



Previous food allergy aggravates allergic markers and intestinal damages in a mouse model of asthma

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organs. Studies with Mx2-luciferase reporter mice, which express luciferase upon IFNAR triggering, revealed significant IFNAR triggering within the liver and intermediate triggering in secondary lymphoid organs. Of note, viral titers in the liver of infected IFNAR^{-/-} mice were increased when compared to WT mice. Additionally, VACV infected IFNAR^{-/-} mice showed dramatically enhanced cytokine responses as well as elevated liver enzyme levels in the serum. Histological analysis of liver of VACV infected WT mice revealed that such mice developed mild hepatitis around day 5 post infection. In contrast, livers of infected IFNAR^{-/-} mice showed signs of severe hepatitis, massive influx of lymphocytes and inflammatory islets including acute necrotic areas. VACV infection of macrophage-specific IFNAR^{-/-} (LysM-Cre[wt/+]|IFNAR^{fl/fl}) mice revealed that IFNAR signaling of macrophages was needed to protect mice from severe liver damage, whereas IFNAR signaling of hepatocytes (Alb-Cre[wt/+]|IFNAR^{fl/fl} mice) was dispensable. Collectively our results indicated that locally induced IFN-I played a crucial role in balancing cytokine responses and were necessary to trigger macrophage-mediated liver protection.

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Crosstalk between interferon-beta, foam cell formation and inflammatory responses

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Macrophage-derived foam cells are critical components of atherosclerotic lesions and the ways in which the inflammatory response of foam cells influences atherogenesis is of great interest. Previously we demonstrated that interferon-beta (IFN-β) promotes atherogenesis. But how IFN-β influences foam cell formation and inflammation is not understood yet. Hence, we assessed the functional involvement of IFN-β in these processes in a normal versus high cholesterol environment. First, we performed a microarray study on IFN-β-stimulated bone marrow-derived macrophages (BMDMs) under normocholesterolemic conditions, which showed upregulation of immune response pathways and downregulation of cholesterol biosynthesis. Secondly, we loaded BMDMs with acLDL followed by 6 h IFN-β treatment, which surprisingly impaired the induction of IFN-β target genes, like CCL5 and CXCL10. To validate these findings *in vivo*, LDLR^{-/-} mice were put on normal chow (NC) or a high cholesterol diet (HCD) for 10 weeks. Peritoneal macrophages (PEMs) were collected 4 days after intraperitoneal thioglycolate administration, combined with IFN-β (5000 U/ml) or PBS administration 24 and 8 h before sacrifice. Lipid loading increased following IFN-β treatment, accompanied by increased scavenger receptor-A (SR-A) gene expression. This lipid loading also resulted in PEM IFN-β-hyporesponsiveness, since several IFN-β target genes were again less expressed compared to NC PEMs. In addition, *ex vivo* culturing of PEMs from IFN-β-treated animals on HCD versus NC showed an overall decreased inflammatory activity, as gene expression of inflammatory markers was reduced and secretion of IL-6, TNF and NO was decreased. Currently we assess how HCD interferes with IFN-β-induced effects by investigating the IFN-β-induced activation of transcription factors like STAT1, IRF3 and IRF9 in control and acLDL loaded BMDMs. Altogether, IFN-β promotes foam cell formation, possibly by increased lipid influx via SR-A. Interestingly, increased lipid loading results in hyporesponsiveness to IFN-β. More research is needed to reveal the biological relevance for this hypercholesterolemia-induced hyporesponsive state.

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Previous food allergy aggravates allergic markers and intestinal damages in a mouse model of asthma

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Aims: Increasing clinical data suggest a link between food allergy and the later development of respiratory allergy. This progression may be triggered by exposures to different allergens but the mechanism implicated remains unknown. This study aimed to identify the impact of a first exposure to food allergen on the development of a new form of allergy caused by exposure to a novel allergen using a mouse model.

Method: In our model, mice were intraperitoneally sensitized to wheat proteins (modified gliadins) to induce a systemic response, then they were exposed orally to the same allergen and finally they were intranasally exposed to HDM (Dermato-

phagoides farinae extract) a respiratory allergen without adjuvant to assess an impact on lung mucosa.

Results: After food and respiratory allergen exposures, mice displayed stronger amount of blood markers: IgE specific and histamine. Moreover, splenocyte secretion of IL-4 and IL-17 were increased whereas weaker levels of IFNγ were observed. In parallel Peyer patches lymphocytes secreted higher amount of IL-4 with a decreased in IFNγ, IL-10 and TGF-β productions. These mice exhibited intestine damages, higher paracellular flux and modification of transcellular permeability. In contrast, airway hyper-responsiveness, inflammatory cells and cytokines in lung remained unchanged compared to the respiratory allergy model.

Conclusion: We show that dual exposure induces a raise in specific IgE and local Th2 and Th17 cytokines secretion before triggering phase. During the latter, gut morphology and functions were affected but not lung in dual exposed mice compared to single one underlying the organospecific impact. Altogether, our data make a step further in the elucidation of the mechanisms linking allergy history to immunological and clinical status potentially linked to atopic March development.

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The role of cytokines in the cerebrospinal fluids of patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME)

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Objectives: Previous research has provided evidence for a dysregulation in cytokine levels in the periphery of patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME). To date few studies have examined cytokines in the cerebrospinal fluid. The purpose of this research is to examine the role of cytokines in the symptom presentation of CFS/ME patients.

Methods: Cerebrospinal fluid (CSF) was collected from 18 CFS/ME patients and 5 healthy controls. The CSF samples were examined for the expression of 27 cytokines [interleukin (IL)-1β, IL-1ra, IL-2, IL-4, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p70, IL-13, IL-15, IL-17, basic FGF, eotaxin, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1 (MCAF), MIP-1α, MIP-1β, PDGF-BB, RANTES, TNF-α and VEGF] using the bio-plex human cytokine 27-plex assay.

Results: Of the cytokines examined, only four were significantly reduced in the CFS/ME patients in comparison to the controls.

Conclusions: The results show a decrease in pro-inflammatory cytokines in the CSF of CFS/ME patients and this may contribute to the clinical disease progression.

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Deregulated gp130/Stat3 signalling in lung cancer development

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Lung cancer (LC) is the most common and lethal cancer worldwide and, in Australia, accounts for ~7500 deaths annually. A causal correlation between LC and cigarette smoking is well established, however only 10–15% of smokers develop LC, suggesting there are other ill-defined genetic, epigenetic and/or environmental factors which predispose individuals to LC. Regarding the former, interleukin (IL)-6 signals via the gp130 signal-transducing receptor subunit to primarily activate the latent transcription factor STAT3, as such, the pro-inflammatory and oncogenic properties of the IL-6/gp130/STAT3 signalling axis can be established. Since IL-6 expression and STAT3 activity are up-regulated in human LC, we explored the downstream consequences of increased IL-6/STAT3 activity in the well documented Kras[G12D] mouse LC model. For this purpose, we utilised gp130[F/F] (FF) mice that carry a knock-in mutation in gp130 leading to deregulated IL-6/STAT3 signalling, and crossed these mice with the LoxP-Stop-LoxP Kras[G12D] mice which harbour a conditionally-activated oncogenic Kras allele. Inhalation of FF:Kras[G12D] and WT:Kras[G12D] mice with a Cre recombinase adenovirus activated the Kras allele at 6 week of age, and mice were observed over 6 weeks.

There was a severe and diffuse development of invasive adenocarcinoma *in situ* (AIS) in the lungs of FF:Kras[G12D] mice only. The percentage density of lesions in the lungs of FF:Kras[G12D] mice was increased compared to WT:Kras[G12D] littermate controls, and associated with an increase in the number of proliferative cells and inflammatory infiltrates (determined by immunohistochemistry). In contrast, partial suppression of deregulated IL-6/STAT3 signalling by crossing FF:Kras[G12D] mice onto an IL-6^{-/-} or Stat3^{-/+} background led to a recovery of normal lung tissue and a decrease of both proliferative and inflammatory cells.