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Chapter 5

Macrophages — Masters of Immune Activation, Suppression and Deviation

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Additional information is available at the end of the chapter

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1. Introduction

Immunostimulation is fundamental to efficient host responses to pathogens; a comprehensive understanding of which will inform the development of the next generation of vaccines. Integral to vaccine development is the mode of delivery to the appropriate host tissue. Mucosal tissue, with its ability to both tolerise and activate host immune responses, represents an ideal site for vaccine delivery. The continued study of such mucosal tissue with respect to its ability to exert immune activation, suppression and in deed deviation, will be of benefit to the design of next-generation vaccines.

Mucosal immunity is governed by the interaction of the barrier epithelial cells of the mucosal surface with the underlying immune cells. The most important immune cells, which are responsible for determining immune responsiveness at these surfaces, are those of the innate immune system; antigen presenting cells (APCs) such as dendritic cells (DCs) and macrophages (Mϕs). DCs play an important role in antigen processing and presentation, thus priming antigen-specific effector T cell responses by homing from the challenge site to the local lymph node. Mϕs, on the other hand, stay within the mucosal tissue at the forefront of the challenge site and play a major role in immune fate decision: activation, deviation or suppression. Under certain genetic, environmental and immunological conditions, these resident tissue macrophages are rendered dysfunctional and play a pivotal role in establishment and persistence of pathology. Taking into consideration their tissue residence and their potential to prime a wide range of immune responses, this review will focus on immunostimulation in the context of mucosal Mϕ function in both homeostasis and pathology in the oral mucosa and gastrointestinal tract (GIT). In addition, immunostimulation via Mϕ functionality can only fully be appreciated by considering the relative relationship of activation with both immune-deviation and suppression; such functionality will also be considered in this review.

2. Macrophages

Macrophages have long since been recognised to play a central role in the immune response. They are mononuclear phagocytic cells, which have been demonstrated to be involved in pathogen recognition, clearance, antigen processing and presentation, inflammation and tissue repair as well as pro-and anti-tumoral responses. Tissue Mϕs perform a range of important homeostatic functions and exist in many different tissue-specific forms: microglia in the brain, alveolar Mϕs in the lung, Kupfer cell in the liver, osteoclast in the bone, as well as splenic, intestinal, bone marrow and lymph node-associated subcapsular sinusoidal/ medullary Mϕs. Thus, Mϕs are central to innate immune inflammatory mechanisms and the priming of adaptive responses to both intracellular and extracellular pathogens as well as immune regulation and tumour surveillance; such diversity of effector functionality would suggest mucosal macrophages to be ideal targets for vaccine therapy.

2.1. Mϕs exhibit distinct functional subsets

In general, Mϕ functions are conferred by environmental stimuli, pre-programming or the route of differentiation. As such, Mϕs exist in several subsets, which exhibit discrete functional and phenotypic traits. A certain level of confusion exists however, as to whether the Mϕ subset has been generated by the use of distinct activation signals or as a consequence of longer-term culture/differentiation, or is even pre-programmed in the monocytes. There is some evidence to suggest that monocyte pre-programming is of some functional relevance, where there is a level of heterogeneity, and monocytes potentially exist as a classical ($CD14^{++}CD16^{-}HLA\text{-}DR^{+}$) subset and a pro-inflammatory subset ($CD14^{+}CD16^{+}HLA\text{-}DR^{++}$) [1,2] biased towards high level TNFα production and present in high numbers in inflammatory pathologies [3,4]. In its simplest guise, Mϕ subsets have been described to exist as two functionally distinct forms, in particular associated with Th_1 or Th_2 adaptive responses: a pro-inflammatory subset (classically activated, type I or M1) and an anti-inflammatory/regulatory subset (alternative activation, type II or M2) [5,6], although further studies have suggested several subdivisions may exist within the M2 subset (reviewed in [7]).

M1 macrophages, also referred to as classically activated Mϕs, are generally pro-inflammatory Mϕs, which exhibit a functional phenotype that is anti-microbial (mediating resistance to intracellular pathogens), tissue destructive and anti-tumoral [8]. Upon activation, these Mϕs express a plethora of pro-inflammatory cytokines (TNFα, IL-1β, IL-6, IL-12, IL-18, IL-23), chemokines (CXCL1, 2, 3, 5, 8, 9, 10, CCL2, 3, 4, 5, 11, 17 and 22)[9], proteases and ROS/RNS. As a consequence of this wide array of cytokines expressed, M1s play a pivotal role, not only in innate responses, but also adaptive, antigen-specific responses. As M1s secrete a high level of IL-12, they promote Th_1 differentiation, hence cell mediated immune mechanisms for the defence against intracellular pathogens [10,11]. In addition, Holscher et al., 2001, described the protective role of IL-12p40; this subunit is also common to IL-23, which is produced by M1s and is important in the differentiation and activation of Th_{17} cells [12,13]. Mϕs can be polarised to the M1 phenotype in the presence of IFNγ and in combination with inflammatory stimuli such as LPS or TNFα. In addition, this M1 phenotype can also result from differentiation in

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the presence of GM-CSF [14,15] and further polarising signals such as anoxic environments [16], β-chemokines [17] and phorbol myristate acetate, PMA [18,19]. The presence and activation of pro-inflammatory M1s would have to be tightly controlled, as over-activation or dysregulation of M1s may result in uncontrolled pro-inflammatory pathology. The involvement of such a distinct Mϕ subset has been suggested to be central to the tissue-destructive pathology associated with the chronic inflammatory bowel disease, Crohn's disease [20].

In addition to the profile of factors listed in the paragraph above, the general profile of the M1 effector phenotype is IL-10^{lo} IL-12^{hi} IL-23^{hi} [21]. Associated with the M1-polarising stimuli, IFNγ and LPS, are distinct expression and activation profiles of intracellular signalling components. M1 polarisation is transduced via the transcription factors STAT-1 and NFkB, driving the expression of immune mediators characteristic of this subset, and via the activity of SOCS3 [22]. Finally, the M1-specific transcription factor, STAT-1, has been demonstrated to inhibit STAT-6 activation; this factor is required for M2 polarisation [23], thus an M1-associated transcription factor cross-regulates/suppresses M2 polarisation/activation. These observations alone were suggestive that there was a level of plasticity that existed between M1 pro-inflammatory Mϕs and the anti-inflammatory/regulatory M2 Mϕs.

M2 macrophages, which are also referred to as alternatively activated Mϕs, were found to exhibit a functionally distinct phenotype to that of M1s, originally via the ability of IL-4 to induce MR expression, followed by another Th_2 cytokine, IL-13 [24,25]. M2 functionality was generally described as an anti-inflammatory/immunoregulatory phenotype, which also mediates tissue remodelling and repair, resistance to parasites and tumour promotion, all of which was dependent on the activation/differentiation signals encountered [6,26]. Extensive research has found a wide range of M2 polarising signals to exist: these priming signals include IL4/IL13, IL-10, TGFβ, M-CSF, Vitamin D_3, immune complexes and the Th_2-derived cytokine, IL-21 [27] and reviewed in [28]. The versatility in polarising signals and effector functionality of M2 Mϕs resulted in the proposal that M2s exist in a variety of subsets: M2a (tissue repair), M2b (B cell IgG production) and M2c (anti-inflammatory/scavenging mechanisms) (reviewed in [7,26]) (refer to figure 1 below).

M2 polarisation is induced by a wealth of exogenous factors, presented above, which drive distinct signalling/transcription factor pathways as well as signature gene expression. There is an ever-increasing understanding of these endogenous molecular pathways initiated by polarising factors such as IL-4. Whereas p65 NFκB subunit expression is associated with M1 polarisation, M2 polarisation has been described to be orchestrated by p50 NFκB [30, 31], whereby p50 NFκB inhibits NFκB-dependent M1 polarisation. In addition, p50-deficient mice exhibit exacerbated M1-driven inflammatory responses with a concomitant suppression of M2-driven responses (allergy and anti-helminth immunity). In addition to p50 NFκB, M2-like differentiation/ polarisation has been demonstrated to be induced by agonists of PPARγ [32], CREB-controlled C/EBPβ [33] and epigenetic regulation of M2-defining gene products in mice (arginase-1, Ym1, FIZZ1 and mannose receptor) via the IL-4-STAT6-dependent histone demethylation of H3 by the histone demethylase, jmjd3 [34, 35]. Finally, signalling components not only positively regulate Mϕ differentiation and activation; the generation of alternatively activated (M2) Mϕs has been reported to be

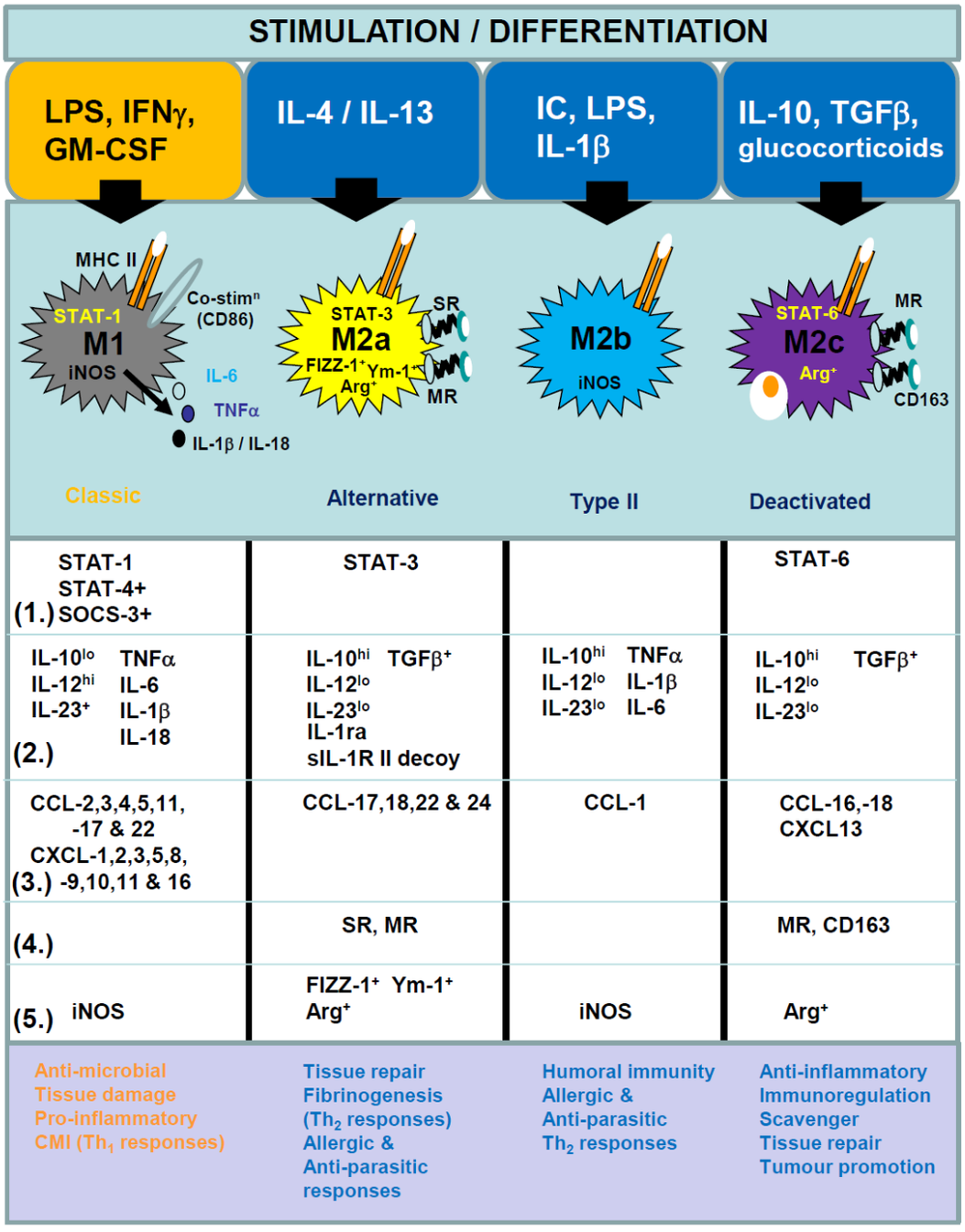

Figure 1. Activation and differentiation drive a range of functional macrophage phenotypes Mϕ effector subsets exist as pro-inflammatory M1 and regulatory or anti-inflammatory M2 phenotypes. M1s are elicited through activation by LPS and IFNγ and differentiated by GM-CSF, whereas M2s can be subdivided into M2a, M2b and M2c according to stimulation/differentiation and functional phenotype. Functional phenotype is characterised by a series of molecular markers listed in the incorporated table under the categories of (1.) signalling molecules, (2.) cytokine expression profile, (3.) chemokine profile, (4.) scavenger receptor expression and (5.) tryptophan metabolism (inducible nitric oxide synthase, iNOS, and arginase, Arg) and the poorly defined effector molecules, FIZZ-1 and Ym-1. The overall function of these Mϕ subsets is summarised in the lower segment of the table, ranging from pro-inflammatory, anti-tumour responses to anti-inflammatory, regulatory and tissue reparative responses. This figure is adapted from [28] and information presented in [7, 9, 23, 26, 29].

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repressed by the negative regulator, src homology 2-containing inositol-5'-phosphatase, SHIP, a potent negative regulator of the PI3K pathway [36].

2.2. Functional and phenotypic plasticity of macrophages

Tissue-resident macrophages can thus express a wide variety of functional phenotypes, which is governed by the manner in which they are activated, differentiated or pre-programmed. This results in potentially two distinct opposing types; pro-inflammatory M1 Mϕ and anti-inflammatory/regulatory M2 Mϕ. If these subsets represent a terminally differentiated phenotype, then it is probable that Mϕs are incapable of functional plasticity. What is becoming clear however, is that M1 and M2 Mϕs do exhibit a level of plasticity and that tissue Mϕs are more likely represented on an intermediate sliding scale between pro-inflammatory/immune activatory and anti-inflammatory/regulatory functionality. Indeed, this functional plasticity and manipulation of Mϕ subset has been observed in many studies. A study focussing on bone marrow-derived Mϕs, observed that cytokine functional phenotypes could be altered/reversed in the presence of Th_1 or Th_2 cytokines and that this plasticity in function was determined by changes to tissue microenvironment and whether these cytokines were encountered before or concomitantly with an activation stimulus [37]. This plasticity or reversal of Mϕ cytokine phenotype has recently been reinforced by the demonstration of a reversible, bi-directional differentiation of pro-inflammatory (M1) and anti-inflammatory (M2) monocyte-derived Mϕs in response to GM-CSF and M-CSF [38]. In addition, the control of these M-CSF and GM-CSF Mϕ and the invading monocyte populations has been demonstrated to be controllable via the use of neutralising antibodies to these differentiation factors in both homeostasis and inflammatory pathology of antigen-induced peritonitis and lung inflammation [39]. This study suggested that M-CSF-derived Mϕs played a non-reductant (M2-like regulatory) role whereas GM-CSF Mϕs maintained the inflammatory response (M1-like pro-inflammatory), contributing to prolonged monocyte and neutrophil infiltration. This is suggestive of the possibility of *in vivo* control of Mϕ effector phenotype through reduction in numbers and manipulation of plasticity.

Macrophage plasticity is not only determined by the differentiation factors but also by the local environmental stimulation factors, the intracellular signalling molecules activated and by the effector cytokines expressed/secreted by the macrophages. These environmental factors not only modulate Mϕ functional plasticity, the Mϕs themselves are able to cross-regulate each other thus moving or consolidating Mϕ effector response along this sliding scale of functionality between pro-inflammatory and anti-inflammatory/regulatory responses. These exogenous regulators include M1 and M2-associated cytokines (IFNγ, IL-12, IL-10, IL-4) which cross-regulate each other and immune complexes (ICs) which, through binding of their respective FcγR, can revert activation status or suppress/modulate cytokine expression, such as suppress IL-12 and induce IL-10 to an M2-like phenotype [40,41]. There is a wide range of intracellular signalling molecules, which play distinct roles in this cross-regulation and plasticity between M1 and M2 subsets. Pro-M1 responses can be mediated by SHIP-1 [42], p65 NFκB and IRF5 [43]; all of which, suppress M2s. On the flip-side, pro-M2 responses have been demonstrated to be mediated by tpl-2, p50 NFκB [31], STAT-6 [34], C/EBPβ and c-maf [33]; again, these

molecules suppress the development of the other canonical Mϕ subset, M1s (reviewed in [44]). Indeed, the importance of the NFkB signalling pathway has been further consolidated by a study demonstrating that IKKβ played an anti-inflammatory role by suppressing classical Mϕ activation/M1 Mϕ phenotype via negative cross-talk with STAT-1, which is involved in the expression of IL-12, iNOS and MHCII [45] and via the maintenance of the IL-10^{hi}/$IL12^{lo}$ functional phenotype [46].

Considering Mϕ subset phenotype, its environmental differentiation factors, activatory stimuli and effector cytokine profile; macrophage responses can be modulated by a wide range of factors which includes both positive and negative regulators. As such, the potential involvement of macrophages as an immunotherapeutic target for several pathologies can only be appreciated by a full understanding of both activatory and regulatory signals: immunostimulation, immunosuppression and immune deviation.

3. Stimulation and suppression of Mϕ effector responses

Macrophages exhibit a wide variety of receptors, which transduce a multitude of immunostimulatory signals. These activatory receptors are centred on responsiveness to conserved broad-spectrum molecular patterns associated with immune responsiveness to pathogens or endogenous, self-associated, danger signals. Pattern recognition receptors (PRRs) which stimulate or co-activate immune responses include the toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin receptors (CLRs) and scavenger receptors (SRs). In addition to these PRRs, Mϕs can also be activated by immune complex recognition via FcRs and cytokine stimulation through their cognate receptors.

Toll-like receptors respond to a wide repertoire of PAMPs, expressed on bacterial, viral, fungal and parasitic pathogens, and DAMPs; generally activating innate inflammatory-or anti-viral responses through the involvement of discriminatory utilisation of receptors, adaptor proteins and either NFκB-or IRF-dependent signalling pathways [47]. Indeed, the utilisation of such signalling pathways, in Mϕ polarisation, make it impossible to totally devolve consideration of polarisation, activation, cross-regulation and suppression. TLRs are expressed according to the localisation of pathogens; TLR2 (CD282), TLR1 (CD281), TLR6 (CD286), TLR4 (CD284) and TLR5 (CD285) being expressed on extracellular membranes, recognise extracellular pathogens, whereas TLR3 (CD283), TLR7 (CD287), TLR8 (CD288), and TLR9 (CD289) are expressed intracellularly, associated with endosomal membranes and recognition of intracellular resident pathogens. The extracellular facing TLRs were found to recognise a range of conserved PAMPs expressed by bacteria, including lipopeptides, LPS and flagellin, whereas TLRs 3, 7, 8 and 9 recognise dsRNA, dsDNA and hypomethylated CpG DNA motifs, respectively, expressed by viruses and bacteria.

TLRs activate a range of important signalling pathways and transcription factors, where their PAMPs activate MAPKs (ERK-1/2, p38 MAPK and JNK), which enhance gene expression and, in the case of p38, mRNA stability via AU-rich repeats present in the 3'UTRs. Activation of MAPK-dependent transcription factors along with other transcription factors are responsible

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for a wide repertoire of gene expression and immune functionality. Indeed, activation of TLR4 by LPS has been observed to activate ERK-1/2, JNK and p38 MAPKs as well as NFκB and IRF3; these signalling pathways give rise to a multitude of immune mediators which include TNFα, IL-1β, IL-6, IL-8, IL-12, iNOS, IL-10, MHC II. Macrophage activation can thus exhibit a wide range of functions, which include pro-inflammatory, anti-microbial responses, anti-inflammatory/regulatory responses and priming of adaptive immune responses through their capacity to process and present antigen.

Taking into consideration the previous sections, LPS and other PAMPs may be able to induce a wide variety of immune mediators; the expression of which will also be determined by other activatory stimuli, differentiation factors and both exogenous and endogenous suppressive molecules. TLR signals can be negatively regulated by a multitude of molecules (reviewed in [48]) which include; Myd88s, IRAK-M, IRF-4 [49,50], TREM-2, ST2 [51], Tollip, TRIAD3A, SOCS-1, SOCS-3, SHP1, SHP2, SIGIRR [52]. In addition to endogenous suppressors of TLR activation signals, it is becoming evident that TLRs can cross-regulate each other, resulting in suppression of distinct TLR signalling pathway or endotoxin tolerisation of Mϕs through homo-or hetero-tolerisation of distinct TLRs and their ensuing effector functionality (reviewed in [53]). Such mechanisms of tolerisation have been demonstrated to be differentially utilised, dependent on Mϕ subset as well as activation signal [54]. Such complex, inter-twined signalling pathways enable a level of innate "specificity" of anti-microbial activation response as well as a way in which these activatory signals are fine-tuned, suppressed or modulated.

NOD-like receptors (NLRs); due to their intracellular expression, originally thought to specifically respond to intracellular pathogens and their PAMPs, it has become apparent that NLRs are integral to the innate detection of both extracellular and intracellular-resident pathogens. The superfamily of NLRs consists of NOD1 and NOD2 which are intracellular receptors for peptidoglycan (D-γ-glutamyl-meso-DAP and muramyl dipeptide, respectively) [55]. NOD1 and NOD2 activate NFκB through the recruitment and activation of RIP2 and resulting activation of the IκB kinase complex [56]. As a result, NOD-signalling can induce pro-inflammatory, anti-microbial defences via the expression of a wide array of NF-κB-dependent gene products (reviewed in [57]).

In addition to the NFκB-activating NODs, the NLR family is also made up of a collection of receptors involved in the activation of caspases [58], specifically caspases 1 and 5 that are integral for the inflammasome construction, activation and processing of the pro-cytokines pro-IL-1β and pro-IL-18 into the mature and secretable IL-1β and IL-18. The inflammasome is activated by extracellular ATP and hypotonic stress, both representative of endogenous danger signals or DAMPs. ASC is an adaptor protein which recruits caspase-1 into an inflammasome activation complex; knock-out mice have demonstrated ASC to be essential for LPS-induced activation of caspase-1, where these mice failed to activate pro-caspase-1 or produce IL-1β and IL-18, even in the event of stimulation by both LPS and ATP (activation of the $P2X_7$ receptor) [59]. This requirement for inflammasome-mediated caspase-1 activation, hence IL-1β maturation and secretion, in response to LPS (a TLR4 ligand), emphasises a collaborative role for TLR and NLR pathways in the production of IL-1β and the ensuing inflammatory response. Other NLR family members, NALP1, NALP3 and Ipaf, have all been demonstrated to be

associated with ASC in the inflammasome, playing an integral role in caspase-1-dependent activation of pro-inflammatory cytokines [60]. NLRs have also been reported to suppress both NFκB and caspase activation pathways. With respect to inhibition of NFκB, NALP10 and NALP12 display a suppressive activity, whereas NALP7 and NALP10 are suppressive for caspase activation (reviewed in [61]). Again, it is imperative to the direction of Mϕ functional responses that the expression profile of NLRs be characterised, along with potential cross-communicating PRRs; this total profile gives scientists an insight of potential control of Mϕ functionality as being activatory, suppressive or even being able to deviate/modify the cellular response.

RIG-like receptors (RLRs): are key intracellular innate immune sensors of viral infection. Whereas the predominant viral PRRs in DCs (particularly pDCs) are TLR3, TLR7, TLR8 and TLR9, RLR viral sensing and expression is predominant in Mϕs [62]. Currently, the main RLRs are retinoic acid inducible gene-1 (RIG-1) and melanoma differentiation-associated gene (MDA)5; both of which detect dsRNA [63,64]. Similar to the viral-sensing TLRs, RLRs activate NFκB and IRF3 signalling pathways, resulting in gene expression of pro-inflammatory cytokine genes and anti-viral type I interferons (IFNα and IFNβ). Upon viral infection, these interferons exhibit a positive feedback loop which up-regulates RLR expression. MDA5 has been demonstrated to be important in the detection of picornovirus and polyinosine polycytidylic acid, poly(I:C)-induced IFNα production. On the other hand, the importance of RLRs to macrophage anti-viral responses is enforced by observations that RNA helicases eg. Lgp2, inhibits RIG1 signalling [65] and that an evasion mechanism utilised by hepatitis C virus is the production of RLR signalling inhibitory proteins [66,67]. This overlap in structure/functional relationships between TLRs and RLRs is suggestive that these receptor types function in tandem to provide ubiquitous anti-viral protection. Additionally, it is unclear as to whether RLRs also interact and mediate inflammasome activity, as a study by Johnston et al in 2005, has shown that a pox virus pyrin domain protein interacts with ASC-1 (NLR family member) and inhibits inflammatory and apoptotic inflammasome activity [68]. This viral escape mechanism, targeting NLR-mediated inflammasome activity, is also suggestive that RLRs cross-communicate with NLRs; thus efficient anti-viral protection is truly a trinity of innate reception between TLRs, NLRs and RLRs (reviewed in [61]).

Scavenger receptors (SRs) and C-type Lectin receptors (CLRs): this is a large group of receptors widely expressed on macrophage cells [69] which scavenge pathogenic material and cellular debris, initiating clearing responses through receptor-mediated endocytosis, phagocytosis or signals inflammatory responses. Responses elicited are dependent on patterns being recognised and combinations of PRRs being employed. The CLRs, being lectin receptors are generally sugar receptors, whereas SRs recognise and respond to a wider range of molecular patterns; however, there is a level of overlap, hence confusion between receptors of these families. Scavenger receptors are a broad family of PRRs, which involve both opsonin-mediated phagocytosis and opsonin-independent PRRs; the latter even including TLRs, lectins, complement receptors (CRs), CD14, CD36, scavengers of ACAMPs (see later section). Scavenger receptors include the SR-A class of receptors (SR-AI, SR-AII, MARCO), SR-B (CD36, SR-BI and Croquemort, CD163 – haemoglobin scavenger receptor), SR-C class (dSR-CI) and

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SR-E (LOX-1) as well as other SR-A-like class members (SR-CLI – a potential CLR on the basis of C-type lectin domain expression), SR-D (macrosialin). In general, these scavenger receptors recognise a wide range of PAMPs including LTA, LPS, bacterial DNA, whole bacteria, sugar moieties and DAMPs, thus clearance of dead and dying host tissue, as well as pathogenic material (reviewed in [70]). The majority of the signalling scavenger receptors (Dectin-1, Dectin-2, Mϕ Mannose Receptor) are CLRs and will be covered in the next section.

CLRs play a major role in recognition and activation of anti-microbial immunity against a diverse range of pathogens, which include fungi, bacteria, viruses and parasites. They are receptors which contain one or more carbohydrate recognition domains (CRDs) which bind a wide variety of carbohydrate ligand moieties. Generally, CLRs can be categorised as either having a built-in endogenous signalling activity or requiring interaction with a partner adaptor protein which possesses signalling activity (reviewed in [71]). CLRs signal via integral ITAMs or partner ITAM-bearing adaptors such as FcγRs. Integral ITAM-bearing CLRs generally signal through a syk/CARD9 pathway which ultimately results in NFκB activation; such signalling CLRs include Dectin-1, Dectin-2 and Mincle. These CLRs are particularly prominent in mounting anti-fungal responses; Dectin-1 responds to β-glucans expressed in the fungal cell wall by initiating a variety of cellular responses which include phagocytosis, respiratory burst, activation of inflammasomes, cytokine production and the polarisation of adaptive responses to cell mediated immunity mediated by Th_1 and Th_{17} cells. In addition, Dectin-1 exhibits cross-talk with TLR2 and other myd88-dependent TLRs, thus again, co-operation of PRRs is critical for tailoring appropriate immune responses (reviewed in [72]). Dectin-2 and Mincle both recognise fungal α-mannans with Dectin-2 being associated with innate recognition and induction of Th_{17} responses. Of particular importance to the recognition and signal activation in response to fungal infection is the observation that Dectin-2 (signalling) can heterodimerise with Dectin-3, thus CLRs demonstrate a level of co-operativity with each other and fine-tuning of their responses to the fungal pathogen [71].

Bacterial sensing utilises Mincle, mannose receptor (MR) and DC-SIGN. MR has been shown to be involved in the recognition and responsiveness to *Klebsiella* and *Streptococcus* sp but so far, has not been recognised to contain a signalling motif. To initiate antibacterial responses, it is likely that the MR co-operates with other PRRs. Mincle however signals through the pathway detailed above, in order to activate NFκB-mediated responses required for innate and consequent cell mediated immune responses to Mycobacterial infection through recognition and binding of mycobacterial cord factor, trehalose-6,6′-dimycolate, TDM. Mycobacteria are also recognised and a response initiated through ManLam (mannosylated lipoarabinomannan) binding to DC-SIGN which is expressed by DCs; whether this CLR is expressed by Mϕs is yet to be definitively characterised [71]. DC-SIGN has also been described as being involved in viral recognition by binding to the gp120 envelope protein of HIV-1; this mechanism however may be more representative of a mode of viral transmission rather than anti-viral immunity. CLRs such as CLEC9A (DNGR-1) has been shown to be protective, by facilitating antigen cross-presentation, hence controlling infection of vaccinia virus and herpes simplex virus. Finally, both Dectin-2 and MR are involved in immunity to parasites, whereby Dectin-2 recognises Schistosoma mansonii egg antigen SEA resulting in the activation of the

NLRP3 inflammasome and alleviating Th_2 pathology. Of particular interest is the fact that Dectin-2 can also promote Th_2responsiveness, as opposed to suppressing it, when responding to the common allergen of house dust mite [71]. MR drives protective Th_2 responses during S.mansonii infection whereas enhances uptake of infectious circariae. These last few observations with respect to Dectin-2 and MR and their ability to drive Th_2 responses would appear to conform to the previously observed study of Mills et al, whereby M2 macrophages were associated with Th_2 immunity [5]; indeed, MR at least, has been assigned as an M2 marker. On the flip-side, Dectin-1 has been associated with initiation of Th_1 and Th_{17} anti-fungal responses; it would appear that any potential activation and modulation of specific immune responses would have to consider the role of pathogen associated carbohydrate expression and their respective CLRs expressed on host macrophages.

Siglecs: sialic acid-binding Ig-like lectins are members of the immunoglobulin superfamily involved in the recognition and reception of sialylated glycoconjugates, involved in endocytosis, positive and negative activation signals. Sialic acids are a family of nine-carbon sugars which are derivatives of neuraminic acid or keto deoxynonulosonic acid and appearing in different glycosidic linkages, typically at the exposed, non-reducing ends of oligosaccharide chains attached to proteins and lipids. It is thought that sialic acid residues either, mask subterminal sugars, prevent non-specific cell-cell interactions or act as ligands for modulating selective cell-cell interactions [73]. Currently, there are 13 Siglec family members expressed in humans and classified into two distinct subsets; siglecs 1 (CD169), 2 (CD22) and 4 are activatory receptors whereas siglecs 3 (CD33) and 5 (CD170) to 11, 14 and 16 (CD33-related siglecs) exhibit suppressive activity through two conserved ITIMs (immunereceptor tyrosine-based inhibition motif) in the cytoplasmic domain which are responsible for the recruitment of the signal suppressive phosphatase enzymes SHIP (lipid phosphatise), SHP-1 and SHP-2 (protein tyrosine phosphatises), which result in raised activation thresholds and antagonism of ITAM-dependent activation. More recently, tyrosine phosphorylation of CD33 and siglec-7 can recruit SOCS3 which leads to ubiquitination and proteosomal degredation of the Siglec; regulation of the negative regulator! [74,75]. Thus, expression and activation of distinct expression profiles of siglecs can either positively or negatively regulate immune and inflammatory responses. Monocytic cells have been shown to express Siglec-3 (CD33) and Siglecs-5,-7,-9 and-10, whereas generally, Mϕs express sialoadhesin (Siglec-1) and Siglecs-3 and-5 (reviewed in [76]), yet differentiation of monocytes to pro-and anti-inflammatory Mϕs using GM-CSF and M-CSF, respectively, showed retention of the monocyte Siglec phenotype [77]. This wide array of CD33-related siglec expression on monocytes and macrophages is suggestive of a degree of functional redundancy exists between these siglecs however, the specific expression profiles between cell types is indicative of specificity of function. More recently, research has uncovered more functional information regarding CD33-related siglecs; they may not just exert inhibitory responses through suppression of ITAM-dependent signals, as over-expression of siglec-9 in Mϕs both inhibits the TLR-induced expression of the pro-inflammatory cytokine, TNFα, but also induced the anti-inflammatory cytokine, IL-10 [78]. Again, as with other Mϕ receptors, the importance of a balance between positive and negative signals within the immune system is paramount.

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FcγRs: are a family of receptors which bind the Fc region of IgG/IgG immune complexes and are responsible for mediating both activatory and suppressive responses by transducing their ligand-binding signal through either an endogenous cytoplasmic ITAM or ITIM motif, respectively. Three classes of FcγRs are expressed on immune cells such as Mϕs, these include the high affinity FcγRI (CD64) which binds monomeric IgG and the low affinity receptors FcγRII (CD32) and FcγRIII (CD16) that bind IgG immune complexes. Activatory receptors which possess cytoplasmic ITAM sequences include FcγRIIIa, FcγRI and FcγRIIa whereas the CD32 subtype, FcγRIIb is suppressive, containing a cytoplasmic ITIM sequence (reviewed in [79]). Thus recognition and clearance of IgG immune complexes may induce either an activatory or inhibitory signal which is dependent on expression profile of these FcRs and potential cross-talk with other PRRs. Ligation of FcγRIIIa induces the expression and secretion of Mϕ-derived TNFα, the mechanism of production and activation of which has been found to be associated with pathological inflammation [80]. Ligation of FcγRI however, was found to reverse Mϕ pro-inflammatory responses [81]. Indeed, taking into consideration the format of presentation of IgG, the immune response cell and their FcγR expression profile, Mϕs can be activated or inhibited with respect to inflammatory responses; differential FcγR-driven induction and suppression in collagen-induced arthritis model have resulted in this being considered as a realistic therapeutic regimen in the treatment of RA [82]. The final thing to consider with respect to FcγR-induced responses in Mϕs is the fact that these responses may differ between M1 and M2 subsets and that these responses may be deviated by manipulation of FcγR signalling or indeed exhibit suppression of inflammatory responses or manipulation of functional plasticity. Manipulation of these Mϕ receptors would represent a realistic option when considering their association with alternative activation, M2-like anti-inflammatory Mϕs.

Other macrophage suppressive receptors: Two further immunosuppressive molecules that control Mϕ functionality which are worthy of consideration are CD200R and SIRPα (CD172a); both members of the immunoglobulin superfamily (IgSF). CD172a interacts with a broadly expressed ligand, CD47, which results in the suppression of Mϕs through interaction with the tyrosine phosphatases, SHP1 and SHP2 [83] and reviewed in [84]). In addition, this interaction is made more complex by the observation of bi-directionality of signalling, where CD47 ligation has been found to selectively suppress monocyte IL-12 production, whereas TNFα, IL-1 and IL-6 was not suppressed. In contrast, the immunosuppressive cytokines, TGFβ and IL-10, were not altered by CD47 ligation; suppression of IL-12 was independent of TGFβ and IL-10 [85]. Thus, molecules such as CD172a and CD47 represent an attractive target couple for multi-mechanistic immune suppression. CD200R ligation, on the other hand, transduces a simpler immunological signal. CD200 (OX-2) is a cell surface glycoprotein containing Ig-like domains that interacts with CD200R expressed on Mϕs [86]. The human homologue of CD200R was characterised by Wright and colleagues who found that its cytoplasmic domain contained known signalling motifs [87]. The role of CD200R ligation was appreciated to be potentially suppressive where CD200-deficient mice were shown to display increased susceptibility to autoimmune disease models affecting joints. In accordance with this study, CD200Fc fusion protein was found to exhibit beneficial immunomodulation of arthritis and allograft rejection [88,89]. Indeed,

the CD200Fc anti-arthritic response targeted pro-inflammatory cytokines in murine CIA, suppressing mRNA gene expression of TNFα, IL-1β, MMP13 but also IL-10 [90]. It is probable that CD200R represents a family of closely-related receptors; four homologues exist in the mouse, two of which, however, may exhibit activatory properties rather than suppressive, as they have been shown to pair with an ITAM-containing adaptor protein DAP12 [87]. Considering these early observations, it is likely that such IgSF members represent realistic therapeutic targets for immune suppression, activation and deviation of Mϕ-mediated pathological mechanisms associated with cancer, transplantation and inflammation.

Cytokine expression and responsiveness: Dysregulation and aberrant functionality of Mϕs is widely associated with pathology. Macrophages are central to phagocytosis and the modulation of inflammatory responses, through the induction and regulation of cytokine expression. Mϕs not only phagocytose pathogens and particulate material, they are important for the clearance of dead and dying host cells, utilising a wealth of scavenger receptors such as SRA, CD36, CD68, integrins, CD14, complement components and the phosphatidyl serine receptor (reviewed in [91]). Clearance of necrotic host cell material is generally associated with the induction of inflammatory responses, where necrotic cells are recognised by Mϕs and result in the production of TNFα and the driving of Th_1-mediated immune responses. In contrast, Mϕs recognise apoptotic cells [92], resulting in an anti-inflammatory environment, characterised by the production of TGFβ, PGE2 [93] and IL-10 [94]. In fact, the defective clearance of apoptotic cells has been linked with autoimmunity [95]. Recognition of apoptotic cells is thus important in immunoregulation modulated by Mϕs. Mϕs recognise and distinguish between apoptotic and necrotic cells via danger-associated molecular patterns (DAMPs) and apoptotic cell-associated molecular patterns (ACAMPs). This dichotomy in responsiveness is reflective of Mϕ subset functionality; indeed M2-like, alternatively activated Mϕs express a wide array of receptors for ACAMPs; it is likely that recognition of apoptotic cells will activate and programme M2 cells towards an anti-inflammatory and regulatory phenotype, whereas DAMPs and necrotic cells drive an immune activatory, pro-inflammatory response (reviewed in [96]).

Cytokines are not only induced by phagocytic recognition and clearance of dead and dying cells. They are produced by Mϕs and a wide variety of other immune cells as part of immune activatory or regulatory responses. As such, Mϕs are modulated by a variety of cytokines; the predominant Mϕ-modulatory cytokines include TGFβ, IL-10, IL-12, IL-4/IL-13, IFNγ and TNFα. IL-4/IL-13 and TGFβ/IL-10 have been described above to be associated with priming M2 Mϕ subset polarisation (M2a and M2c, respectively); whereas IL-12 and IFNγ play an important role in the polarisation and functionality of M1 cells and concomitantly, suppressing development and activation/functionality of M2s. The relative expression of these cytokines is thus imperative to subset functionality and cross-regulation.

TGFβ and IL-10 modulate Mϕ polarisation and functional plasticity to that of an M2c subset which exhibits a characteristic cytokine phenotype of IL-10^{hi}, IL-12^{lo}, IL-23^{lo} and TGFβ^{+}which is associated with anti-inflammatory responses, scavenging, immunoregulation, tissue repair and tumour promotion. Both TGFβ and IL-10 directly suppress immune activation via the

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down-regulation of the expression of MHC II, B7 costimulation (suppressing APC function) and pro-inflammatory cytokine production, with an indirect effect through cross-regulation of M1-derived cytokines and functionality. In contrast to this TGFβ-mediated suppression of Mϕ-driven functionality, pro-inflammatory cytokines such as TNFα modulate M1-driven responses, favouring anti-microbial killing, CMI and tissue-destructive pro-inflammatory responses. TNFα activates Mϕs following IFNγ priming, which results in a strong activation of NFκB and enhanced cell migration to inflammatory sites and consequent iNOS-mediated anti-microbial killing [97]. It also primes a sustained inflammatory response [98] and Mϕ survival, important to inflammation and to the pathology of sepsis [99]. TNFα and other pro-inflammatory cytokines such as IL-1β, not only play a pivotal role in the initiation and maintenance of the inflammatory response, but also modulate immunosuppressive mechanisms through the process of Mϕ endotoxin tolerance. Thus, the state of Mϕ activation, polarisation of subset functionality and the relative contribution of activatory, suppressive and immune-deviation signals associated with Mϕs, is of paramount importance in determining an appropriate immune response or pathological response as a consequence on Mϕ immune dysfunction (refer to figure 2 below). Finally, one last consideration regarding Mϕ functional responses to cytokines is that responsiveness has been demonstrated to be dysregulated, especially, with regards anti-inflammatory IL-10 signal transduction by IL-10 receptors in a chronic inflammatory environment [100]. Consideration of cytokine responsiveness of Mϕs can only be realistically appreciated when considering the local environment; homeostatic or pathogenic!

Macrophage functionality and inflammatory pathology: Mϕs are particularly abundant in mucosal tissues such as the oral cavity and the gastro-intestinal tract. Dysregulation of Mϕ functionality in such mucosal tissue has been shown to have grave impacts on mucosal function and to result in Mϕ-driven pathology. This section will focus on Mϕ dysregulation and impact on host tissue in the context of M1-and M2-driven responses associated with oral (chronic periodontitis and oral squamous cell carcinoma) and the GIT (Crohn's disease, ulcerative colitis and colorectal cancer) mucosal pathology. These pathologies display pathological mechanisms aligned to M1-or M2-like functional phenotypes; to fully appreciate these dysregulated responses, it is imperative to appreciate the functional phenotype of healthy, homeostatic mucosal macrophages. From studies focussing on the characterisation of gut mucosal Mϕs, in general mucosal Mϕs exhibit a functional phenotype similar to M2 Mϕs. Intestinal Mϕs express phagocytic scavenger receptors (CD33, CD36, CD68), HLA-DR, immunoregulatory receptors (CD200R and TGFβRI/RII) and immunoregulatory cytokines (IL-10, TGFβ) whereas fail to express the co-stimulatory molecules (CD40, CD80, CD86), pattern recognition receptors (CD14, TLRs), TREM-1, FcRs, CRs and the pro-inflammatory cytokines (TNFα, IL-1β, IL-6, IL-18). On the other hand, in general, inflammatory Mϕs express a wide variety of functional markers which include: PRRs (CD14, TLR2, TLR4, TLR5), FcRs (CD16, CD32, CD64, CD89), CRs, HLA-DR, co-stimulatory molecules, chemokine receptors (CCR5, CXCR4) and pro-inflammatory cytokines/markers (TREM-1, TNFα, IL-1β, IL-6, IL-18, CCL20) [28,101-103].

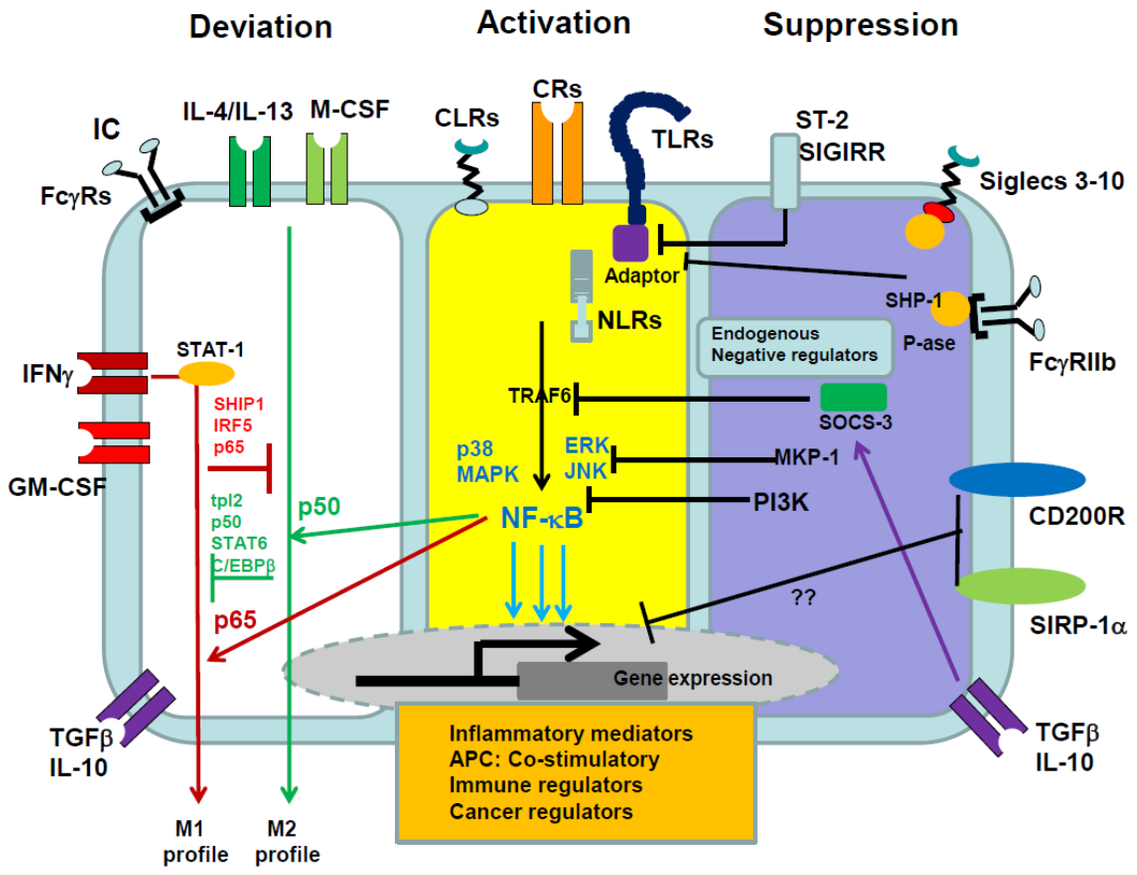

Figure 2. Macrophage effector functionality is determined by a variety of activation, suppression and deviation. Mϕ effector responses can be positively initiated by a range of receptors (yellow box) which include CLRs, TLRs, NLRs and complement receptors (CRs) which induce a range of activatory signalling pathways (p38, ERK and JNK mitogen activated protein kinases, MAPKs, and NFκB), resulting in specific gene expression. These positive signals can be suppressed (purple box) by a range of exogenous (SIGIRR, ST2, Siglecs, FcγRIIb, CD200R, SIRP-1α, TGFβR, IL-10R) and endogenous signals (SOCS3, MKP-1, PI3K, ITIM-associated SHP-1, SHP-2, SHIP-1). Finally, Mϕ functionality can deviate between M1 and M2 phenotype (white box), determined by exogenous factors (IL-4, IL-13, M-CSF, IFNγ, GM-CSF, TGFβ, IL-10) and internal signalling molecules (STAT1, STAT6, p65 NFκB, p50 NFκB).

3.1. M1-driven pathology

Crohn's disease (CD) is an inflammatory bowel disease (IBD) characterised by tissue-destructive transmural inflammatory skip lesions which present along the whole length of the GI tract. CD is characterised by dysfunctional innate immune responses, which result in a Th_1/Th_{17} axis of inflammatory destruction. This granulomatous inflammation is characterised by high expression of IL-12/IL-23, resulting in the predominance of Th_1/Th_{17} cells that produce IFNγ, TNFα and IL-17 [104]. This dysregulated pro-inflammatory response is believed to be associated with mutations to PRRs and pathogen sensing ability of the innate immune system. Genetic mutations in the CARD15 gene which encodes NOD2, an intracellular sensing receptor for bacterial peptidoglycan, are associated with CD Mϕs and have been demonstrated to modulate NFκB activation and up-regulate expression of the pro-inflammatory cytokines TNFα, IL-1β and IL-12 [105], whereas NOD2 activation would normally mediate anti-

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inflammatory signals induced through TLR2 [106]. In addition, NOD2 mutation also results in impaired recruitment of monocytes to mucosal tissue and their differentiation to a homeostatic intestinal Mϕ phenotype as well as impairment of Treg activity [107]. Thus, the combination of a dysregulated innate response in favour of pro-inflammatory cytokines, aberrant anti-inflammatory mechanisms, coupled with adaptive immune system bias towards a Th_1/Th_{17} cell mediated inflammatory response, result in the breaking of mucosal immune tolerance in favour of the tissue-destructive inflammatory mechanisms observed in the pathology of Crohn's disease and its perpetuation by both pathogenic and commensal luminal contents (reviewed in [108]). This loss in regulation results in a mucosal environment that is IL-10^{low} IL-12^{high}, which induces M1-like Mϕ activation/differentiation and the up-regulation of expression of pro-inflammatory cytokines and co-stimulatory molecules [109].

The oral mucosa plays a significant role in tolerance induction; it is thought that dysregulation of mucosal Mϕ functionality contributes to the breaking of this tolerance and drives oral inflammatory pathologies such as oral lichen planus, recurrent aphthous stomatitis and chronic periodontitis [110]. Chronic periodontitis (CP) is a persistent inflammatory condition of the periodontal tissue, characterised by bouts of relapse and remission that, if left untreated, could result in destruction of periodontium and tooth loss. CP results from activation of host inflammatory response as a consequence of constant microbial challenge mounted to a dysbiotic microbial population present in the oral cavity, of which *Porphyromonas gingivalis* (PG) is a prominent member [111,112]. PG is an intracellular oral pathogen, which invades oral epithelial cells, dendritic cells and macrophages; clearance of such would require a Th_1-dependent cell mediated response [113,114]. PG-LPS subverts both host innate and adaptive responses away from clearing responses by low endotoxin activity along with preferential utilisation of TLR2 rather than TLR4 and by inducing Th_2-dependent humoral responses, respectively [115,116]. There is a dense population of Mϕs in the oral mucosa which react to PG by producing large amounts of pro-inflammatory cytokines (TNFα, IL-1α, IL-1β, IL-6, IL-8, IL-12, IL-18, IL-32, MCP-1) at the expense of anti-inflammatory cytokines (IL-10) [117]; displaying an M1 phenotype. What is a cause for concern, is that PG induces an M1-like response whereas deviates the adaptive response to one of a non-clearing Th_2-humoral response. This, coupled with the fact that PG differentially induces endotoxin tolerance in M1 and M2-like Mϕs [54], presents scientists with real problems with regards utilising Mϕs as therapeutic targets for the treatment of CP.

Less complicated is oral lichen planus (OLP); an inflammatory condition presenting as white striations or plaques in the buccal mucosa, tongue and gingiva [118]. This pathology is characterised by a dense T cell infiltrate with a corresponding destruction of basal membrane and recruited monocytes, which display an M1 cytokine expression phenotype, with high levels of GM-CSF, TNFα and IFNγ produced at the site of inflammation [118,119]. T cells associated with OLP have been described to produce IFNγ [120], as such, IFNγ can activate $CD8^+$cytotoxic T cells, NK cells and can feedback to activate M1 Mϕs and perpetuate their inflammatory effector response. These Mϕs are situated close to the basal membrane and can contribute to its inflammatory destruction, through the action of TNFα produced [121]. Therefore, M1 Mϕs drive the progression of OLP by activating a Th_1-mediated inflammatory

response and perpetuation/exacerbation of this immunopathological response through a positive feedback mechanism.

3.2. M2-driven pathology

In contrast to CD, ulcerative colitis (UC or idiopathic proctocolitis) is an IBD where its site of involvement is confined to the large bowel (colon and rectum) and characterised by ulcerations in the mucosal lining layer. Patients with UC present with abdominal pain, bleeding anaemia and dietary restriction, resulting as a consequence of inflammatory destruction of the superficial mucosal layer, which is possibly driven by dysbiosis or inappropriate recognition and responsiveness to commensal gut organisms [122]. This pathology is driven by a M2/Th_2-mediated pathogenic mechanism resulting in a predominance of Th_2-derived IL-4, IL-5 and IL-13 cytokine production. These cytokines induce B cell class switching and the production of IgE with the consequent activation of mast cells and eosonophils, which degranulate toxic components upon cross-linkage of IgE and initiation of an ADCC response. As with CD, there is an increase in monocyte recruitment to the gut mucosa, where there is a high proportion of Mϕs expressing a less mature phenotype that are $CX3CR1^+TLR2^+CD33^+$[123]. These $CX3CR1^+$Mϕs have been described to suppress the severity of DSS-induced colitis and may represent a beneficial Mϕ subset with respect to inflammatory pathology [124]. Manipulation of this Mϕ phenotype may represent a realistic approach in controlling this M2/Th_2-driven inflammation. Thus there is a real need to characterise the inflammatory Mϕ subset which is involved in driving this disease. One observation that informs the scientific community with respect to Mϕ involvement in UC is the fact that CD1d-restricted type II NKTs induce colitis in mice [125]; it is probable that $CD1d^+$cells, where CD1d expression has been reported to be restricted to Mϕs, initiate or perpetuate this inflammatory pathology in humans. In addition to expression of IL-4, IL-13 and TNFα, serum levels of IL-23 have been associated with severity of disease in UC patients [126]; whereas CD pathology involved an immune axis of M1/Th_1/Th_{17}, the link with IL-23 production is suggestive of an M2/Th_2/Th_{17} axis driving UC immunopathological inflammation. In order for successful regimens to be adopted for the treatment of UC, it is imperative that this immunopathological axis is further characterised with respect to Mϕ functional phenotype and how these Mϕs can be modulated by expression analysis of both cell-associated immune activatory and suppressive molecules.

Macrophages have been realised to play a significant role in the immunopathology associated with tumorigenesis and the progression of solid tumours. Tumour initiation and development has been linked with NFκB activation and inflammation; indeed, it is now well established that tumour associated macrophages (TAMs) exhibit a pro-tumoral, anti-inflammatory and immunoregulatory M2 phenotype. As inflammation contributes to the progression of UC, links have been suggested between UC (an M2/Th_2 pathology) and the development of colorectal cancer (CRC). Comparisons exist between UC and CRC with respect to the up-regulation of both pro-inflammatory cytokines and the immunoregulatory cytokine, IL-10 [127], thus both pro-and anti-inflammatory mechanisms contribute to cancer progression. With respect to Mϕ functionality, NFκB activation through classical or alternative activation

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pathways (p65 versus p50 NFκB) exhibit functional plasticity where TAMs display pro-inflammatory, anti-tumoral M1-like responses or, conversely, anti-inflammatory, pro-tumoral M2-like behaviour [128].

In the case of oral mucosa, M1-driven chronic inflammatory pathology such as OLP and the resulting pro-inflammatory and anti-microbial environment (ROS/RNS) can induce mutagenesis and malignant transformation of oral epithelial cells resulting in oral cancer. One such oral cancer is oral squamous cell carcinoma (OSCC), characterised by a significant leukocyte infiltration of lymphocytes and particularly monocytes, recruited by MCP-1, which become TAMs [129]. These TAMs, facilitated by priming factors, such as M-CSF and IL-10, secreted by cancer cells, develop a pro-tumoral M2 phenotype (IL-10, EGF, FGF, PDGF, VEGF)[130] resulting in advanced stages of tumour progression [131,132]. This M2-like effector phenotype of TAMs results in an immunosuppressive, anti-inflammatory and tissue reparative environment, which benefits tumour growth. In addition to suppressing pro-inflammatory cytokines, activation of anti-tumour T cell responses through APC function is suppressed as the expression of MHC molecules is down-regulated and inhibitory co-stimulatory molecules, such as B7-H4, are up-regulated [133-135]. Finally, the M2 cytokines, IL-10 and TGFβ, can induce Tregs, which further strengthen the suppression of host anti-tumour responses [136]. Thus, TAMs modulate cancer cell survival/growth whereas the environment presented by the tumour cells influences the functional plasticity of the TAMs and that, through the bi-directionality of cellular interactions, it may be possible for the TAM plasticity to be harnessed in the control of tumour cell growth and even initiate tumour resolution.

4. Conclusions and future perspectives

Macrophages offer attractive drug targets for the treatment of a wealth of Mϕ-mediated diseases of the oral and gastrointestinal mucosa. The role of Mϕs in driving inflammatory diseases such as CD, OLP, CP, UC, and cancer (CRC and OSCC) is being extensively researched. With their role in the immunopathogenic mechanisms of these diseases, Mϕs are now a realistic candidate for "re-education" of their functional responses; either by immune activation, suppression or deviation. Mϕs exhibit pathogenic responses via M1-functionality, as is the case in CD, OLP and CP, whereas M2 effector phenotype drives UC, CRC and OSCC. These pathogenic immune cells express a wealth of immunoactivatory receptors (TLRs, NLRs, RLRs, CLRs, FcRs, SRs and cytokine receptors) and, as such, can be induced to exhibit pro-inflammatory responses, anti-inflammatory responses, anti-microbial killing responses as well as antigen processing and presentation, hence priming humoral and CMI adaptive responses against extracellular and intracellular pathogens. In addition, they also express immunosuppressive molecules (exogenous and endogenous PRR inhibitors, FcγRIIb, CD200R, SIRP-1α, Siglecs, NLR splice variants, IL-10, TGFβ) and may exhibit a sensitivity to endotoxin tolerance. Finally, Mϕs also possess receptors/molecules by which immune responses may be modulated or deviated; through FcRs, IL-4/IL-13/M-CSF/IL-10 and IFNγ/GM-CSF to the benefit of the host. Future aims of manipulating Mϕ effector functionality would focus on activation of M1 Mϕs to produce anti-tumour and

pro-inflammatory cytokines, hence fostering a hostile anti-tumour innate environment as well as priming adaptive anti-tumour responses for the treatment of colorectal cancer and oral squamous cell carcinoma. In addition to immune activation of anti-tumour responses, harnessing immune receptors for immune deviation would appear to be a potentially effective approach; whereby the functional plasticity of M2-like TAMs was manipulated and re-programmed to a more anti-tumour setting by encouraging deviation of response to be M1-directed [137]. Although translatability of these approaches has proved, as yet, unsuccessful, this activation and re-programming approach has been appreciated for quite some time [138,139].

With the similarity and connectivity between cancer and inflammation, it would appear reasonable to use similar Mϕ-modulation approaches to the treatment of mucosal inflammatory pathology. With respect to CD, OLP and CP, the M1-driven pathologies, Mϕ-based immunotherapy is likely to focus on approaches that either suppresses, induce tolerance or deviate a response by encouraging a redressing of the balance between M1/M2 by immune-deviation towards an M2-driven response. Such a change towards M2 functionality can potentially be activated through M2-biassed signals through scavenger receptors or deviation via IC-FcγR, M-CSF or IL-4/IL-13 polarisation signals. More recently, this immune deviation can be encouraged by the introduction of products derived from M2-skewing extracellular pathogens such as helminth worms; the potential for medicine to travel full circle back to a more sophisticated look at old therapies! Finally, these destructive M1-driven inflammatory pathologies may warrant suppression. This can be achieved by manipulating mechanisms and molecules associated with endotoxin tolerance through chronic reception of pro-inflammatory cytokines or PAMPs through TLRs and through the induction of a range of intracellular negative regulators such as Tollip, SHP-1, SHIP1, p50 NFκB, PI3K, as well as extracellular/membrane-bound regulators (CD200R, SIRP-1α, ST-2, SIGIRR, IL-10R and TGFβR).

Through the presentation of the complex field of Mϕ biology with respect to Mϕ subsets; priming of monocytes through defined differentiation pathways, Mϕ effector phenotype and functional plasticity can be potentially manipulated in our favour for the treatment of M1-driven and M2-driven pathology. The future therapeutic regimens which focus on macrophage functionality in CD, OLP, CP, UC, CRC and OSCC can only hope to be successful from considering total Mϕ functionality with respect to immune activation, suppression and deviation.

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