac disease have sustained the hypothesis of a viral infection triggering the disease [35]. Infections might increase gut permeability with increased antigen penetration and/or may drive the immune system toward a TH1-type response typical for celiac disease. Rotavirus seems to be a good candidate because frequent rotavirus infections predicted a higher risk of celiac disease autoimmunity (3.76 for ≥ two infections) [36,4].

In short, increased production of IL-15 and increased levels of MIC (by gluten or by virus infection?) non-specifically activate cytotoxic NKG2D-positive cells and play and important role in the immunopathogenesis of celiac disease. Consequently antibodies to IL-15 have been proposed to treat refractory celiac disease [12,31].

COPD is a generic name for chronic inflammatory lung disease such as emphysema and chronic bronchitis caused by oxidant stress, such as smoke exposure and indoor biomass fuel combustion.

For COPD the only proven genetic risk factor is severe deficiency of α1-antitrypsin [37] which is however present in only 1–2% of individuals with COPD. Novel genetic factors for COPD that predispose smokers to airflow obstruction have yet to be identified.

As celiac disease, COPD is characterized by increased number of activated cytotoxic CD8 T cells with high levels of IFN-γ [38-42] and increased apoptosis of epithelial cells [43]. Significant correlation has been reported between cytotoxic granzyme B expression and apoptosis of bronchial epithelial cells [42]. Lung CD8 T cells in COPD are predominately effector/memory T cells at all disease stages, but their expression of CD69 and T-bet increases as FEV1 decreases. A correlation has been shown between numbers of lung CD8 T cells and apoptotic cells of all types identified in microscopic sections [44], but to date, no studies have directly proven that CD8 T cells are responsible for parenchymal cell apoptosis in emphysema.

An autoimmune pathogenesis was proposed by some groups in COPD. The oxidant injury induced by smoking or other exogenous factors could lead to antigenic modification that would be recognized by CD8 T cells in the context of class I MHC.

In addition, a role of IL-15 in increased type 1 immune responses in COPD has to be proved. IL-15 induces proliferation and differentiation of human CD8 T cell subsets, as well as increased effector functions (i.e., cytokines, cytotoxicity) [45]. *In vitro* stimulation of lung CD8 T cells by IL-15 increased intracellular perforin expression in CD8 T cells [39].

Immunohistochemical staining of frozen human lung tissue from COPD showed that IL-15 was predominantly expressed by alveolar macrophages but not by the airway epithelium as *in vitro* [46,47].

Murine and human data also suggest a role for tobacco smoke-induced upregulation on pulmonary epithelium of MIC ligands and cytotoxic T cell NKG2D-positive cells activation in COPD pathogenesis.

Respiratory viruses rhinoviruses (RVs) and Respiratory Syncytial Virus (RSV) are causing majority of COPD exacerbations. Airway epithelial cells and macrophages are major site for productive virus replication. Virus infection is without obvious cytopathology suggesting that they could rise an immune response.

RSV infect repeatedly during life suggesting deficient memory immune response and RSV may cause persistent or latent infection [48,49]. RSV persistence may serve as a reservoir for transmission and re-infection.

It has been suggested that persistence of RSV RNA in the lungs could contribute to the development of chronic airway disease [50-52]. In support of this

possibility viral persistence was reported in animal models [50,53,52,51,54,55]. In a mouse model, chronic persistence of RSV and increased IFN-γ expression in the lungs likely contributed to the development of chronic airway disease as demonstrated by persistent lung inflammation and airway hyperreactivity [51].

Latent virus infection in stable COPD was also reported [56,57,58]. Has been recently shown that RSV is able to lie latent in a population of dendritic cells for many months and that replication can be triggered by exogenous nitric oxide or an iNOS inhibitor [59]. RSV was also found in sputum samples obtained from COPD patients outside the epidemic period [58]. Tobacco smoke contains significant quantities of nitric oxide and this may contribute to chronic or recurrent replication of the virus, which in turn may contribute to inflammation and enhanced rate of decline in lung function.

Respiratory epithelial cells and macrophages are major place of virus infection, and viruses modulate surface and soluble molecules important in activation/inhibition of innate and adaptive immunity, e.g. IL-15. Because in COPD both epithelial cells and macrophages could be a source of IL-15 production we started to determine in laboratory how respiratory syncytial virus modulates their IL-15 production and surface molecules such as MHC class I and MIC, and what happen if there is an excess of IFN-γ in the milieu environment [60,61] (Zdrenghea et al, manuscript in preparation).

Respiratory virus RSV increased IL-15 production in monocyte-derived macrophages in a dose-response and replication-dependent manner. Rhinoviruses increased IL-15 production in a serotype-independent and replication dependent-manner (Figure 1) (Laza-Stanca et al, submitted). IFN-γ by itself increases IL-15 production in macrophages in a dose-dependent manner. When excess IFN-γ (50ng/mL) was present in medium, macrophages infected with RV16 (MOI 1) produced higher levels of IL-15.

We found that RSV increased surface HLA class I molecules on respiratory epithelial cells in a replication, dose- and time-response dependent manner (Figure 2). IFN-γ also increased HLA class I on alveolar A549 and bronchial BEAS-2B cells and slightly increased RSV-induction of HLA class I.

MICA & MICB molecules share structural homology with HLA class I molecules as they possess three alpha domains, but do not associate with β2-microglobulin and do not present peptides on the cell surface bind non-specific activatory receptors NKG2D (natural killer group 2, member D), with role in non-specific activation of NKG2D-positive NK and CD8 T cells.

MICA&MICB are proteolytically cleaved as soluble molecules (sMICA/sMICB), found in biological fluids with controversial effect on NKG2D expression: soluble MICA molecules decrease NKG2D surface expression on CD8 T cells and NK cytotoxic activity against MICA+ cancer target cells. However in rheumatoid arthritis or celiac disease, soluble MICA fails to down-regulate NKG2D (perhaps reflecting the activities of TNF-α or IL-15).

In our hands, RSV infection of respiratory epithelial

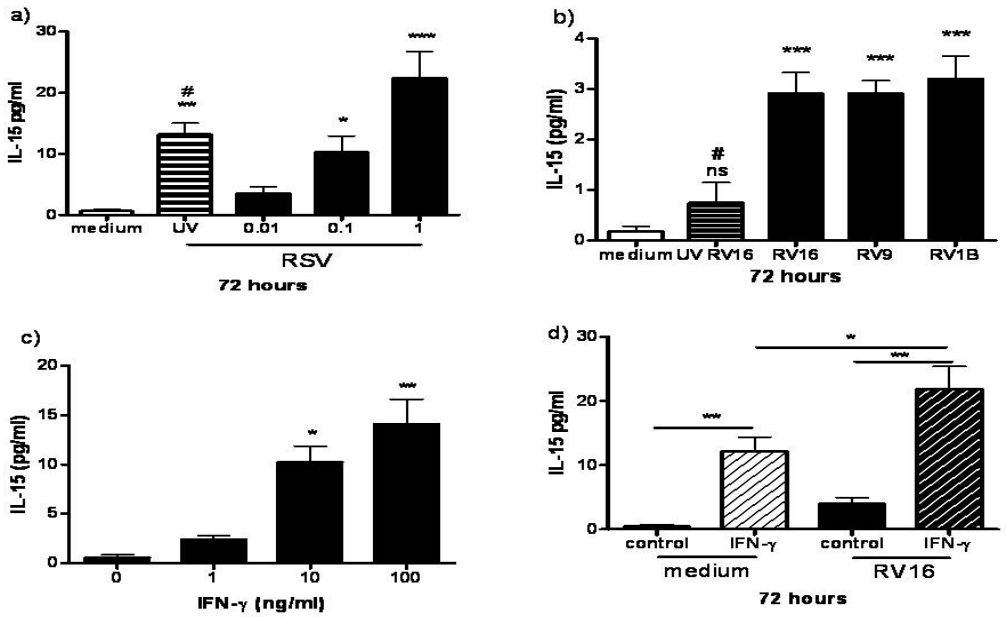

Figure 1. Respiratory viruses increases IL-15 production in THP-1-derived macrophages a) RSV increases IL-15 in macrophages in a dose-response and replication-dependent manner. b) RVs increase IL-15 in a serotype independent and replication dependent-manner. c) IFN-γ increases 15 production in macrophages in a dose-dependent manner. d) IFN-γ (50ng/mL) upregulates RV16 (MOI 1) –induced IL-15 production.

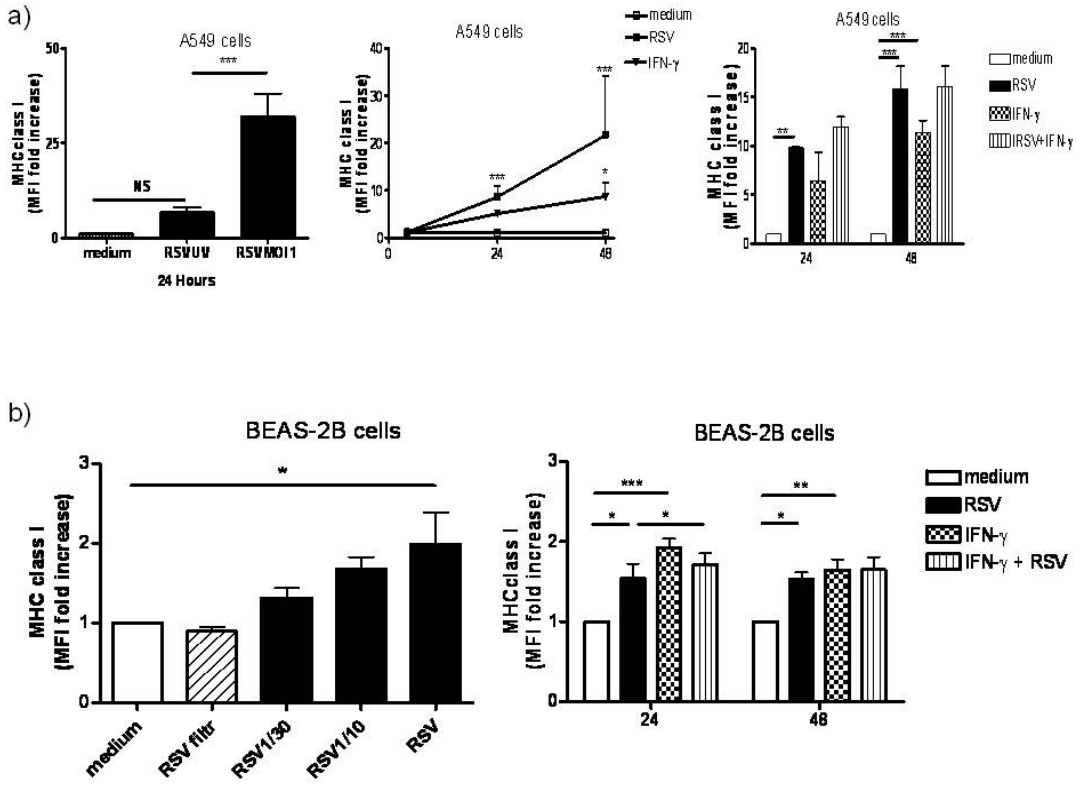

Figure 2. RSV and IFN-γ increases HLA class I levels in respiratory epithelial cells.
a) Alveolar A549 and b) bronchial BEAS-2B cells were cultured with RSV MOI 1 with or without IFN-γ, cells harvested and HLA class I surface molecules determined by flow cytometry. Data are mean±SEM from at least 3 experiments.

cells increased MICA levels, at surface and as soluble molecules (Zdrenghea et al, manuscript in preparation). Interestingly, IFN-γ presence in culture during RSV inhibited this increased. Further work will be done to determine the levels of soluble IL-15, surface MICA and soluble MICA, frequency of NKG2D-positive cells and IL-15-receptor levels on NK and T cells in COPD patients exposed to virus infections.

Conclusions

In both organ-specific disease, celiac disease and chronic obstructive lung diseases, an autoimmune pathogenesis was suggested. Tissue cells are targeted by the cellular immune system; i.e. enterocytes in coeliac disease and respirator epithelial cells in COPD. It was suggested that interleukin-15 is overexpressed in the targeted tissue cells and natural killer group 2, member D (NKG2D)-positive cells are involved in disease pathogenesis.

If IL-15 will be proved to be involved in COPD pathogenesis, IL-15 could become a therapeutic target as in celiac disease.

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