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Editorial Open Access

Macrophages: Tissue-Resident Determinants of Immunomodulation

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Editorial

Macrophages (MΦs) are mononuclear phagocytes that are found in almost every tissue and are generated from myeloid progenitor-derived monocytes, which differentiate to tissue MΦs upon migration from the peripheral circulation to specific tissue environments. MΦs play a dominant role in the clearing of antigenic materials (pathogenic, infection- and tissue trauma, host-derived) by phagocytosis, driving innate immune responses or instruction of adaptive responses. In fact, MΦs exhibit a wide range of functionality which includes phagocytosis, antigen processing and presentation, pathogen killing, inflammation, anti-inflammatory responses, immune suppression, tissue repair, both pro- and anti-tumour responses and activation/instruction of other innate and adaptive immune cells. Such a wide array of functionality, which at times appears to be at opposite ends of a spectrum of effector functionality, cannot surely be exhibited by just one type of effector MΦ. Indeed, MΦs exhibit a functional mosaic which is likely to be shaped by many factors that present themselves in the local tissue environment. This functional mosaicism presents as a consequence of a plethora of environmental influences which include activation and differentiation factors as well as a level of pre-programming in the monocyte recruited to the tissue; all of which coming together to result in distinct functional effector phenotypes or MΦ subsets.

Macrophage polarisation and effector phenotype

With the early characterisation of distinct T helper effector subsets by Mosman and Coffman [1], which described T_{h1} and T_{h2} cells, later characterised as driving cell-mediated immunity and humoral responses respectively, it was suggested that these responses may be further defined by distinct functional phenotypes of APCs/MΦs. Activation of MΦs by LPS in the presence of the T_{h1}-derived cytokine, IFNγ, has been described to result in classically activated MΦs which exhibit an immune activatory/pro-inflammatory phenotype whereas activation by the T_{h2} cytokines, IL-4 and IL-13, drive an alternative activation phenotype defined by anti-inflammatory/regulatory and scavenging/phagocytic function. This alternative activation phenotype of MΦs was also observed for MΦs stimulated in the presence of antibody-immune complexes transduced through FcRs [2]. The inclusion of animal studies with defined genetic backgrounds however, indicated that MΦ functionality could be programmed prior to or independent of activation stimuli. This heterogeneity in MΦ effector phenotype was demonstrated in responses elicited in C57/Bl6 mice versus Balb/c mice, where CMI responses predominated in the C57/Bl6 mice and humoral responses in the Balb/c mice. These M1 and M2 subsets fed back to T cells, effectively driving T_{h1} and T_{h2} responses respectively [3]. Thus, the route of differentiation may also drive this functional heterogeneity; this was eloquently backed up by studies describing differential effector function in MΦs differentiated by GM-CSF or M-CSF. GM-CSF primed towards a pro-inflammatory M1-like phenotype whereas M-CSF primed towards an M2-like anti-inflammatory or regulatory phenotype [4]. In general, M1 MΦs exhibit anti-microbial and anti-tumoral characteristics (expressing iNOS), they are immune activatory (express HLA-DR and CD86), pro-inflammatory (secrete TNFα, IL-1β, IL-6, IL-12, IL-18, IL-23 at high levels, whereas secrete low levels of IL-10) and are associated with the expression and activation of distinct signalling molecules (TREM-1, STAT1, STAT4 and SOCS3). M2 MΦs represent the opposite end of a functional spectrum from the M1 subset. M2s are characterised by phagocytic scavenger receptor expression (MR, CD206), arginase expression and activity, secretion of immune regulatory anti-inflammatory cytokines (TGFβ, IL-10) and favouring humoral and pro-tumoral responses [5]. A simple dichotomy of response between pro-inflammatory and anti-inflammatory responses of M1 and M2 MΦ subsets would appear to be a gross over-simplification. In reality, MΦ effector phenotype and subset is determined by the local environment in whatever tissue the MΦ resides; this environment being dictated by tissue homeostasis, physiological responses to stressors and pathology. Thus, the MΦ can exhibit a wide heterogeneity of effector response which is reflective of a wide variation in tissue environment. As a consequence, MΦs exhibit a functional mosaic or sliding scale of responses between the canonical M1 and M2 phenotypes. This is reflected in the ever increasing description of functional MΦ subsets. Several "variations" on the theme of M2 MΦs have been described on the basis of activation and phenotype: these include M2a (alternative), M2b (type II), M2c (deactivated), M2d and regulatory MΦs [6-10]. In addition, some MΦ subsets have been also described in pathological environments which include M4, Mox, HA-mac, M(Hb) and Mhem [11], all of which represent a spectrum of effector functionality, where M4 is closer to the M1 phenotype on the basis of low IL-10 expression and Mox, HA-mac, Mhem, M(Hb) are closer to the M2 phenotype (IL-10^{hi}, scavenger $receptor^{hi}$).

One aspect that further clouds our understanding of MΦ subset functionality is the fact that, to a certain extent, MΦ effector phenotype may already be pre-programmed in the monocyte. The description of classical, intermediate and non-classical monocytes, based on the differential expression of CD14 and CD16, further complicates this functional mosaic of MΦs. Classical monocytes ($CD14^{hi}$ $CD16^{-ve}$) express IL-10^{hi} $CD163^{+ve}$ and iNOS whereas non-classical monocytes ($CD14^{lo}$ $CD16^{hi}$) express iNOS, high levels of HLA-DR, TNFα, IL-12 and low levels of CD163 and IL-10 [12]. Intermediate monocytes are $CD14^{hi}$ $CD16^{lo}$ Arg^{+} $CD163^{+}$ $HLA\text{-}DR^{lo}$, it is conceivable that non-classical monocytes are indeed pre-programmed to a pro-inflammatory M1-like phenotype whereas classical and intermediate monocytes are primed towards M2-like MΦ subsets, with classical monocytes maintaining the capability to be programmed towards either M1 or M2. Thus MΦs exhibit a wide range

of functional plasticity, polarisation of which is determined by a combination of pre-programming, differentiation and activation which is reflective of the tissue environment.

Mucosal MΦs and pathology

Tissue environment determines MΦ polarisation in both homeostatic and pathological conditions. Atherosclerosis research has resulted in the description of M4, Mox, HA-mac, M (Hb) and Mhem [11], all of which are conditioned by the pro-inflammatory environment associated with atherosclerotic lesions. Mucosal macrophages are also defined by their environment: intestinal MΦs generally exhibit an anti-inflammatory suppressive, tolerisable functional phenotype defined by IL-10, TGFβ and phagocytic receptors (CD36, CD68, CD206) which resembles that of an M2-like subset [13]. Dysfunction in mucosal macrophages drives pathological responses whereas chronic inflammatory pathology, such as that observed in Crohn's disease (CD), is characterised by a destructive pro-inflammatory environment, indicative of M1-like MΦ involvement. These intestinal MΦs are associated with genetic mutations in the bacterial sensing molecule, NOD2, exhibiting a pro-inflammatory phenotype (TNFα, IL-1β and IL-12) [14] which is in stark contrast to healthy homeostatic intestinal MΦs which display an inflammatory tolerance whilst maintaining phagocytic capability and anti-microbial activity (IL-10, TGFβ, CD36, CD68) [15]. In contrast, humoral-mediated inflammation, such as that observed in ulcerative colitis (UC), or immunosuppressive pathology in the case of colorectal cancer (CRC), are associated with an M2 MΦ - T_{h2} axis, defined by IL-4 and IL-13 production. The profile of pro-inflammatory cytokines and IL-10 exhibited in UC is comparable to those expressed in CRC [16]. Tumour associated macrophages (TAMs) are generally M2-like MΦs that are anti-inflammatory, immunosuppressive and express functional markers which favour tumour development [17]. Thus tissue MΦs, their subset and functional phenotype also drive a spectrum of pathological conditions: modulation of these MΦ phenotypes represents a realistic therapeutic approach in the treatment of disease.

Macrophages – future immunotherapeutic approaches

Macrophages play a pivotal role in both homeostatic and pathological mechanisms. These functional responses are exhibited by a diverse array of MΦ subsets or by a wide plasticity which is partially or totally determined by monocyte recruitment, MΦ activation stimuli or differentiation factors encountered in the tissue microenvironment. Manipulation of these functional macrophage subsets may determine future immunotherapeutic approaches. Such immunomodulatory approaches to manipulation of this functional plasticity will involve selective activation, tolerisation, deviation and differentiation of monocyte subsets. Ideally, immunomodulation would redress the balance of pathogenic MΦs to a more homeostatic setting. For example, manipulating the functional plasticity of tissue MΦs to reprogramme M1-like pro-inflammatory MΦs to express an M2-like suppressive anti-inflammatory phenotype would be advantageous in the treatment of chronic inflammatory diseases such as CD. Conversely, reverting immunosuppressive M2-like TAMs to a cytotoxic, anti-tumour MΦ may be advantageous in the case of CRC. Alternatively, selective tolerisation of MΦ subsets may also represent a valid therapeutic option; whereby M1- or M2-driven pathologies are treated by active suppression of the pathogenic MΦ subset. Such a therapeutic approach would only be viable upon rigorous characterisation of the molecular and cellular microenvironment, as current research has suggested selective tolerisation of MΦ subsets but that this may be defined by the stimulus encountered [18]. Finally, in a robust chronic microenvironment such as that which presents in solid tumours, the strong pro-tumour environment, coupled with the plastic nature of MΦs introduced as a therapeutic, immunomodulation or selective tolerisation regimens may not persist long enough to show clinical improvement. As a result, in some diseases, MΦs may not represent a target for immunotherapy but may present themselves as delivery vehicles capable of delivery of a therapeutic payload at the heart of a pathological manifestation. Such an approach has recently been described in the MΦ-delivery of an oncolytic virus which inhibited tumour growth and matastasis [19]. Future MΦ-mediated immunotherapeutic regimens will only succeed with full characterisation of microenvironmental influences on monocyte/MΦ programming, MΦ differentiation and activation/tolerisation signals. Reprogramming/manipulation of MΦ effectors within this functional spectrum, that defines specific tissue environments as homeostatic or pathological, will change the clinical application of immunotherapy.

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