4th European Congress
of Immunology
Vienna 2015

September 6-9 / Vienna waits for you!

ABSTRACT BOOK

www.eci-vienna2015.org

WS.E.02.2
Metabolic requirements for γδ cell development

***S. Martin**, N. Sumaria, D. J. Pennington;*
Blizard Institute, London, United Kingdom.

Introduction: Gammadelta (γδ) T cells unusually express features of the innate and adaptive immune systems, providing anti-pathogen and anti-tumour responses in a rapid yet antigen receptor-driven manner. However, their generation in the thymus remains unclear, particularly the mechanisms that underpin the differential development of γδ T cells that secrete either IL-17A or IFN-γ. The rapidly developing field of immunometabolism has provided significant evidence that metabolism underpins the growth, proliferation and functionality of αβ T cells. With this newly evolving field in mind, this project investigates the metabolic requirements for the development on γδ T cells.
Materials & Methods: We used foetal thymic organ culture (FTOC) to analyse the development of IL-17A-secreting and IFN-γ-secreting γδ T cells under different metabolic conditions; for example by using the metabolic inhibitors rapamycin, 2-deoxyglucose and metformin. γδ T cell subsets were assessed using a new flow cytometry gating strategy that was recently established in the lab.
Results & Conclusion: IFN-γ-secreting γδ T cells appear to rely heavily on glycolysis during development as both rapamycin and 2-deoxyglucose significantly impaired their generation. By contrast, IL-17A-secreting γδ T cells were largely unaffected. Instead, IL-17A-secreting γδ T cell number was decreased in the presence of an inhibitor of oxidative phosphorylation. These observations suggest that different modes of energy production differentially affect the development of γδ T subsets with distinct cytokine-secreting potentials.

WS.E.02.3
Immunological recognition of dietary proteins are required for intestinal development and barrier function

*S. Hartmann[1], A. Visekruna[1], H. Mollenkopf[2], K. Rajalingam[3], **U. Steinhoff**[1];*
[1]Institute for Microbiology and Hospital Hygiene, Marburg, Germany, [2]Max-Planck Institute for Infection Biology, Berlin, Germany, [3]Institute for Immunology, Mainz, Germany.

Introduction: The aim was to investigate the impact of food proteins on intestinal homeostasis and immune recognition under physiological conditions.
Material and Methods: We compared mice fed a conventional diet with animals raised on an amino acid containing diet (FAF). We analysed intestinal and non-intestinal immune compartments for diet-specific immune reactivity, compared the gene expression profile and investigated the influence of proteins on barrier integrity.
Results: FAF animals gained normal body weight and had litter sizes comparable to mice with a conventional diet. Dietary proteins induced an activated, CD_4+CD_{44}+Helios+ T cell population, predominantly in Peyer´s patches (PP). These cells are distinct from Foxp3+regulatory T cells and are microbiota-independent. Diet-reactive T lymphocytes remained innocuous through equilibrium between activation and apoptosis. Macrophage-mediated uptake of apoptotic T cells from PP, but not from other tissues, resulted in strong IL-10 expression. In contrast, replacement of dietary proteins by amino acids resulted in low numbers of activated and apoptotic CD_4+CD_{44}+Helios+ T cells together with reduced amounts of IL-10 and downregulation of genes involved in intestinal integrity such as trefoil factors and gastrokines.
Conclusion: Dietary protein are essential for the maintenance of intestinal homeostasis through controlling the transcription of pro-and anti-inflammatory genes and by regulating activation

WS.E.02.4
Macrophages rearrange the mitochondrial electron transport chain upon sensing live bacteria

*J. Garaude[1,2], R. Acín-Pérez[1], S. Martínez-Cano[1], M. Ugolini[3], E. Nistal-Villán[4], S. Hervás-Stubbs[4], L. E. Sander[3], J. A. Enríquez[1], **D. Sancho**[1];*
[1]CNIC, Madrid, Spain, [2]IRMB, Montpellier, France, [3]Charité Hospital Berlin, Berlin, Germany, [4]CIMA, Pamplona, Spain.

The mitochondrial electron transport chain (mETC) is a catabolic endpoint whose adaptations accompany fuel source fluctuations, stress responses or innate immune signals to ensure optimum cellular functions. Macrophages tightly scale their core metabolism upon activation by innate immune receptors, but the precise regulation of mETC plasticity by pathogen sensing is currently unknown. Here we show that innate recognition of live bacteria by macrophages triggers the re-organization of mETC super-complexes (SCs). SCs that contain complex I (CI) and form the respirasome are decreased, which is associated with reduced CI activity and CI-mediated synthesis of ATP. In contrast, complex II (CII) activity is enhanced, promoting succinate oxidation to drive oxidative phosphorylation. Chemical inhibition of CII impairs macrophage activation and bactericidal activity in vitro and in vivo. The Src-family tyrosine-kinase Fgr controls CII-activity induction and mediates mETC adaptations upon bacteria recognition. Notably, heat-killed E.coli do not trigger mETC re-organization and induction of CII activity on macrophages. In line with this, both bacterial RNA, which signifies bacterial viability, and the RNA-mimicking Toll-like receptor (TLR)-3 ligand polyinosinic:polycytidylic acid [poly(I:C)] induce CII activity. Consistently, macrophages deficient for the TLR adaptors TIR-domain-containing adapter-inducing interferon-β (TRIF) and myeloid differentiation primary response 88 (MyD88) are unable to re-organize the mETC or to induce CII activity. We thus identify TLR-mediated mETC adaptations as an early immune-metabolic checkpoint that potentially scales innate immune responses during bacterial infection.
Funding: CNIC, Spanish SAF-2013-42920R, European ERC-2010-StG 260414, Marie Curie CIG-332881 and French La Ligue Contre le Cancer #CG/59-2013

WS.E.02.5
Placental heme oxigenase 1 expression promotes immune adaptation to pregnancy and fetal growth in mice

***M. E. Solano**, M. K. Kowal, G. E. O'Rourke, R. Barikbin, K. Karimi, P. C. Arck;*
University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Maternal immune tolerance to fetal semi-allogeneic antigens is required to sustain fetal development, i.e. by promoting an adequate implantation and placentation. The placenta mediates the nutrient and gas exchange between mother and fetus. Thus, placental insufficiency is often associated to intrauterine growth restriction. The enzyme heme oxygenase (HMOX)-1 is highly expressed in the placenta and is involved in its vascularization. HMOX-1 plays also a regulatory role in inflammatory processes, i.e. by modulating CD8+T cell function. Hereby, we aimed to examine whether altered placental HMOX-1 expression in mice affects fetal development through an impaired maternal immune adaptation to pregnancy.
BALB/c HMOX-1+/- x HMOX-1+/- and wild type (wt) pregnancies were analyzed on gestation day (gd) 16.5. HMOX-1-/- implantations exhibited decreased fetal weight and placental vascularization, as observed in histological placental tissue sections, than their litter-mates wt controls in HMOX-1+/- pregnancies. Further, flow cytometric analysis revealed decreased frequencies of CD8+CD_{122}+T cells in uterus-draining lymph nodes in HMOX-1+/- dams when compared to HMOX-1+/+ dams. In non-pregnant females, cobalt protoporphyrin induced HMOX-1 resulted in increased CD8+CD_{122}+T cells in uterus-draining lymph nodes. Adoptive transfer of HMOX-1+/+ CD8+CD_{122}+T cells to HMOX-1+/- dams alleviated the fetal growth restriction in HMOX-1-/- implantations and improved the placental vascularization when compared to PBS injected dams.
We conclude that reduced HMOX-1 expression in mutant mice results in impaired immune adaptation to pregnancy characterized by decreased CD8+CD_{122}+T cells, altered placental function and signs for intrauterine growth restriction. To prevent these effects pharmacological interventions could target HMOX-1 to modulate immune tolerance during pregnancy.

WS.E.02.6
Immunometabolic phenotype of prototypical Th1- and Th2-type mouse strains

***N. Pejnovic**[1,2], N. Jovicic[1,3], I. Jeftic[1,2], I. Jovanovic[1], G. Radosavljevic[1], N. Arsenijevic[1], M. L. Lukic[1];*
[1]Center for Molecular Medicine and Stem Cell Research, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia, [2]Institute of Pathophysiology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia, [3]Institute of Histology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia.

Introduction: Immune reactivity plays an important role in obesity-associated metabolic disorders. We investigated immunometabolic differences in C57Bl/6 and BALB/c mice, the prototypical Th1 and Th2 mouse strains.
Materials and Methods: Male 8-week old C57Bl/6 and BALB/c mice were placed on high-fat diet (HFD, 60% kcal fat) or chow (10% kcal fat) for 24 weeks and histological, immunophenotypic and gene expression analyses were performed.
Results: Chow-fed BALB/c mice had higher body weight and weight gain, lower glycemia, more pronounced liver steatosis, but lower inflammation and collagen deposition in liver than C57Bl/6 mice. In response to HFD C57Bl/6 mice exhibited higher weight gain, glycemia, HbA1c and liver glycogen content, increased amount of visceral adipose tissue (VAT) and number of VAT associated CD_{11c}+ dendritic cells (DCs), F4/80+ macrophages and CD_3+$CXCR_3$+ T cells than BALB/c mice. Livers of HFD-fed C57Bl/6 mice contained more numerous myeloid DCs, proinflammatory CD_{11b}+Ly6Chigh monocytes/macrophages, CD8+ T lymphocytes and higher levels of TNF-α, IL-6 and IFN-γ compared with BALB/c mice. In contrast to C57Bl/6 mice, HFD in BALB/c mice induced marked liver steatosis and increased hepatic LXRα and PPARγ. In C57Bl/6 mice HFD induced liver fibrosis and increased hepatic procollagen 1α and TGF-β mRNA, and IL-33, IL-13 and TGF-β levels in liver homogenates, whereas BALB/c mice had scarce collagen deposition in liver.
Conclusion: We show inherent immunometabolic differences in C57Bl/6 and BALB/c mice, Th1- and Th2-dominant strains on standard and high-fat nutrition. Differential immunometabolic characteristics across different mouse strains need to be considered in studies of metabolic disorders.