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Meeting Report

Clinical and fundamental aspects of monocyte, macrophage and dendritic cell plasticity

Geert Raes[1,2], Patrick De Baetselier[1,2] and Jo A. Van Ginderachter[1,2]

In September 2011, more than 300 European and international scientists met at the 25th Annual meeting of the European Macrophage and Dendritic Cell Society (EMDS) in Brussels, Belgium. They discussed various clinical and fundamental aspects of monocyte, macrophage and DC biology. A central emerging theme was how the plasticity of these cells is reflected in different organs and tissues and is affected by various immune and physiological stimuli.

Introduction

The scientists gathering at the EMDS 2011 meeting did not need to await the announcement of the Nobel Prize in Physiology Medicine to Bruce Beutler, Jules Hoffmann and Ralph Steinman [1] to be convinced of the crucial role of TLRs and myeloid cells (MCs), such as DCs, in both innate and adaptive immune responses. Indeed, cells of the myeloid lineage – in particular monocytes, macrophages and DCs – are central orchestrators of inflammation and innate and adaptive immunity, but, conversely, can also contribute to the resolution phase of inflammation and wound healing and thus play an important role in a range of normal physiological processes and diseases. Hereto, MCs are among the most versatile cells of the immune system and exhibit a high degree of functional and phenotypic plasticity in response to the micro-environmental triggers to which they are exposed. The importance of these cells has been highlighted recently in this Journal with a *Viewpoint* series on dendritic cells introduced by Ralph Steinman [2] and a *Viewpoint* series on macrophages introduced by Siamon Gordon and Alberto Mantovani [3]; the latter being published to coincide with the EMDS 2011 meeting.

MC diversity and plasticity as reflected in distinct tissues and organs

The diversity and plasticity of MCs are exquisitely reflected in the differentiation of committed progenitors into distinct lineages and by the various roles distinct subsets of these cells play in a range of organs and tissues, either under steady state or during inflammation.

In this context, the earliest hematopoietic progenitors and immature MCs might participate in immune regulation. Fiona Powrie (University of Oxford, UK) presented recent work from her laboratory, revealing a marked accumulation of MCs, including granulocytes and monocytes, in colitis. Further analysis revealed striking changes in haematopoietic progenitor populations in the bone marrow, as well as locally in the colon. Inflammation-driven changes in haematopoiesis may thus represent a novel therapeutic target in colitis. The same holds true for multiple tumor types, whereby increased myelopoiesis leads to the accumulation of myeloid-derived suppressor cells (MDSCs), which are immature MCs of the granulocytic or monocytic lineage characterized by their immunosuppressive activities [4]. Suzanne Ostrand-Rosenberg (University of Maryland, USA) reported that MDSCs developing under the influence of highly inflammatory tumors (e.g. IL-1β-secreting tumors) are more resistant to Fas-FasL-mediated apoptosis and have a prolonged survival than MDSCs in a less inflammatory environment. Despite this increased resistance to apoptosis, tumor-conditioned MDSCs can still be killed in vivo by T cells expressing Fas, suggesting that MDSC levels in tumor-bearing individuals can be decreased by activated T cells and could be therapeutically regulated by Fas–FasL interactions [5].

A number of talks focused on the role of infiltrating versus organ-resident MCs in determining inflammatory disease outcome. Frank Tacke (University Hospital Aachen, Germany) presented an overview of how inflammatory $CD11b^+$ $F4/80^+$ $Ly6C^+$ monocyte-derived cells massively accumulate intrahepatically in murine models of acute and chronic liver injury [6, 7] and reported a distinct systemic and intrahepatic increase of non-classical $CD14^+$ $CD16^+$ monocytes in

human patients with chronic liver diseases [8]. Interestingly, hepatic monocyte recruitment can be therapeutically blocked by a novel MCP-1-specific antagonist ("Spiegelmer") [9]. Catarina Raposo (Weizmann Institute, Israel) reported that, following spinal cord injury, there is a massive accumulation of activated immune cells at the CNS parenchyma. The infiltrating monocytes do not contribute to the local inflammation, but instead the glial scar matrix facilitates acquisition of an anti-inflammatory, IL-10-producing phenotype by the infiltrating monocytes, promoting resolution of the resident microglial inflammatory response and, in an apparent feedback loop, these monocytes, in turn, produce matrix-degrading enzymes, and thereby contribute to scar resolution and thus to the regeneration of the injured CNS [10]. In the tumor microenvironment, infiltrating Ly6C$^+$ monocytes differentiate into two main subsets of tumor-associated macrophages (TAMs): MHC II^{hi} and MHC II^{low} TAMs [11]. Jo Van Ginderachter (VIB-Vrije Universiteit Brussel, Belgium) documented that MHC II^{hi} TAMs are more prominent in slow growing tumor variants, while MHC II^{low} TAMs predominate in fast growing tumors. The macrophage mannose receptor (CD206) is a marker for these MHC II^{low} TAMs. Steve Schoonooghe from the same lab reported that nanobodies (15 kD antigen-recognition domains of camelid heavy chain-only antibodies) raised against CD206 specifically target the receptor in vivo and presented a successful strategy to reduce extratumoral binding in the spleen and liver, while maintaining tumor targeting of the CD206 nanobodies, offering perspectives for specific imaging and therapeutic targeting of MHC II^{low} TAMs in vivo.

Besides these inflammatory settings, the contributions of MCs to homeostasis are as important. Previous data from the Powrie laboratory have indicated that a CD103$^+$ subset of mucosal DCs contributes to intestinal tolerance by inducing de novo generation of Foxp3$^+$ Tregs via a TGF-β- and retinoic acid-dependent mechanism [12]. Mark Travis (University of Manchester, UK) reported that, under steady-state conditions, CD103$^+$ intestinal DCs are superior than CD103$^-$ DCs in inducing enhanced levels of Foxp3$^+$ Treg cells in a TGF-β-dependent manner, even in the absence of retinoic acid. The increased Treg cell-inducing ability of CD103$^+$ DCs is dependent on increased expression levels of the TGF-β-activating integrin αvβ8, resulting in an enhanced ability of these cells to activate TGF-β [13]. These data highlight a novel mechanism for maintaining intestinal homeostasis. In addition, for the maintenance of homeostasis, DCs and macrophages need to tightly control the activity of inflammatory transcription factors, such as NF-κB. Rudi Beyaert (VIB-UGent, Belgium) reported a cell-type-specific role of A20 – a deubiquitinating enzyme inhibiting NF-κB activation – in autoimmune disease etiology, whereas DC-specific A20 deletion leads to inappropriate DC activation and systemic autoimmunity [14], A20 deficiency in macrophages/neutrophils triggers inflammation predominantly in the joints, leading to erosive polyarthritis [15].

MC plasticity in response to various immune and physiological stimuli

A prototypic example of MC plasticity is the bidirectional interaction between MCs and lymphocyte subsets and the modulation of macrophage activation states during Th1 versus Th2 immunity, resulting in M1 (classically activated) versus M2 (alternatively activated) macrophage phenotypes [16]. Judith Allen (University of Edinburgh, UK) proposed that Th2 immunity likely evolved to utilize the innate injury repair pathways for controlling the damage caused by large metazoan parasite entry and migration, as well as for containing or expelling them [17]. Thus, the evolutionary origins of the Th2 arm of the immune system as an adaptive repair process may explain the association of alternatively activated macrophages with wound healing and tissue-preserving anti-inflammatory processes. Although Th2 immunity itself can be "inflammatory", the Allen lab recently discovered that under Th2 conditions inflammation is fundamentally different. Rather than relying on recruitment of monocytes from the blood, macrophage accumulation in the tissues can result from IL-4-driven expansion of the local resident population [18]. This form of "alternative inflammation" would avoid the collateral damage often associated with monocyte- and neutrophil-dominated classical inflammation. In addition, as was recently published in this Journal [19], the proliferation of tissue-resident macrophages could be an important mechanism contributing to restoration of homeostasis following acute inflammation. In this context, the proliferation of mature macrophages is beginning to be understood at the molecular level. Starting from previous observations that combined deficiency for the transcription factors MafB and c-Maf (Maf-DKO) enables unlimited expansion of fully functional, differentiated macrophages without malignant transformation or stem cell intermediates [20], Michael Sieweke (Centre d'Immunologie de Marseille-Luminy, France) reported on molecular details that render self-renewal compatible with differentiation. Genome-wide enhancer analysis has now revealed that Maf-DKO cells maintain a macrophage-specific enhancer signature at high fidelity and, as compared with the enhancer profile of embryonic stem cells, activate a network of self-renewal genes on an existing tissue-specific enhancer platform. These findings provide the exciting perspective that activation of self-renewal in differentiated cells may be possible without the extensive chromatin reorganization associated with lineage reprogramming to self-renewing pluripotent stem cells.

Further elaborating on the M1 and M2 scheme of macrophage activation, master regulators of cellular activation such as transcription factors represent exquisite tools for the characterization of these macrophage subsets. Irina Udalova (Imperial College London, UK) reported that transcription factor interferon regulatory factor 5 (IRF5) is a master regulator of inflammatory M1 macrophage polarization. IRF5 is highly expressed in M1 macrophages and regulates the

majority of M1-associated markers. IRF5 regulates gene expression via two independent mechanisms, involving direct binding to DNA and recruitment via interactions with another transcription factor NF-κB RelA [21]. At the other end of the spectrum, Antonio Sica (University of Piemonte Orientale A. Avogadro, Italy) further elaborated on their identification of the p50 subunit of NF-κB as a key regulator of M2-driven inflammatory reactions [22].

As another signal inducing a tissue-preserving (M2-like) phenotype in macrophages, Andreas Weigert and coworkers (Goethe-University, Germany) believe that apoptotic cell death serves as a signal to indicate overshooting inflammation/tissue damage that programs macrophages to repair the damage, e.g. by promoting angiogenesis. They have shown that angiogenic macrophage activation by apoptotic cells requires release of sphingosine-1-phosphate (S1P) from apoptotic cells, which couples to S1P receptors 1/3 on macrophages. Downstream of S1PR1/3, macrophages selectively produce prostaglandin E2, which is required for inducing endothelial cell migration and angiogenesis in vivo. Since the prostaglandin E2 high profile is prominently induced in macrophages activated with dying tumor cells as compared with e.g. T cells, this mechanism may also contribute to tumor angiogenesis. Another microenvironmental trigger known to induce angiogenic macrophages is hypoxia. Maria Escribese (Centro de Investigaciones Biológica, Spain) presented evidence that hypoxia conditions human macrophage polarization at the phenotypic (polarization markers) and functional (cytokine production) level. In addition, Luigi Varesio (Gaslini Institute, Italy) reported on their finding that hypoxia strongly up-regulates a cluster of genes encoding immune-related cell surface receptors in DCs and on the identification of Triggering Receptor Expressed on Myeloid cells 1 (TREM-1) as a marker of hypoxic mature DCs with pro-inflammatory properties [23].

Finally, as an example of a metabolic signal, the role of iron for macrophage function and host resistance toward infection was discussed by Günter Weiss (Medical University of Innsbruck, Austria). While minute amounts of iron in the macrophages are necessary to promote the formation of toxic radicals, higher iron concentrations lead to inhibition of pro-inflammatory immune effector pathways by inhibiting the activity of the central Th1 cytokine IFN-γ [24]. On the other hand, microbes have an essential demand for iron, which they need for their growth and pathogenicity. During systemic bacterial infection, macrophages, cytokines, and the acute-phase protein hepcidin alter body iron homeostasis, rendering this essential nutrient less available for invading pathogens while ameliorating anti-microbial, pro-inflammatory immune effector pathways. Accordingly, pharmacological modification of iron transport favorably affects the course of a *Salmonella typhimurium* infection [25].

DC biology

In response to direct activation by microbial stimuli or by extrinsic inflammatory mediators, DCs undergo a terminal differentiation program (maturation), rendering them immunogenic. Such a differentiation program encompasses the upregulation of MHC class II and costimulatory molecules at the DC surface, the migration of DCs to the T-cell zones of the draining LNs and the release of cytokines, altogether promoting the differentiation of naïve T cells into effector cells. For each of these steps, several novel findings were reported.

Gianluca Matteoli (European Institute of Oncology, Milan, Italy) reported that migration of DCs, but not their capacity for antigen uptake, processing, and presentation, is dependent on the actin capping activity of the signalling adaptor epidermal growth factor receptor kinase substrate 8 (Eps8). Owing to the migration deficit of Eps8-deficient DCs, Eps8 null mice are impaired in promoting T-cell priming and fail to mount a contact hypersensitivity response [26]. Once in the draining LN, DCs direct the polarization of T-cell responses. Andrew MacDonald and coworkers (University of Edinburgh, UK) found that DCs deficient in the methyl-CpG binding domain protein 2 (MBD2) are severely impaired in their ability to induce Th2 development. Next, they identified RELMα expression in DCs to be MBD2-dependent and have shown that RELMα-deficient DCs display impaired Th2 induction ability. Christophe Desmet (University of Liège, Belgium) reported that aluminum-based vaccine adjuvants, known as Th2 inducers, boost adaptive immune responses through the induction of DNA release from host cells. Subsequently, host DNA activates $CD11c^+CD11b^+Ly6C^+Ly6G^-$ inflammatory DCs, which in turn stimulate 'canonical' T helper type 2 responses [27]. Of note, DCs also present lipid antigens to invariant NKT cells. Laszlo Nagy (University of Debrecen, Hungary) showed that this process is dependent on the lipid-activated nuclear receptor PPARγ, which in turn regulates the expression of the lysosomal protease cathepsin D and maturation of saposins, a group of lipid transfer proteins required for lysosomal lipid antigen processing and loading [28]. Finally, as an important new clue as to how B lymphocytes in LNs can be triggered by non-opsonized antigens, Florence Niedergang and coworkers (Université Paris Descartes, France) have found that antigens taken up by DCs via macropinocytosis and stored in late endocytic compartments can be released from these compartments into the extracellular medium. These "regurgitated" unprocessed antigens can then be taken up by B cells [29].

Concluding remarks

Plasticity is a hallmark of cells of the myeloid lineage such as monocytes, macrophages, and DCs and is intimately related to the pleiotropic functions played by the various subsets and activation states of these cells in a range of physiological and pathological processes. Therefore, a better understanding of MC diversity and plasticity holds promise for the development of MC-targeted therapeutic strategies. During the meeting, an important focus of the current research on the ontogeny of the

distinct subtypes of these cells, ranging from the progenitor and precursor pools into the pools of mature blood-borne and tissue-associated cells, was highlighted. Progress is also being made to define more precisely tissue-specific functions of these cells and the way these are regulated by various micro-environmental triggers during homeostatic as well as pathologic conditions. In this context, the identification of epigenetic regulators and key transcription factors, as well as improved imaging technologies, offer perspectives for further refinement of our understanding of MC plasticity and diversity in vitro and in vivo.

Meeting URL: Information on the EMDS as well as the meeting program can be accessed via www.macrophage.de

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[1] Myeloid Cell Immunology Laboratory, VIB, Brussels, Belgium

[2] Unit of Cellular and Molecular Immunology, Vrije Universiteit Brussel, Brussels, Belgium

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Full correspondence: Dr. Geert Raes, VIB Myeloid Cell Immunology Laboratory, Unit of Cellular and Molecular Immunology, Vrije Universiteit Brussel, Pleinlaan 2, B-1050 Brussels, Belgium
Fax: +32-2-629-19-81
e-mail: Geert.Raes@vib-vub.be

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