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EMBO Workshop "Immunology and metabolism"

Bart Staels, David Dombrowicz & Ursula Grohmann

Recent findings have identified roles for the immune system in what had been considered prototypic metabolic diseases, while metabolic control has emerged as an important determinant of immune function. Giovanna Chimini, Lee Leserman, Diane Mathis and Philippe Naquet organized the EMBO Workshop on Immunology and Metabolism, which took place in January 2011 at the Centre d'Immunologie de Marseille-Luminy in Marseille, France. The meeting brought together around 100 scientists to discuss interactions between metabolism and inflammation, and was sponsored by Sanofi-Aventis and the CIML.

Several presentations addressed the interplay between metabolic and inflammatory risk factors in the development of obesity, type 2 diabetes (T2D) and atherosclerosis. The immune system impacts on these processes at several levels and inflammation in adipose tissue contributes to the development of insulin resistance. Gwen Randolph (Mount Sinai School of Medicine, New York, USA) showed that antigen-presenting dendritic cells (DCs) and macrophages within the muscular wall of collecting lymphatic vessels extend pseudopods into the lumen of adipose lymphatic vessels. Through these, they import lymph-derived antigens into adipose tissues in a CCL21/CCR7-dependent manner. In the absence of CCR7 expression, lymph-derived antigens were not found in adipose DCs or macrophages and inflammation was abated, suggesting that the collecting lymphatic ducts communicate with the surrounding adipose tissue and macrophages to control the immune response. Jaap Neels (University of Nice, France) discussed the roles of the IL8 (CXCL8)-CXCR2 chemokine-

chemokine receptor system and paxillin/α4-integrin interactions in monocyte/macrophage rolling and arrest on adipose tissue endothelial vessel walls. He demonstrated their important role in the subsequent macrophage infiltration of adipose tissue and development of insulin resistance. He also highlighted the role of $CD11c^+$ cells in the induction of high fat diet-induced insulin resistance and the expression of inflammatory markers. Deficiency or inhibition of 5-lipoxygenase (LO)–mediated leukotriene production altered M1/M2 content in adipose tissue and protected against insulin resistance. Diane Mathis (Harvard Medical School, USA) identified a specific subset of regulatory T cells (Tregs) in abdominal fat that express higher levels of PPARγ1 than other Tregs. Abdominal fat Tregs produce high amounts of IL-10 and their deletion leads to increased inflammation, obesity and insulin resistance upon high-fat diet feeding. Luca Mazzarella (European Institute of Oncology, Milan, Italy) reported that insulin or IGF at high levels inhibit the induction of human $Foxp3^+$ Tregs. This may lead to an increased inflammatory state.

Several other mechanisms were reported to be involved in inflammation in adipose tissue. The plasma concentration of CD40L is elevated in T2D and metabolic syndrome patients. Marjorie Poggi (Cardiovascular Research Institute, Maastricht, The Netherlands) reported that antibody-mediated depletion of CD40L improved metabolic control in a mouse model of a high-fat diet, Jean-François Tanti (INSERM U895, Nice, France) showed that macrophage-derived IL-1β and TNF increase adipocyte expression of TPL2 (MAP3K8). This controls cytokine-induced lipolysis and down-regulates insulin signaling. Conversely, Tpl2 inhibition in adipocyte-macrophages co-cultures reduces production of inflammatory cytokines.

Anna Krook (Karolinska Institutet, Sweden) discussed cytokine control of skeletal muscle glucose metabolism. She showed that IL-6 and IL-13 are induced during exercise in muscle,

inducing myotube formation, glycogen synthesis and glucose uptake in skeletal muscle cells. Intriguingly, the skeletal muscle of T2D patients displays IL-6–resistance and secretes less IL-13, due to induction of the inhibiting microRNA Let7. David Patsouris (U. Lyon Sud, France) found that the skeletal muscle of obese mice displays increased levels of inflammatory markers (TNF, MCP1) along with the presence of macrophages. David Simar (U. New South Wales, Australia) compared insulin signaling in the monocytes of lean and obese individuals, the latter having decreased cell surface GLUT4 expression related to increased JNK, IKKβ and IRS1-Ser phosphorylation.

Several presentations addressed the regulation of high-density lipoprotein (HDL) production, which is protective against cardiovascular disease. Laurent Yvan-Charvet (Columbia U., USA) suggested an intriguing and novel regulatory role for ABCA1 and ABCG1. These are well known controllers of cholesterol efflux from macrophages. Both *ABCA1* and *ABCG1* genes are highly expressed on hematopoietic stem cells (HSC). The genetic deletion of these transporters in mice leads to proliferation of HSC, resulting in increased levels of circulating and infiltrating neutrophils, monocytes and eosinophils, with pro-atherogenic consequences. Eric Moses (Texas Biomedical Research Institute, USA) showed that variants of the gene coding for the pantetheinase Vanin 1, might determine plasma HDL-C concentrations and therefore atherogenesis. Laure Perrin-Cocon (INSERM U851, Lyon, France) showed that HDL phospholipids inhibit DC maturation and LPS-induced NF-κB activity, identifying a novel immune-modulatory and potentially anti-atherosclerotic mechanism of HDL.

Ziad Mallat (U. Cambridge, UK) addressed the contribution of B lymphocytes to atherogenesis, and reported the beneficial effect of anti-CD20 mediated B cell depletion. This led to decreased atherosclerosis, reduced IFN-γ levels and IgG anti-oxidized LDL antibody

production, but enhanced IL-17. Interestingly, CD20-depletion did not markedly influence anti-oxLDL IgM-producing B cells.

Kenneth Rock (U. Massachusetts, USA) discussed the induction of inflammation by sterile stimuli, such as urate and cholesterol crystals, via activation of the NRLP3 inflammasome that matures IL-1β. Phagocytosis of these crystals by macrophages triggers the inflammasome via lysosomal rupture and cathepsin B activation, a mechanism that may contribute to the induction of atherosclerosis. Host sterol metabolism is essential for controlling viral replication. Peter Ghazal (U. Edinburgh, UK) presented data on the impact on sterol metabolism of virus-induced activation of pattern recognition receptors (PRR), which suggests the existence of an innate immune mediated cross-regulation between infection and sterol metabolism.

The pleiomorphism of the monocyte-macrophage lineage and a precise definition of their activation status were also major topics of discussion. David Hume (U. Edinburgh, UK) performed gene expression profiling in various monocyte populations to identify specific transcription networks. Surprisingly, many surface markers thought to be subpopulation-specific, such as CD11c (a DC marker), are rather more specific for the inflammatory response than the cell subset. Extensive expression profiling of mouse and human CSF-1–treated macrophages showed that 10% of genes are discordantly expressed and 25% showed significant differences in expression levels. Many gene pathways were found to be differentially expressed in human and mouse macrophages, including the arginase and tryptophan metabolic pathways. Graham Thomas (U. Edinburgh, UK) studied modifications of gene expression profiles in alternative (M2) macrophages induced by nematode infection. Parasite mainly affected pathways involved in energy metabolism, in particular arachidonic acid metabolism, with a large increase in 5- and 15-LO expression. Sophie Lotersztajn (Henri Mondor Hospital, Créteil, France) discussed the protective role of the endocannabinoid

receptor CBR2 in alcoholic liver disease. The receptor prevents alcohol-induced M1 polarization of Kupffer cells and favors transition into an M2 phenotype. Réjane Paumelle (INSERM U1011, Lille, France) showed that deficiency of the anti-oncogene and cell cycle regulator p16INK4A polarizes macrophages from M1 to M2 in a manner independent of its cell cycle controlling activities. Liver Kupffer cells also belong to the monocyte/macrophage lineage. Ilse Scroyen (INSERM U626, Marseille, France) presented data linking fatty liver disease and LPS-induced plasminogen activator inhibitor-1 (PAI-1) with its hypoglycemic effect. Kupffer cells aggravate this process, possibly through the NFκB pathway, although they are not primary actors.

Christopher Glass (U. California San Diego, USA) reviewed the crucial positioning of nuclear receptors at the crossroads between metabolic and inflammatory pathways in his Keynote address. He summarized the mechanisms of anti-inflammatory activities via trans-repression of PPARγ, LXR and GR. Trans-repression by LXRs and PPARγ occurs via their SUMOylated forms, which inhibit the removal of the co-repressor NCoR from inflammatory response gene promoters. Recent findings have identified Coronin2A (Cor2A) as an NCoR complex protein. Cor2A interacts with SUMO-LXR and is thus a SUMO-LXR docking site. Cor2A knock-down also resulted in decreased inflammatory gene expression and Cor2A was found to be necessary for NCoR clearance from the promoter via the recruitment of actin upon LPS stimulation. Bart Staels (INSERM U1011, Lille, France) discussed the counterintuitive presence of M2 macrophages in human atherosclerotic lesions. These macrophages display decreased cholesterol handling due to low LXRα expression. Consequently, PPARγ activation does not enhance ABCA1 expression, but stimulates phagocytic activity via regulating thrombospondin-1 expression. Antonio Castrillo (IIBM CSIC-UAM, Madrid, Spain) showed that $LXR^{-/-}$ mice lack marginal zone macrophages, potentially due to differences in bone marrow progenitors in LXRα, but not LXRβ-null mice. As shown by

Andres Hidalgo (CNIC, Madrid, Spain), the control of senescent neutrophil efferocytosis by macrophages enables LXRαβ to have an unexpected role in the regulation of circadian oscillations in haematopoietic stem and progenitor cell (HSPC) transport, which is negatively correlated with bone marrow CXCL12 levels. Christine Delprat (CNRS UMR 5239, Lyon, France) showed that IL-17A promotes foam cell formation by regulating lipid metabolism genes as well as LXRα and PPARγ in Langerhans cell histiocytosis. Percy Knolle (U. Bonn, Germany) identified a role for PPARγ in experimental autoimmune encephalomyelitis (EAE). PPARγ activation delays disease onset via its effects on $CD4^+$ T lymphocytes. $PPAR\gamma^{-/-}$ $CD4^+$ T cells are prone to develop into Th17 cells due to increased expression of the nuclear receptor RORγt. Signals upstream of the glucocorticoid receptor also play a role in metabolic diseases linked to inflammation. Katia Karalis (Children's Hospital, Harvard Medical School, USA) showed that LPS treatment of corticotropin-releasing hormone-deficient mice induces anorexia.

Another theme of the meeting concerned the role of oxidative stress and the generation of reactive oxygen species (ROS) in the modulation of inflammatory responses. Anna Rubartelli (IST, Genova, Italy) showed that ROS production and subsequent activation of the antioxidant system are required for Toll-like receptor-induced IL-1β secretion by myeloid cells. An improper redox response results in altered inflammasome activation and IL-1β secretion. Shyam Biswal (Johns Hopkins U., USA) reported roles for Nuclear factor erythroid-2 related factor (Nrf2) and its inhibition by Kelch-like ECH-associated protein 1 in the expression of antioxidant and detoxification enzymes. Nrf2 inactivation ameliorated atherosclerosis due to decreased activation of metabolic enzymes, decreased glucose uptake and oxidation, and decreased fatty acid synthesis. In contrast, constitutive Nfr2 activation in cancer cells enhanced metabolism and inflammation. Alice Carrier (INSERM U624, Marseille, France) showed that ROS levels are controlled by Tumor Protein 53-Induced

Nuclear Protein 1, a p53-target which is repressed by miR155 in cancer cells, further establishing a link between redox state, metabolism and cancer. Leonore Herzenberg (Stanford U., USA) discussed the effect of N-acetylcysteine, an acetaminophen detoxifier, which increases GSH levels in individual cases of cystic fibrosis and HIV. She emphasized the beneficial effect of culturing cells under physiologic conditions (5% 0_2). Samuel Rommelaere (CIML, Marseille. France) studied the complex action of epithelial vanin 1, a pantetheinase that provides tissue cysteamine. Vanin 1-deficiency aggravates T1D but protects animals from acute colitis and modulates resistance to infectious disease.

Amino acid catabolism is an ancestral survival strategy that controls immune responses in mammals. Indoleamine 2,3-dioxygenase (IDO) catalyzes the first step of tryptophan (Trp) catabolism. Ursula Grohmann (U. Perugia, Italy) showed that IDO may have evolved in mammals to acquire signaling functions for the induction and maintenance of long-term immune tolerance. In plasmacytoid DCs, IDO signaling requires TGF-β–induced tyrosine phosphorylation of two immune tyrosine-based inhibitory motifs (ITIM) contained in the non-catalytic domain of the enzyme. As shown by Andrea Nino Castro (U. Bonn, Germany), IDO is a key feature of regulatory DCs that exert microbicidal activity in a model of chronic inflammation sustained by *Listeria* cells. The effect does not depend on Trp starvation, but is mediated by tryptophan metabolites. Interestingly, human obesity is often associated with reduced plasma Trp and increased adipose and hepatic IDO expression (Odile Poulain-Godefroy; CNRS UMR 8199, Lille, France). A shift in Tregs/Th17 balance was associated with IDO increase in the subcutaneous adipose compartment, but was not observed in visceral adipose tissue. In T cells, IDO inhibits the mammalian target of rapamycin (mTOR), a central component of nutrient and hormone sensitive signaling pathways. mTOR signaling proceeds via two downstream complexes, TORC1 and TORC2. Using $TORC1^{-/-}$ and $TORC2^{-/-}$ mice, Jonathan Powell (Johns Hopkins U., USA) demonstrated that TORC2 is involved in the

control of weight and triglycerides, whereas TORC1 drives organ-specific autoimmune/inflammatory diseases such as EAE. Andy Johnson (U. Pennsylvania, USA) showed that activation of S6K, a kinase downstream of mTOR, is delayed in 'exhausted' $CD8^+$ T cells responding to chronic viral infection, but is partially restored by ligation of the inhibitory receptor PD-1.

This meeting highlighted the increasingly complex bi-directional interactions between immune cells and inflammation with metabolic alterations and cancer. Oxidative metabolism and nuclear receptors mechanistically link processes previously considered to be unconnected. The IDO-mTOR axis may represent a novel link between metabolic and immune/inflammatory pathways. Analyses of transcripts from particular immune subpopulations and cell-specific inactivation or overexpression of proteins controlling these pathways should yield exciting discoveries in this emerging field.

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