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M2-like macrophages and tumor-associated macrophages: overlapping and distinguishing properties en route to a safe therapeutic potential

Ofer Guttman* and Eli C. Lewis

Ben-Gurion University of the Negev, Faculty of Health Sciences, Department of Clinical Biochemistry & Pharmacology, Israel

Abstract

Macrophages are innate leukocytes ubiquitously present in nearly all tissues, and hold critical importance for tissue homeostasis, initiation and progression of immunological responses and tissue regeneration after injury. Two of the hallmarks of macrophages are variability and plasticity. Macrophages may polarize into either pro- or anti-inflammatory phenotypes (M1-like and M2-like macrophages, respectively), and various stimuli may shift their polarization across this spectrum. Typically, M1-like macrophages are involved in the onset and progression of autoimmune disorders, while M2-like macrophages have been demonstrated to effectively ameliorate such disorders by inducing the resolution of inflammatory responses and driving cellular proliferation and tissue regeneration. Many of the properties of M2-like macrophages are also characteristic of tumor-associated macrophages (TAMs), which are monocyte-derived cells that are subverted by tumors into potent pro-tumor agents capable of dampening anti-tumor cytotoxicity and facilitating tumor proliferation, angiogenesis and metastatic spread. Use of M2-polarizing immunotherapy for treatment of autoimmune disorders is a novel concept that holds promise for resolution of such disorders. However, concerns may be raised regarding the safety of such approaches as they may create tumor-permissive conditions. Here, we review current knowledge regarding the role of macrophages in autoimmunity and tumor immunology, and discuss the potential benefits and caveats of M2-polarizing therapies.

Abbreviations: T1D: Type 1 Diabetes, T2D: Type 2 Diabetes, IBD: Inflammatory Bowel Disease, MS: Multiple Sclerosis, TAM: Tumor-Associated Macrophage, TGFβ: Tumor Growth Factor β, TNFα: Tumor Necrosis Factor α, VEGF: Vascular Endothelial Growth Factor, EGF: Epidermal Growth Factor: bFGF: Basic Fibroblast Growth Factor

Introduction

Macrophages comprise one of the central pillars of the immune system. While they represent a major component of the *innate* immune system, macrophages are uniquely poised as regulators of interaction between non-immune tissues and nearly all leukocyte compartments, both innate and adaptive [1-3]. Furthermore, tissue macrophage is intimately associated with the differentiation of numerous immune and non-immune cell populations, and may take part in nearly all forms of wound healing and tissue regeneration upon encountering appropriate conditions [4]. Such functions are primarily carried out in a paracrine fashion, by secretion of a wide variety of growth factors and cytokines, as well as nitric oxide (NO) and reactive oxygen species (ROS).

One of the most intriguing aspects of macrophage biology is their high degree of heterogeneity and plasticity. This is evident by the multitude of macrophage-secreted factors [5,6] and by the ability of the cells to attain a site- and context-specific phenotype [7]. Macrophages are a source of both pro- and anti-inflammatory factors and populations of pro- and anti-inflammatory macrophages may be found in close proximity [8]. In addition to their paracrine activities, macrophage act as professional antigen presenting cells (pAPCs); plasticity is seen in this regard as well, as various macrophage subsets may hold a distinct antigen-presenting capacity [6]. The versatility of the cells is intentional; a pro-inflammatory profile would serve to, e.g., readily decontaminate an infected tissue while promoting local injury and facilitating antigen-specific helper T cell localization. In contrast, an anti-inflammatory profile would most commonly promote tissue maintenance, wound resolution and tissue repair, a feat commonly exerted by resident tissue macrophages upon inflammatory resolution. While pro-inflammatory macrophages are often termed M1-like and anti-inflammatory macrophages are termed M2-like, polarization towards either M1 or M2 is not binary; M1 and M2 macrophages merely represent two extremes of a continuum of activation states.

The relationship between macrophages and tumor cells is intricate. Macrophages are capable of directly killing tumor cells by secretion of excessive levels of NO. Similarly, inflammatory macrophages are central in supporting cytotoxic T cell responses by presentation of tumor antigens to helper T cells and local secretion of Th1-supporting cytokines [4,6]. By encouraging helper T cells, the environment becomes well suited for cytotoxic T cells to undertake cytotoxic killing of tumor antigen-bearing tumor cells. However, one finds that tumors *do* contain macrophages, and that these tumor-associated macrophages (TAMs) are in fact *central* for tumor survival.

TAMs may dampen anti-tumor immune activity, as well as secrete

Correspondence to: Ofer Guttman, PhD, Department of Clinical Biochemistry & Pharmacology, Faculty of Health Sciences, Ben-Gurion University of the Negev, 1 Rager st., Beer-Sheva 84101, Israel, Tel/Fax: ++972-6400830, E-mail: guttmano@post.bgu.ac.il

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tumor-promoting growth factors, drive angiogenesis and facilitate metastatic spread [3,5,6,9-13]. In a way, this renders TAMs somewhat similar to M2-like macrophages [5,6,9,14]. Most notably, they share the capacity to drive tissue remodeling and curb local deleterious immune reactions. Based on these virtues, clinical use of M2-polarizing therapies holds promise in the treatment of autoimmune and autoinflammatory disorders. However, concomitantly, concerns are raised as to potential pro-tumor effects inherent to such approaches. In the present review, we highlight differences and similarities between TAMs and M2-like macrophages in an attempt to optimize emerging novel therapeutic approaches for macrophage manipulation in immune disorders and in cancer.

Origins of macrophage populations as foundation to a rich local assortment

The process of macrophage development remains a matter of debate. According to an early model, all macrophages that are present in an adult animal originate from bone marrow hematopoietic progenitor cells [15]. Such progenitor cells were previously thought to mature in an orderly manner into blood-borne monocytes, then infiltrate tissues and subsequently differentiate into mature macrophages [16]. However, recent evidence is suggestive of tissue resident macrophages originating from embryonic cells. These include yolk sac–derived macrophages in the liver, skin, spleen, brain and lungs [17-19], as well as chimeric macrophages in lungs and kidneys that display evidence for both yolk sac and hematopoietic stem cell origins [17-19]. These findings hold far-reaching implications. As will be further discussed in this review, significant differences exist in the polarization and activation of local resident macrophages and macrophages derived from tissue-infiltrating monocyte. These differences are particularly evident in pathologies associated with loss of immunological homeostasis, such as occurs in autoimmune disorders or might be an outcome of tumor evasion of the immune system.

The recruitment of monocytes towards inflamed tissues involves both immune and non-immune cell populations. Distressed tissues, including tumors, induce the secretion of monocyte-recruiting chemokines such as RANTES (CCL5), SDF-1 (CXCL12) and fractalkine (CXC3L1) [20-22]. Growth factors may also contribute to monocyte attraction to the inflammatory tissue, such as transforming growth factor β(TGFβ), vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) [22-24]. The presence of a gradient of chemoattractants is critical for the expression of integrin molecules by endothelial cells adjacent to the inflammatory site; such integrins include VCAM-1, ICAM-1, E-selectin and p-selectin [25-27]. Sufficient expression of selectins on the surface of endothelial cells will promote binding, rolling and attachment of blood-borne leukocytes to the endothelial wall [28].

M1/M2 macrophage polarization

While monocyte recruitment is a major component in tissue inflammatory responses, the manner in which infiltrating monocytes thereafter polarize may critically skew subsequent occurrences. Being a highly versatile cell type, macrophages may polarize to different inflammatory profiles according to local conditions. While the M1/M2 nomenclature is widely used, this classification system represents the two extremes of observed macrophage profiles and does not exclude the presence of intermediary polarization states.

The M1-like pro-inflammatory polarization state is the result of activation by interferonγ (IFNγ) and LPS. M1-like macrophages are characterized by their inclination to secrete Th1-inducing cytokines, such as tumor necrosis factor α (TNFα), IL-12, IL-18 and IFNα/β, possession of an advanced antigen-presenting capacity and a robust expression of inducible nitric oxide synthase (iNOS), accompanied by release of large amounts of local NO [11-13,29-31]. Indeed, M1-like macrophages are capable of directly killing tumor cells by secretion of NO [32,33], as well as by presenting tumor antigens to $CD4^+$ Th1 cells and driving the activity of cytotoxic $CD8^+$ T cells at the tumor site [34,35]. Accordingly, M1-like macrophages have been shown to inhibit tumor development and progression *in vivo* [32,36-39]. Thus, the ability of M1-like macrophages to directly kill tumor cells as well as their intimate association with anti-tumor Th1 responses, suggests that manipulation of tumor-infiltrating macrophage may comprise a unique opportunity in boosting anti-tumor immunity.

M2-like macrophages are typically involved in removal of tissue debris, tissue remodeling and repair. They may also take part in initiation of allergic reactions. This polarization state includes a wide variety of possible phenotypes. Therefore, a classification system has been established that divides M2-like macrophages into several subclasses: M2a-like polarization is induced by stimulation with IL-4 and IL-13 and is associated with Th2-type allergic immune activation [5,40]. The M2b-like profile is observed in macrophages exposed to the combination of IL-1β and immune complexes (*i.e.,* soluble antigen-binding antibodies), and is considered an immunoregulatory phenotype. Interestingly, M2b-like macrophages are characterized by simultaneous secretion of anti-inflammatory agents (predominantly IL-10) and inflammatory cytokines, such as TNFα and IL-6 [5,11]. M2c-like polarization is brought about by high concentrations of local IL-10; these macrophages secrete high levels of TGFβ, IL-10, various growth factors and interestingly, versican, an ECM proteoglycan that interacts with cells by binding to non-integrin and integrin receptors, and α1-antitrypsin, an immunomodulatory acute phase reactant that promotes wound healing [3,5,11]. These cells are considered anti-inflammatory and are often associated with the phase of inflammatory resolution, concomitant with wound healing and tissue regeneration [3,5,11].

The three subclasses of M2-like macrophages share certain properties, such as expression of IL-10, reduced expression of co-stimulatory molecules (such as CD80/86 and CD40) and limited antigen-presenting capacity [41]. However, it is apparent that they are differentiated by virtue of separate secretory profiles and by order of temporal appearance along the course of an inflammatory reaction [42]. Significantly, numerous other activation phenotypes have been described for macrophages beyond the three established M2-like polarization states; it is increasingly apparent that macrophage polarization is variable in separate tissues and in the presence of distinct conditions.

Macrophage polarization within tissues susceptible to autoimmunity

For scope consideration, we will hereby explore the role of macrophages in autoimmune settings by collecting evidence from three autoimmune and autoinflammatory pathologies: type 1 diabetes (T1D), inflammatory bowel disease (IBD) and multiple sclerosis (MS).

Macrophages are dangerous but essential inhabitants of the endocrine pancreatic islet

While insulin-secreting β cells comprise the majority of pancreatic

islet cells, regulation of islet development, function and physiological glucose homeostasis is primarily steered by non-β cells [43], including intra-islet resident macrophages. For example, an agitated macrophage might spread inflammatory signals in its immediate vicinity, effectively shutting down insulin release and promoting local insulin resistance, as exercised by, e.g., TNFα [44]. Intra-islet macrophages have been depicted throughout embryonic development and adult life [45]. In a study that examined mice with a mutation in the gene for granulocyte-macrophage colony stimulating factor (GM-CSF) (op/op mice [46]) whereby the animals lack macrophages in pancreatic islets and most other peripheral tissues, animals display a significantly diminished β cell mass [46]. Consistent with such an unexpected role for resident islet macrophages, Calderon *et al.* have established that steady state islet macrophages display M1-like pro-inflammatory polarization properties [44]. Interestingly, when macrophage depletion was followed by introduction of naïve bone marrow cells, donor-derived islet-infiltrating monocytes rapidly acquired this very same inflammatory polarization [44]. Both these studies depict a critical role for islet resident macrophages during steady state conditions.

Dysregulation of intra-islet immune cell compartments and the emergence of chronic inflammatory conditions within the islets are common characteristics of both T1D and T2D. Nonetheless, significant immunological differences separate the two syndromes: autoimmune T1D is categorically associated with the mounting of serum autoantibodies specific to β cell antigens [47] and with autoreactive $CD8^+$ cytotoxic T cell responses directed against β cells [48,49], two entities that are not included in the clinical definition of T2D. However, macrophages appear to be a critical component of both syndromes: M1-like polarization is intimately associated with promotion of peripheral insulin resistance, islet inflammation and loss of β cell mass [50,51]. Accordingly, adoptive transfer of M2-like macrophages was found to prevent the onset of autoimmune diabetes in the NOD mouse model [52]. Similarly, in models of T2D, ablation [53] and depletion [54,55] of macrophages reduced β cell loss and induced improved glucose reactivity.

The role of islet resident macrophages extends beyond the immunological context, as macrophages have been found to be indispensable for β cell proliferation elicited by the β cell–toxic agent, STZ, *in vivo* [56-58]. In a seminal study, the sustained *induction* of inflammatory conditions in the pancreas by partial bile duct ligation (pBDL) was shown to promote M2-like polarization of local macrophages and to facilitate macrophage-dependent β cell proliferation through secretion of TGFβ and epidermal growth factor (EGF) [56]. This study effectively demonstrates that while depletion of M1-like pro-inflammatory macrophages may assist in reduction of short-term damage and loss of β cell mass, it might not be an ideal approach to deplete islets from macrophages altogether; properly activated M2-like macrophages seem to be effective drivers of β cell proliferation upon local injury, and may thus *restore* functional pancreatic islets to the diabetic patients.

Gastrointestinal tract macrophages are posted at a chronically hostile border

The gastrointestinal (GI) tract has a steady-state population of resident macrophages that may be divided into discrete populations of pro-inflammatory and anti-inflammatory (regulatory) macrophages [59]. The heterogeneity of GI tract macrophage populations is thought to provide a 'safety valve', ensuring that the *status quo* of a healthy tissue is maintained while an uninterrupted capacity to mount anti-bacterial activities is present on call [59]. It is perhaps for this reason that intestinal macrophages constitutively express the immunoregulatory cytokine, IL-10 [60,61], and do *not* readily respond to bacterial stimuli with pro-inflammatory cytokine production [62]. This form of immune tolerance may, however, shift rapidly during acute GI tract infection or mucosal degradation, during which an intense infiltrate of inflammatory macrophages is observed, along with significantly increased secretion of inflammatory cytokines, as well as NO and ROS [63-66]. It remains unclear whether the rapid appearance of inflammatory macrophages during acute GI tract infection is brought about by infiltration of inflammatory monocytes from the circulation, or rather by polarization of pre-existing resident macrophages.

Intended to readily eradicate invasive bacteria [62,67-69], the inflamed GI tract also plays a key role in the onset and progression of various forms of IBD. IBD is characterized by the presence of chronic inflammatory conditions in the GI tract, which lead to degeneration of mucosal barriers and the replacement of functional intestinal tissue with non-functional fibrous tissue. Innate leukocytes, and in particular macrophages, are thought to hold a central role in this pathology [70-72]. Treatment of severe combined immunodeficient (SCID) mice with dextran sodium sulfate (DSS) results in the onset of colitis [73], demonstrating the central role of innate leukocytes rather than adaptive leukocytes in IBD. Furthermore, while IL-10 KO animals develop colitis without the need for an exogenous trigger, such as DSS, depletion of phagosomes effectively ameliorates colitis [74], as does blockade of monocyte recruitment in a colitis model [75].

While these studies effectively demonstrate the importance of M1-like pro-inflammatory macrophages for disease onset, it is important to note that M2-like macrophages have been shown to exercise *protective* properties in colitis models [76-78]. Studies employing adoptive transfer of M2-like polarized macrophages [79,80], as well as M2-polarizing agents [81,82] or agents that inhibit M1-polarization [83] have revealed a capacity of M2-like macrophages to diminish IBD severity and to promote intestinal wound healing [84].

Macrophages poised between injury and recovery in the central nervous system

MS is thoroughly different from IBD. It involves sterile inflammation and is not characterized by the formation of fibrotic tissue, and furthermore involves the prototypical loss of myelin and degradation of axon functions in the central nervous system (CNS) [85]. While MS was long thought to be induced by the activity of autoreactive T cells, increasing appreciation is being afforded to the intricate role of macrophages in this pathology.

Unlike in the case of pancreatic islets or the GI tract, the CNS does not have a population of resident macrophages [86,87]. Rather, CNS-associated inflammation induces the recruitment of circulating monocytes which then differentiate into macrophages and act to remove cellular debris and to secrete cytokines and growth factors. The high degree of variability in macrophage functions in MS is well documented. Studies have demonstrated disease-facilitation by pro-inflammatory M1-like macrophages [88,89], and amelioration of symptoms by depletion of macrophages [90]. However, evidence also points to a clear tissue-regenerative role for macrophages present in the CNS [91]. Studies employing macrophage transplantation to a neuronal lesion site [86,92] demonstrated superior recovery from neuronal damage, while mice that lack the CCR2 chemokine receptor, involved in monocyte recruitment to neuronal injury sites, displayed

accelerated loss of neuronal functions in a model of Alzheimer's disease [93,94].

Experimental autoimmune encephalomyelitis (EAE) is a commonly-used animal model of MS, which is characterized by inflammation-induced neuronal degeneration of a relapsing-remitting nature [85]. A pathological M1/M2 ratio in favor of M1-like macrophages has been shown to promote relapsing EAE while adoptive transfer of M2-like macrophages was shown to support remission and neuronal recovery [95].

Macrophage polarization in tumors

Tumors benefit from promoting TAM polarization

Inflammation has long been considered a prerequisite for tumor development, and monocyte-derived cells (including macrophages) predominate as the major leukocyte subtype found within the majority of tumors [9,11,96]. Yet the plasticity of macrophages allows them to readily polarize to either pro- or anti-inflammatory profiles. Thus, it is intriguing to find that the inflammatory axis in established tumors is typically accompanied by macrophages that display M2-like characteristics, such as poor antigen-presenting capabilities, as well as abundant release of IL-10, TGFβ, VEGF and EGF, and low expression of IL-12 and IFNα/β [6,9,11,30]. Much like one would find in resident macrophages scattered within steady-state tissues. Yet unlike tissue-resident macrophages, TAMs are thought to originate in inflammatory monocytes that infiltrate tumor sites and subsequently undergo maturation to macrophages [97-99].

The precise factors that govern TAM differentiation have yet to be fully elucidated, as each tumor is characterized by unique physical conditions and cytokine milieu. However, certain common features may be suggested. Hypoxic conditions are a nearly universal feature of primary tumors, and hypoxia-induced stabilization of hypoxia-inducible factor 1α (HIF1α) and HIF2α in macrophages leads to expression of genes associated with M2-like polarization [100]. Indeed, HIF1α and HIF2α are commonly present in TAMs within various types of tumors. Interestingly, tumor cell–derived lactic acid was found to mediate HIF1α-associated VEGF expression and the subsequent polarization of TAMs towards the M2-like phenotype [101]. Cytokines derived from both tumor cells and local non-monocyte immune compartments are also central in macrophage differentiation. IL-10 and TGFβ released from tumor cells and regulatory T cells (Tregs) are powerful drivers of TAM polarization [5,9], as is colony stimulating factor-1 (CSF-1) [30,35]. Blockade of the CSF-1 receptor attenuates tumor growth and enhances $CD8^+$ T cell infiltration [102,103]. It appears that tumors utilize diverse mechanisms to dampen Th1-type cytotoxic responses, in part by diverting T cells towards a Th2-type response; Th2 cells secrete large amounts of IL-4 and IL-13 that promote M2-like polarization of TAMs [9]. In support of this concept, studies have shown that *in vivo* treatment with IFNγ [104] or augmentation of the NF-κB pathway [105] may reverse M2-like polarization of TAMs towards M1-like characteristics.

TAMs can promote both tumor growth and tumor spread

TAMs promote a tumor-favorable environment. These unique macrophages have been shown to exert broad activities such as dampening of anti-tumor cytotoxic responses, promotion of tumor cell proliferation and facilitation of angiogenesis, as well as recruitment of naïve blood-borne monocytes to the tumor site [9,12,13,106,107]. Yet, TAMs may incorporate elements characteristic of both M1-like and M2-like macrophages.

While expression of iNOS and secretion of NO is primarily a feature of M1-like macrophages, TAMs have been shown to express iNOS, albeit at a relatively low level [108]. While NO is toxic to tumor cells at excessive concentrations, low but persistent levels of NO may *benefit* tumor development by augmenting genetic instability, thus aiding tumor cells in overwhelming the meticulous regulation of cellular proliferation [109]. Expression of iNOS by TAMs may therefore be regarded as the subversion, or 'hijacking' of a classic M1-like tool towards *pro*-tumor purposes.

Secretion of growth factors is among the most important tumor-promoting functions of TAMs. Growth factors commonly secreted by TAMs include VEGF, EGF, TGFβ and bFGF [110]. While growth factor secretion is an integral part of macrophage functions in wound healing, sustained exposure of tissues to growth factors may promote proliferation of tumor cells and tumor-associated cell populations [11,30,107]. Aside from VEGF, a TAM-derived angiogenesis factor with obvious implication on tumor progression, growth factors have been shown to induce the proliferation of epithelial cells bearing cancer-associated mutations [111]; TAM-derived TGFβ was shown to induce epithelial-to-mesenchymal transition (EMT) [112], as well as persistent activation of cancer-associated fibroblasts, which then promote tissue remodeling and drive tumor cell proliferation [113].

Metastatic spread is also affected by TAMs. A unique paracrine loop appears to form between TAMs and tumor cells in the migration process necessary for metastatic spread. Specifically, relocation of tumor cells from tissues towards blood vessels is dependent on EGF signaling and is blocked by inhibition of EGF receptor signaling [114]. The stimulation of TAMs and tumor cells with CSF-1 and EGF, respectively, induces a 'lock-step' migration process in which the two cellular populations promote migration through tissue regions rich in extracellular matrix (ECM) [115]. In parallel, paracrine co-stimulation of tumor cells and TAMs enhances ECM-remodeling capacities of both cellular types [116].

TAMs are capable of suppressing anti-tumor immune responses

TAMs have been shown to curb anti-cancer immune responses through a variety of mechanisms. These include secretion of soluble immunosuppressive agents, such as IL-10, TGFβ and IL-1 receptor antagonist (IL-1Ra) [6,12,117], as well as expression of contact-dependent immunosuppressive receptors, such as PD-L1 [118] and B7-H4 [119]. TAMs utilize such mechanisms along with secretion of specific chemokines in order to dampen cytotoxic $CD8^+$ T cell activity, as well as induce the differentiation of $CD4^+$ T cells into IL-4–producing Th2 cells and drive the recruitment and differentiation of regulatory T cells [41]. Importantly, chemokines associated with the M1-like phenotype such as CXCL9 and CXCL10, or M2-like phenotypes such as CCL17 and CCL22 display reciprocal behavior: M2-inducing signals inhibit the expression of chemokines associated with M1-like activation, and vice-versa [41].

TAMs also exert metabolic control over leukocyte activation at the tumor site. A potent suppressor of adaptive T cell responses, the tryptophan-metabolizing enzyme indolamine 2,3-dioxygenase (IDO) is regularly expressed by TAMs [120]. Similarly, nicotinamide adenine dinucleotide (NAD), another end-product of tryptophan metabolism, is a regulator of IL-6 and TNFα in monocytes [121]. Iron metabolism is a major component of immunoregulation; M1-like macrophages express high levels of Ferritin and low levels of Ferroportin and CD163, in effect sequestering iron and limiting local bacterial growth [122]. In

contrast, M2-like macrophages express high levels of Ferroportin and CD163 and low levels of Ferritin, and thereby deposit extracellular iron that drives immunoregulation, tissue re-modeling and cellular proliferation [122].

Discussion

The importance of M2-like macrophages in the regulation of immune and inflammatory responses is widely accepted, as is their potential to ameliorate a wide range of autoimmune disorders. Further necessitating an evaluation of the clinical use of M2-polarizing agents is the alarming rise in the incidence of autoimmune and autoinflammatory syndromes, such as T1D, T2D, the various forms of IBD and MS. Successful skewing of macrophages in the affected tissue from M1-like pro-inflammatory cells, known for their capacity to decontaminate tissues at the cost of widespread tissue injury, to M2-like tissue-protective cells, may not only halt the progression of autoimmune activation, but also effectively drive the regeneration of disrupted tissues. The capability of M2-like macrophages to induce the proliferation of islet β cells [56] exemplifies the advantage of M2-polarizing treatments over total macrophage depletion. However, M2-like polarization does not represent a discreet activation state; several separate M2-like polarization profiles may be induced [5]. Therefore, clinical manipulation of macrophage polarization must explicitly consider local tissue conditions. In addition, the high degree of similarity between TAMs and M2-like macrophages, particularly M2c macrophages, raises a major point of contention. M2-like macrophage potently drive cellular proliferation and angiogenesis and in many cases exercise immunoregulation over innate and adaptive leukocyte compartments [5]; these properties are also found in TAM populations. To date, no studies have examined models suitable for the elucidation of such an important question. Furthermore, the polarization of macrophages to the M2-like profile does not in itself necessarily represent a tumor-conductive factor. While the polarization of TAMs is thought to be induced by factors secreted by tumor cells, TAMs in and of themselves do not necessarily induce the de novo emergence of tumor cells. It is presently unknown whether adoptive transfer of TAMs may promote tumor development. Yet, any potential use of sustained immunotherapy for treatment of autoimmune pathologies such as T1D or MS, must therefore be preceded by detailed examination of systemic influences and, in particular, address the possible reduction in immune surveillance. Also, sustained immunosuppression correlates with severely reduced wound healing and tissue regeneration and, in the case of T1D, most clinical approaches centered on immunosuppression have proven largely ineffective [123,124].

It is currently unknown whether TAMs, as potent effectors in the progression of tumors, may ameliorate autoimmune disorders. The adoptive transfer of purified TAMs from tumor-bearing animals for the treatment of autoimmune disorders in non–tumor-bearing animals is a novel concept that may offer great insights into the subtle differences between M2-like macrophages and TAMs. Yet when one considers the negative effects of immunosuppression over the benefit of tissue regeneration, it is evident that sustained treatment of autoimmune disorders with immunosuppressive regimens might preclude long-term healing and resolution. The potential use of immunotherapeutic agents aimed at reversing macrophage polarization in affected tissues is therefore an appealing possibility, with the potential for successfully resolving inflammatory conditions, curbing autoimmune responses and driving successful tissue regeneration towards regain of function. However, further studies are required in order to fully explore the immunological and physiological implications of the novel utilization of macrophage polarization strategies.

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