

**O7****Opposing roles for C5aR- and C3aR signaling in the development of maladaptive immunity in allergic asthma**

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Allergic asthma is a chronic airway disease characterized by airway obstruction, hyperresponsiveness (AHR) and inflammation. It is generally accepted that asthma develops in response to a maladaptive T helper type 2 (Th2)-biased immune response, the underlying mechanisms of which remain elusive. Here we demonstrate opposing effects of C3a and C5a, either enhancing or suppressing the development of maladaptive immune responses in experimental asthma. Using a model of house dust mite-induced allergic asthma, we found that C5a receptor (C5aR)-deficient mice suffer from marked airway inflammation, allergen-induced AHR, associated with Th2-biased immune responses. In contrast, C3a receptor (C3aR)-deficient mice showed significantly decreased airway inflammation, AHR and production of Th2 cytokines as compared with wild-type (WT) controls. C3aR expression on pulmonary dendritic cells (DCs) increased during the course of HDM exposure in WT and in C5aR-deficient mice. Importantly, C3aR expression in HDM-treated C5aR-deficient mice was significantly higher than in WT controls. These data support a model in which C3aR signaling contributes to the enhanced type 2 immune responses that we found in C5aR-deficient mice.

In search for mechanisms accounting for the distinct C3aR- and C5aR-mediated *in vivo* effects, we examined the impact of C5aR- and C3aR signaling on cytokine production from CD11c-sorted pulmonary DCs in response to HDM, Toll-like receptor (TLR) 4 or TLR2 ligation. C3aR-deficient DCs produced lower levels of IL-12p40 and IL-10 than DCs from WT mice following HDM, LPS (TLR4) and Pam3Cys (TLR2) challenge. In contrast, IL-12p40 and IL-10 productions from C5aR-deficient DCs were similar to those from WT DCs in response to HDM and LPS stimulation. However, IL-10 production from C5aR<sup>-/-</sup> DCs was impaired following TLR2 challenge. These findings suggest that C3aR and C5aR signaling in pulmonary DCs modulate the production of regulatory cytokines as a potential mechanism to regulate the development of adaptive immunity in experimental asthma.

doi:10.1016/j.molimm.2007.06.014

**Session 2: Inflammatory diseases, therapeutics and diagnostics**

**Sunday 9th September 11.00–13.00**

**O8****Mannose-binding lectin plays a critical role in diabetic cardiomyopathy, hypertrophic remodeling and myocardial ischemia and reperfusion injury**

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Diabetics are known to have an increased risk of cardiomyopathy and acute myocardial infarction (MI), but the etiology is poorly understood. In non-diabetic myocardial ischemia and reperfusion (MI/R) injury, mannose-binding lectin (MBL)-dependent activation of the lectin complement pathway has been shown to play a critical role in tissue injury and inflammation. Oxidative stress, which occurs in diabetes, has been shown to induce lectin complement pathway activation. Other studies have linked oxidative stress to a loss of cardiac progenitor cells (CPC), impairing regeneration of myocytes.

Therefore, in the present study, we investigated the influence of diabetes and hyperglycemia on MI/R injury and the role of MBL in diabetic MI/R, diabetic cardiomyopathy and hyperglycemic induced loss of CPC. In streptozotocin (STZ)-induced diabetic mice, ejection fraction (EF) was decreased by 19% ( $p < 0.001$ ), serum troponin I levels increased 2.8-fold ( $p = 0.002$ ) and myocardial neutrophil infiltration was increased compared to non-diabetic mice following MI/R. Diabetic MBL-deficient mice were significantly protected from MI/R injury compared to diabetic wild type (WT) mice with EF of  $79 \pm 2\%$  versus  $69 \pm 2\%$  ( $p = 0.001$ ), serum troponin I was  $6 \pm 3$  ng/ml versus  $20 \pm 2$  ng/ml ( $p < 0.05$ ) and decreased myocardial inflammation. Echocardiographic measurements in diabetic mice demonstrated signs of dilative cardiomyopathy and heart/body weight ratios suggested hypertrophic cardiac remodeling. Immunohistochemical analysis of CPC revealed significantly lower numbers in diabetic WT hearts compared to non-diabetics. Insulin-treated diabetic WT or untreated diabetic MBL-deficient mice were protected from dilative cardiomyopathy, hypertrophic remodeling and loss of cardiac CPC, suggesting a role for MBL. Patients ( $n = 747$ ) with acute myocardial infarction demonstrated significantly higher functional MBL concentrations in diabetics compared to non-diabetics ( $p < 0.05$ ).

The results from this study demonstrate for the first time that MBL and perhaps lectin complement pathway activation plays a critical role in diabetic MI/R injury, hypertrophic remodeling, and hyperglycemia-induced loss of CPC.

doi:10.1016/j.molimm.2007.06.015