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Tissue Microenvironments Define and Get Reinforced by Macrophage Phenotypes in Homeostasis or during Inflammation, Repair and Fibrosis

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Abstract
Current macrophage phenotype classifications are based on distinct in vitro culture conditions that do not adequately mirror complex tissue environments. In vivo monocyte progenitors populate all tissues for immune surveillance which supports the maintenance of homeostasis as well as regaining homeostasis after injury. Here we propose to classify macrophage phenotypes according to prototypical tissue environments, e.g. as they occur during homeostasis as well as during the different phases of (dermal) wound healing. In tissue necrosis and/or infection, damage- and/or pathogen-associated molecular patterns induce proinflammatory macrophages by Toll-like receptors or inflammasomes. Such classically activated macrophages contribute to further tissue inflammation and damage. Apoptotic cells and antiinflammatory cytokines dominate in postinflammatory tissues which induce macrophages to produce more anti-inflammatory mediators. Similarly, tumor-associated macrophages also confer immunosuppression in tumor stroma. Insufficient parenchymal healing despite abundant growth factors pushes macrophages to gain a profibrotic phenotype and promote fibrocyte recruitment which both enforce tissue scarring. Ischemic scars are largely devoid of cytokines and growth factors so that fibrolytic macrophages that predominantly secrete proteases digest the excess extracellular matrix. Together, macrophages stabilize their surrounding tissue microenvironments by adapting different phenotypes as feed-forward mechanisms to maintain tissue homeostasis or regain it following injury. Furthermore, macrophage heterogeneity in healthy or injured tissues mirrors spatial and temporal differences in microenvironments during the various stages of tissue injury and repair.

Introduction

Defined cytokine stimuli induce different and distinct macrophage phenotypes in vitro [1]. The inconsistency between in vitro macrophage studies and the heterogeneity of tissue macrophages in vivo should relate to their phenotype plasticity in complex microenvironments which are not adequately mimicked by in vitro conditions [2]. As such in vivo studies never really display clear macrophage phenotypes according to the M1/M2 paradigm

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Table 1. Resident macrophages and dendritic cells in various tissues

Organs/cell types	Dendritic cells	Macrophages
Skin	Dermal DCs, Langerhans cells [3]	Dermal macrophages [3]
Brain		Microglia [3]
Lung		Alveolar macrophages [3]
Stomach	Lamina propria DCs [59]	Intestinal macrophages [59]
Ileum	Lamina propria DCs [59]	Intestinal macrophages [59]
Colon	Lamina propria DCs [59]	Intestinal macrophages [59]
Liver	Plasmacytoid DCs, cDCs [130]	Kupffer cells [3]
Spleen	iDCs, follicular DCs [131]	Marginal zone macrophages, red pulp macrophages [3]
Pancreas	Dendritic cell precursors [132]	
Kidney	Interstitial DCs [133, 134]	
Ovary/testis		Ovarian macrophages [109]
Bone marrow		Bone marrow macrophages [135]
Bone		Osteoclasts [3]

DCs = Dendritic cells.

[1–3]. An understanding of this issue also involves the question of whether primed macrophages alter tissues or whether tissues use macrophage differentiation to meet tissue needs, a chicken-or-egg question?

Terminology including the likes of 'host defense', 'immune effector cells' or 'collateral inflammatory tissue damage' represent the underlying concept of the *stranger hypothesis* [4] which implies that the immune system is in control of tissue damage. An alternative view is that the tissues use the immune system to maintain homeostasis by modulating immune cell phenotypes as necessary, probably via changing tissue environments which have the capacity to change immune cell phenotypes along the various stages of healing or persistent injury, the *danger concept* [5, 6].

Maintaining homeostasis is the ultimate goal of tissues in multicellular organisms and means maintaining tissue morphology as well as tissue function [5, 7]. Only a few tissues, such as muscles and bones, can structurally adapt to distinct functional requirements whilst most tissues need to maintain their particular structure for full functionality, e.g. the brain, the kidney, the lung or heart. Traumatic, toxic, ischemic, metabolic, malignant or infectious injuries affect tissue structure and function. A view into less complex multicellular organisms including sponges, plants or worms teaches us that tissues have multiple ways of addressing such dangers [8, 9]. Therefore, it is tempting to speculate that the growing complexity of danger responses provided throughout the evolution of innate and adaptive immunity remains tightly controlled by the needs of tissue to maintain or regain homeostasis [6]. In this review we will summarize the various functions of the different tissue macrophage phenotypes as they are defined by changing tissue environments during the injury and repair phase of tissue damage.

Tissue Needs for Regaining and Maintaining Homeostasis after Injury

In most tissues resident macrophages or a network of interstitial dendritic cells continuously process foreign and self-antigens and present them to the T cell repertoire of the adaptive immune system (table 1) [10–12]. Under normal conditions autoantigen presentation senses tolerogenic signals for immune tolerance, i.e. a central element of tissue homeostasis [10]. Any kind of tissue injury affects tissue integrity by damaging parenchymal cells with some need for repair. Restoring tissue integrity when the injury is limited to the epithelial layer is often simple, achieved via compensatory proliferation of the surviving epithelial cells or local progenitors. For example, abrasion of the epidermis or acute renal tubular injury often heals quickly and can be mimicked experimentally with a scratch assay in monolayers of cultured epithelial cells [13, 14]. However, nonsterile environments or more complex wounding involve other re-

Table 2. The five phases of danger control

	Clotting	Inflammation	Epithelial healing	Mesenchymal healing	Fibrolysis
Time scale	Minutes	Hours to days	Days to weeks	Weeks to months	Months
Danger to control	Bleeding	Sepsis	Chronic inflammation	Tissue instability	Fibrosis
Macrophage contribution	Secretion of tissue factor promotes coagulation	Pathogen killing, secretion of proinflammatory mediators	Secretion of anti-inflammatory mediators/ growth factors	Secretion of profibrotic mediators	Protease secretion and ECM clearance
Side effects	Vascular disease	Collateral tissue damage	Epithelial hyperplasia	Fibrosis/sclerosis	Tissue instability?

sponse mechanisms to address additional dangers to the host (table 2).

The first risk to control is that of fatal blood loss. Therefore, the injured tissue vasculature initiates a number of mechanisms to assure rapid clotting. The tissue environment at this stage is characterized by ischemia and the local release of multiple vasoactive molecules and platelet aggregates which massively release proinflammatory mediators including CC-and CXC-chemokines [15]. In this way coagulation already promotes inflammation, i.e. the second danger response program. Shortly after wounding, neutrophils enter the site of injury to prevent pathogen entry or spreading. However, the antimicrobial activity includes reactive oxygen species (ROS) production and enzyme release which also contributes to tissue damage, referred to as immunopathology or collateral damage [16]. During this phase the tissue environment is dominated by pathogen-associated molecular patterns (PAMPs) from microorganisms as well as by damage-associated molecular patterns (DAMPs) from dying parenchymal cells. PAMPs and DAMPs both activate innate pattern-recognition receptors of the resident immune cells as well as the infiltrating leukocytes for their full activation and proinflammatory phenotype [17]. Platelet-derived growth factors and other as of yet poorly defined elements of the inflammatory response drive reepithelialization to restore the barrier to pathogen entry, a process that is of eminent importance to avoid persistent colitis [18]. The decreasing amount of DAMPs and PAMPs as well as the high number of apoptotic neutrophils represent a change in the tissue environment that promotes a different phenotype of tissue macrophages and the predominance of anti-inflammatory mediators as well as growth factors [16]. This environment will drive parenchymal healing and finally restoration of tissue integrity. However, if parenchymal repair is hampered, e.g. due to an insufficient capacity of local progenitors or persistent injuries, mesenchymal healing, i.e. fibrosis, will occur because the tissue environment remains dominated by growth factors that drive fibroblast proliferation and secretion of extracellular matrix (ECM) molecules [19, 20]. At this stage microenvironments differ a lot within single organs in focal regions of sufficient or insufficient parenchymal repair, e.g. in liver cirrhosis, pulmonary fibrosis or focal segmental glomerulosclerosis of the kidney. Fibrotic tissues are largely ischemic and devoid of growth factors or cytokines. However, this can activate macrophages to release matrix metalloproteinase (MMPs) that have a capacity to remove the fibrous matrix resulting in the smallest possible scar area necessary [13, 21].

Macrophages contribute to most stages of the wound healing process as outlined in table 2 [22–25]. In the following sections we discuss how the different environments during the phases of tissue injury and repair determine tissue macrophage phenotypes and claim that macrophages are mainly amplifiers of their surrounding environment.

Tissue Environments Dominated by PAMPs and/or DAMPs

During infections PAMPs ligate Toll-like receptors (TLR) on tissue parenchymal cells and local dendritic cells leading to the secretion of proinflammatory cytokines and chemokines which create inflammatory tissue environments [26, 27]. DAMPs have a similar potential to ligate TLRs, inflammasomes and other pattern-recognition receptors [17]. In fact, these receptors represent recognition platforms for infectious and sterile forms of danger that disrupt tissue homeostasis [28]. Activation

of innate immunity subsequently involves the recruitment of leukocytes including macrophages as well as IFN-γ-secreting natural killer cells. Upon arrival the infiltrating macrophages become exposed to the PAMP- and/or DAMP-rich environment. Macrophages are well equipped with pattern-recognition receptors [28, 29], hence PAMPs and DAMPs will lead to their full activation through a process similar to what has been referred to as 'classical-M1 macrophage activation' in in vitro studies [1]. Inflammatory macrophages secrete IL-1, IL-12, IL-23, tumor necrosis factor (TNF)-α and ROS, and express inducible nitric oxide synthase (iNOS), major histocompatibility complex class II ($MHCII^{hi}$), IL-1R, which mirrors what has been classified as an 'M1' macrophage by in vitro stimulation with IFN-γ, TNF-α, lipopolysaccharide or granulocyte macrophage colony-stimulating factor (GM-CSF) [1]. This bactericidal macrophage phenotype appears in early phases of tissue injury shortly after the recruitment of neutrophils to enforce local host defense against pathogens. In PAMP-rich environments proinflammatory macrophages are potentially life-saving which outweighs the associated unspecific toxicity of the secreted mediators that cause collateral tissue damage [1, 16]. By contrast, in DAMP-rich but PAMP-free sterile injuries proinflammatory macrophages account for unnecessary tissue damage [30]. M1 macrophage polarization requires IFN-related factor (IRF)5 for NF-κB signaling and subsequent secretion of proinflammatory cytokines and chemokines, ROS and other proinflammatory mediators which define the classically activated, proinflammatory (M1) macrophage phenotype [31]. Classically activated macrophages release MMPs to enable their migration through basement membranes and interstitial ECM networks. However, ECM digestion results in small ECM peptides and glycosaminoglycans which themselves can act as immunostimulatory DAMPs and fuel into the proinflammatory microenvironment [32].

As such the association of M1 macrophages with tissue inflammation is based on macrophage priming by PAMPs and DAMPs in the tissue. In turn, classically activated M1 macrophages further contribute to tissue inflammation and damage. Hence, such inflammatory macrophages amplify the tissue environment they found on arrival. This autoamplifying loop is necessary and continues until control of pathogen growth is achieved [3, 16]. In PAMP-free sterile injuries the duration of this phase depends upon the trigger and can be short lasting, e.g. after transient ischemia reperfusion or toxin exposure [33]. By contrast, inflammation persists when ischemia or toxin exposure continues. For example, fetal dermal wound healing occurs in a sterile environment. Hence, much less proinflammatory macrophages are recruited to the site of injury which, besides the high proliferative capacity of the fetal epithelium, may be a reason why fetal wounds heal faster [34]. Also, keeping wounds sterile in adults is a way to keep them PAMP-free which limits the inflammatory response and promotes wound healing [13]. This can be mimicked in mouse models of sterile wounding. In the early phase of healing macrophages are completely dispensable, the depletion of these otherwise proinflammatory primed macrophages in fact ultimately leads to reduced scar areas [35]. Consistently, in situations of prolonged inflammation, unrestrained inflammatory macrophages severely impair wound healing. For example, erythrocyte-derived iron serves as a DAMP that, in the absence of any PAMP, primes the infiltrating macrophages towards an inflammatory phenotype that has, in the absence of any infection, detrimental effects on the healing [36]. However, some studies also document that the macrophage capacity for microbial killing can be indispensable. For example, wound closure and granulation tissue formation are significantly delayed upon early macrophage depletion, which could only be compensated by a subsequent influx of macrophages [35].

DAMP-/PAMP-Rich Environments in Solid Organs

The same biological program occurs inside solid organs, even though PAMPs are mostly absent in the heart, kidney, brain and glands [37–39]. These organs suffer from DAMP-driven proinflammatory macrophage infiltrates and the associated 'collateral damage' often outweighs the needs of tissue to restore homeostasis (table 3). Thus, blocking the recruitment or the activation of proinflammatory macrophages drastically reduces tissue damage and dysfunction in such sterile injuries. For example, a classically activated proinflammatory macrophage phenotype amplifies inflammation and loss of parenchymal cells in a variety of kidney diseases such as in anti-glomerular basement membrane glomerulonephritis [40], lupus nephritis [41–46], antigen-induced immune complex glomerulonephritis [47], renal allograft injury [48], ischemia reperfusion injury [33, 49–51] and adriamycin nephropathy [52]. The impact of in vivo macrophage reprogramming on disease outcomes has been demonstrated [53]. For example, Met-RANTES and AOP-RANTES, two chemokine mutants, block macrophage recruitment but activate those tissue macrophages towards a proinflammatory phenotype which is sufficient to aggravate glomerular pathology in immune complex glomerulonephritis [47]. Vice versa, blocking the recruit-

Table 3. Macrophage phenotypes in different organs

	Heart/skeletal muscle	Liver	Kidney	Lung	Skin	Central nervous system
Proinflammatory macrophages	Inflammatory MΦs are recruited to skeletal [85] and heart [173] muscle, blocking CCL2/CCR2 axis ameliorates inflammation [174, 175]	CCR2+-MΦs [115, 163] or iron-loaded MΦs [164] promote inflammation, MΦs are PAMP sensors [165]	MΦs promote inflammation [40–44, 46, 48, 50, 52, 55, 81, 153, 154]	Blockade of CCR2 [148] or CXCR3 [149] ameliorates inflammation	MΦ depletion ameliorates inflammation[35], MΦs promote inflammation via osteopontin [145], iron overloaded MΦs promote inflammation [36]	CCR2+-MΦs promote EAE [56, 57], microglia promotes inflammation after SCI [136]
Anti-inflammatory macrophages	CXCR4+ cells reduce myocardial infarct area [79], MΦs suppress inflammation [85] and promote myogenesis [176] after muscle injury	After phagocytosis of apoptotic cells [87, 166] MΦs abrogate inflammation, MΦs limit IRI via IL-10 [88], MΦs limit inflammation in schistosomiasis [89]	MΦs promote repair [50, 67, 72–75, 80, 82, 83, 155]	?	Prolonged TNF-α signaling after MΦ depletion [78]	MΦs promote recovery after SCI [86]
Profibrotic macrophages	MΦs promote fibrosis [173, 177, 178]	Suppression of MΦ infiltration inhibits fibrogenesis [114], CCR2+ MΦs promote fibrosis [106, 167], MΦs promote fibrosis in response to gadolinium [168] or CCL4 [115]	MΦs promote fibrosis [81, 100, 103, 104, 108, 156, 157]	CCR2-KO ameliorates fibrosis [120]. MΦs promote fibrosis via TGFβ [121, 150]	MΦs promote fibrosis [35, 110–112]	CD11b+ cells promote astrogliosis [137], less astrogliosis with M-CSF deficiency [138], IL-6-KO [139], microglia blockade [140, 141] and after glucocorticoids [142]
Fibrocytes	Fibrocytes promote fibrosis [124, 178, 179]	Fibrocytes promote fibrosis [122, 169]	Fibrocytes promote fibrosis [95, 96, 99, 158, 159]	Fibrocytes promote IPF [123], and bleomycin-induced fibrosis [151]	Fibrocytes promote fibrosis in wounds [146] and after sunburn [147]	?
Fibrolytic macrophages	MΦs promote myocardial remodeling [180]	CCR2+ [167] or Arg1+ [170] MΦs reverse fibrosis [126, 171], e.g. via MMP-13 [127] or after phagocytosis of apoptotic cells [172], MΦs recruit neutrophils to degrade fibrotic tissue [128]	MΦs reverse fibrosis [160–162]	CXCL10 blocks fibroblast proliferation [129], CXCL11 attenuates bleomycin-induced fibrosis [152]	TGFβ3 promotes scarless healing [125]	MΦs reverse astrogliosis [143, 144]

MΦ = Macrophage; IRI = ischemia/reperfusion injury; SCI = spinal cord injury; IPF = idiopathic pulmonary fibrosis.

ment and activation of proinflammatory macrophages by interfering with the CC-chemokine ligand CCL2 and its chemokine receptor substantially reduces the numbers of proinflammatory macrophages in inflamed tissues, an effect that was shown to reduce immunopathology in a large number of inflammatory kidney disease models [54, 55]. These observations do not only apply to the kidney, but also to autoimmune diseases of the central nervous system [56, 57]. Infiltrating macrophages are crucial for the full phenotype of experimental autoimmune encephalitis (EAE) and impairment of macrophage recruitment by CCR2-knockout (KO) strongly attenuated the EAE phenotype [57]. Similar data are available for CCl4-induced liver injury and several other infectious and non-infectious types of inflammation in solid organs such as those listed in table 3. For example, the mucosal surfaces of the intestines resemble the PAMP-rich epithelial environment of skin, but there are also immunoprivileged sites in the gut [7, 58]. There is a complex interplay of the gut flora, enterocytes and resident immune cells in which resident macrophages remain unresponsive to PAMPs from gut flora and danger signaling is rather provided by fully responsive infiltrating macrophage precursors, as recently reviewed elsewhere [59].

Tissue Environments Dominated by Apoptotic Cells and Anti-Inflammatory Cytokines

Some pathogens cannot be easily eliminated by IFN-γ-driven innate immunity and Th1 T cell responses. For example, chronic helminth infections include repetitive life cycles of the parasite which involve ongoing damage to many different organs. During evolution Th2 responses developed to limit the growth of extracellular parasites and to provide permanent healing of persistent mucosal barrier injuries [60]. In this context downregulation of Th1 cytokines is linked to alternative macrophage activation involving Th2 cytokines like IL-4, IL-5, IL-10 and IL-13 [61, 62]. Triggering such responses is in the interest of the pathogen for sustained parasitism while they allow the host to somehow limit the consequences of persistent infection, inflammation and immunopathology [60].

We can find the same type of responses in other tissue abnormalities that lack pathogen entry or cell necrosis, like tumor environments, degenerative lesions or slowly accumulating toxins. These microenvironments are dominated by programmed forms of cell death such as apoptosis [63]. Apoptotic cell death and the clearance of apoptotic cells by macrophages are important elements of tissue homeostasis and immune tolerance, hence they are usually not associated with immune activation and can stimulate epithelial healing [63, 64]. In fact, apoptosis of activated neutrophils and T cells is a mechanism that prevents inappropriate or persistent immunopathology [64]. This becomes important also in postinflammatory phases of infections or sterile injuries. For example, transient ischemia/reperfusion is associated with cell necrosis, DAMP release followed by the influx of neutrophils and classically activated macrophages, but only for 2–3 days [33]. The microenvironment changes when the neutrophils undergo apoptosis and macrophages change their phenotype upon the excessive phagocytosis of apoptotic neutrophils which turns them into cells that release anti-inflammatory cytokines such as transforming growth factor (TGF)-β and IL-10 [65]. Serum amyloid-P, also named pentraxin-2, opsonizes apoptotic cells which further promotes the anti-inflammatory macrophage phenotype [66]. Immunosuppressive ('regulatory') T cells further promote the polarization towards anti-inflammatory macrophages via release of IL-10 and TGF-β and by suppressing the response of T effector cells [67]. An integration of these different environmental signals for the deactivation of the macrophage occurs at the level of the transcription factor IRF4 which also acts as an intracellular competitor of IRF5, and thereby blocks TLR and IL-1R signaling [68–71]. Macrophage classifications that are based on in vitro studies have not yet integrated apoptotic cells as a stimulus of differentiation but the phenotype of cultured macrophages stimulated with IL-10 and TGF-β (or glucocorticoids), referred to as the M2c type, shares similarities with anti-inflammatory macrophages (table 3) [1, 72–77]. These cells themselves produce large amounts of IL-10 illustrating that macrophages are able to amplify local environments by secreting similar cytokines in a feed-forward loop [2]. Again dermal wound healing can serve as a paradigm for such non- or post-inflammatory tissue injuries [21]. Macrophage depletion from sterile wounds delays wound healing but also leads to severe hemorrhage, apoptosis of endothelial cells and detachment of the neuroepithelium from the dermis [35]. Thus, macrophages amplify the wound microenvironment for tissue stability as well as endothelial and epithelial repair. In addition, anti-inflammatory macrophages suppress inflammation in the wound because their depletion leads to increased and prolonged TNF-α expression inside the wound [78].

Postinflammatory Environments in Solid Organs

The same anti-inflammatory responses occur inside solid organs following transient sterile inflammation [64], such as ischemia/reperfusion (table 3). In the heart, where this phenomenon occurs during myocardial infarction, macrophages have been shown to be recruited [79] and improve myocardial remodeling [79]. After renal ischemia/reperfusion injury the phenotypic switch from proinflammatory towards anti-inflammatory macrophages is driven by tubular epithelial cell-derived factors as well as by the uptake of apoptotic neutrophils [50, 80]. Lack of IRF4 enables macrophages to undergo this M1-M2 phenotype switch [69] and therefore the aggravated postischemic inflammation continues tubular cell necrosis [81]. In addition, direct IL-4/IL-10 treatment or genetically modified or transfused IL-10-stimulated macrophages help to resolve renal inflammation [72–75, 82]. Steroid-based treatments seem to suppress kidney inflammation by inducing anti-inflammatory macrophages [83, 84]. Even if initially recruited, monocytes display a proinflammatory phenotype and are rapidly primed towards anti-inflammatory capacities after injury in skeletal muscle tissue [85]. Anti-inflammatory macrophage functions are crucial for regeneration, as macrophage depletion leads to a significantly reduced diameter of the individual regenerating muscle fibers [85]. In the central nervous system, axonal regeneration after spinal cord injury is impaired upon depletion or blocking of the recruitment of macrophages [86]. In addition, their anti-inflammatory and therefore regenerative capacities were shown to be entirely IL-10-dependent. It is important to note that all these models involve sterile environments. Another example of healing during sterile organ dysfunction is toxic liver disease. CCl_4 injection induces apoptosis of hepatocytes which are subsequently phagocytosed by Kupffer cells, which resembles efficient DAMP clearance and suppresses inflammation [87]. In hepatic ischemia/reperfusion injury IL-10 expression was crucial for anti-inflammatory capacities of macrophages [88]. In a PAMP- and DAMP-driven model of schistosomiasis liver injury, macrophage-specific deletion of the IL-4Rα was accompanied by 100% mortality due to septicemia [89], which involves direct and indirect effects of IL-10 produced by alternatively activated macrophages in the gut and the liver, respectively [90]. Although this supports the importance of the anti-inflammatory capacities of macrophages, in contrast to sterile inflammation models, these properties were shown to be IL-10-independent. Taken together, these findings emphasize once more that it is the microenvironment, in this case particularly the presence or absence of PAMPs, that is influenced by infiltrating or resident macrophages.

Tissue Environments Dominated by Parenchymal Atrophy and Growth Factors

Most body compartments have an enormous capacity for rapid and complete wound healing when the damage is limited to the epithelium and local progenitor cells survive the insult, and the repair is not compromised by infection or by persistent or remitting injuries [85]. The balance of factors that promote or compromise regeneration determine whether wound healing is rapid and scarless or delayed and associated with atrophy and fibrosis. In sterile injuries to mesenchymal structures the microenvironment is dominated by growth factors to promote tissue repair and scarring [13, 21]. In fact, epithelial cells and noninflammatory macrophages are major sources of profibrotic cytokines [91]. In vitro, IL-4 and IL-13 induce STAT6 signaling to promote a macrophage phenotype that predominantly releases fibronectin and other ECM molecules and that expresses mannose and scavenger receptors, IL-1R11, FIZZ, and YM-1 [1]. These cells have been classified as M2a macrophages [1]. So far it is not clear whether anti-inflammatory and profibrotic macrophages can be clearly distinguished in vivo and it appears likely that macrophage plasticity creates a mixture or continuous variant shifts during wound healing [16]. Fibrocytes seem to represent the ultimate profibrotic macrophage that itself produces large amounts of collagen and shares phenotypic similarities with macrophages as well as fibroblasts [92–96]. The quantitative significance of this phenomenon remains under debate [97, 98]. For example, green fluorescent protein lineage tracing using the collagen 1α1 promoter found this to be a rather rare phenomenon during renal fibrogenesis upon ureteral obstruction in mice [99]. The chemokine receptor CCR1 seems to be essential for the recruitment and activation of profibrotic macrophages and fibrocytes because a lack of CCR1 or CCR1 antagonism prevents progressive tissue fibrosis in many disease states and organs [100–109]. The first reports to document macrophages contributing to dermal fibrosis date back to the mid-seventies [110]. More recently, it has been shown that CXCR3+ macrophages might be the subset responsible for scar formation/fibrosis [111]. In a mouse model of diabetic chronic leg ulcer where scar formation regularly does not occur due to impaired macrophage activation, it can be induced by ad-

ministering GM-CSF [112]. Interestingly, also in this setting in vivo conditions do not consistently match in vitro observations. According to the M1/M2 paradigm, profibrotic macrophages would be expected to be M2 polarized, whereas actually GM-CSF polarizes macrophages towards M1, and indeed fibrosis was found to be accompanied by an induction of proinflammatory cytokines within the wound [112]. As pointed out before, macrophage-mediated fibrosis (i.e. mesenchymal healing) represents a necessary step of fast and durable skin wound healing, but in sharp contrast to focal wounding of the skin or solid organs, it is detrimental in diffuse disease processes such as in progressive scleroderma or interstitial fibrosis of parenchymal tissues [97, 113].

Solid Organ Fibrosis

Progressive fibrosis and subsequent loss of solid organ function involves macrophages in multiple tissues (table 3). For example, decreased liver fibrosis was noted when macrophage infiltration was blocked by targeting the MCP-1/CCR2 axis [114, 115], as well as by deficiency in CCR1/CCR5 [106]. Some data are available for renal fibrosis [100, 103, 104, 116–119]. In the lung CCR2 deficiency attenuated bleomycin-induced fibrosis [120], a process involving subsequent IL-13 signaling through IL-13-Rα1 and IL-13-Rα2 on macrophages to ultimately induce TGF-β [121]. In addition to profibrotic macrophages, so-called fibrocytes, myofibroblasts of bone marrow origin, also contribute to fibrosis. This has been shown, amongst other sites, for the liver [122], the lung [123], the heart [124], as well as the kidney [20, 95] (table 3).

Fibrotic Tissue Environments Dominated by ECM

Organ fibrosis is characterized by loss of parenchymal cells and partial replacement by fibrous tissue, e.g. in progressive liver cirrhosis, lung fibrosis or renal interstitial fibrosis. However, fibrosis does not always lead to end-stage organ failure [110]. More often fibrosis is a transient process to stabilize tissue integrity. For example, dermal wound healing ends in the smallest possible scar, like after a cut of the skin. Evidence for fibrolysis in the skin comes from recombinant TGF-β3 application in humans as well as preclinical models [125] TGF-β3 application prevents excessive proliferation of myofibroblasts and changes their migration towards a pattern normally seen only in the fetal stage where scarless healing occurs [125]. It remains to be proven exactly what role macrophages play in this process and so far little evidence is available on the macrophage phenotype in microenvironments dominated by the ECM.

Evidence for Fibrolysis from Solid Organs

Macrophages are capable of digesting ECM deposits via the secretion of selected MMPs which limit or even reverse fibrogenesis, e.g. in the kidney [125]. For example, macrophage depletion in the late phase of toxic liver fibrosis delays the clearance of liver scars [126], a process associated with MMP13 release by scar-associated macrophages [127]. Surprisingly, even at this stage of the disease macrophages recruit neutrophils to the liver which contribute to fibrotic matrix degradation [128]. In addition, antifibrotic macrophages are a possible source of CXCL10, a chemokine that, independent of ligation to its receptor, CXCR3, blocks the proliferation of fibroblasts in bleomycin-induced fibrosis [129]. It is therefore intriguing to speculate that a macrophage subtype with predominant fibrolytic activity exists in the ischemic environment of scar tissue that has the potential to digest ECM without concomitant secretion of proinflammatory cytokines (fig. 1). Surface markers that identify fibrolytic macrophages have not yet been described, but it should be technically feasible to isolate macrophages from fibrous lesions to characterize their phenotypic characteristics. Although the fibrolytic macrophage might be rare and hard to retrieve from fibrous lesions, it should be instrumental in understanding more about their potential to limit or to reduce tissue fibrosis. It is of note that MMP-secreting macrophages can also contribute to further tissue by degrading basement membranes and subsequent epithelial atrophy such as in the kidney [129]. Therefore, fibrolytic macrophages may also represent basement membrane-degrading macrophages which contribute to tissue atrophy. In fibrotic livers, however, transfer of bone marrow-derived macrophages has been shown to reverse hepatic fibrosis and to improve regeneration and function of the liver [129].

Summary and Conclusions

Macrophage plasticity gives rise to heterogeneous macrophage phenotypes in different and complex tissue environments and these, therefore, will never meet simplistic classifications. However, distinct tissue environments can induce prototypes of tissue macrophage phenotypes conceptually similar to those described in in vitro studies. For conceptual reasons we propose the clas-

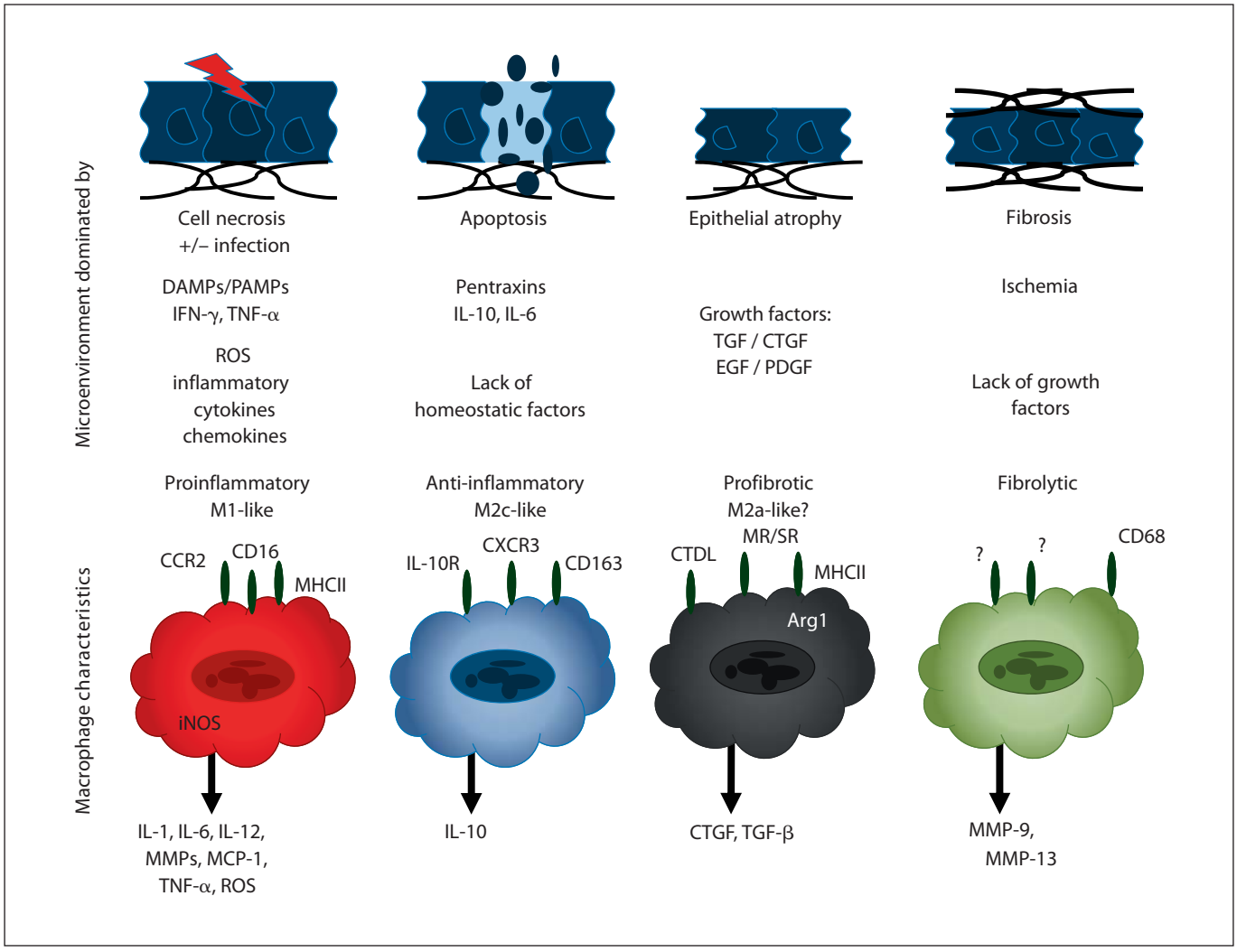

Fig. 1. Tissue microenvironments and predominant macrophage phenotypes. Acute tissue injury induces cell necrosis, hence the local microenvironment will be dominated by DAMPs. In non-sterile organs or during infections, PAMPs add to a tissue environment rich in factors that ligate pattern recognition receptors and drive macrophage polarization towards the M1-like proinflammatory phenotype. After the inflammatory response has cleared the sources of PAMPs and DAMPs, pentraxins and apoptotic cells, e.g. neutrophils, dominate the tissue environment which promotes macrophage polarization towards an anti-inflammatory M2-like phenotype that produces anti-inflammatory mediators which enrich the anti-inflammatory and proregenerative tissue environment. Once inflammation has completely ceased, the microenvironment is dominated by growth factors that promote wound healing, especially in conditions of incomplete or insufficient epithelial repair. This environment drives macrophage polarization towards a profibrotic phenotype that contributes to the secretion of additional growth factors as well as ECM components. The ischemic environment of scar tissue is largely devoid of cytokine and growth factors which drives the few macrophages in place to predominately secrete proteases that have the potential to remove connective tissue, i.e. the fibrolytic macrophages. In vivo all four types of macrophages can coexist in different areas of the same organ with focal lesions of active inflammation, early and late repair, as well as scar formation. This needs to be considered while characterizing macrophage phenotypes from tissue biopsies.

sification of tissue macrophages according to their predominant roles during the different stages of wound healing, a series of danger response programs that have been positively selected during the early evolution of multicellular organisms. As such, PAMP- and DAMP-rich (necrotic) environments prime proinflammatory (M1) macrophages that provide host defense but also inflammatory tissue damage. Postinflammatory environments including tumor stroma are dominated by apoptotic cells including neutrophils which induce a phenotype switch

towards anti-inflammatory or tumor-associated macrophages that themselves suppress immunity and support epithelial growth, either healing or tumor growth. The environment of healing tissue, especially during insufficient epithelial healing, is dominated by growth factors that prime macrophages towards a profibrotic phenotype. Such macrophages themselves secrete profibrotic cytokines and ECM components fostering tissue scarring. Scar tissue is hypoxic and deprived of growth factors and cytokines which allows macrophages to predominantly secrete proteases that remove ECM, the fibrolytic macrophage. As such, macrophages are amplifiers of their surrounding environment, or so to say, the tissue 'uses' macrophages to stabilize and to reinforce the current environment. The same is true with dendritic cells and resident macrophages during homeostasis. Spatial and temporal variations of tissue environments occur especially after injury and during the different stages of tissue repair. These environmental changes are associated with changing macrophage phenotypes, but the chicken-or-egg question remains to be further examined in each disease and each phase of the diseases.

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