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REVIEW

Dendritic cells and the extracellular matrix: A challenge for maintaining tolerance/homeostasis

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Abstract

The importance of the extracellular matrix (ECM) in contributing to structural, mechanical, functional and tissue-specific features in the body is well appreciated. While the ECM was previously considered to be a passive bystander, it is now evident that it plays active, dynamic and flexible roles in shaping cell survival, differentiation, migration and death to varying extents depending on the specific site in the body. Dendritic cells (DCs) are recognized as potent antigen presenting cells present in many tissues and in blood, continuously scrutinizing the microenvironment for antigens and mounting local and systemic host responses against harmful agents. DCs also play pivotal roles in maintaining homeostasis to harmless self-antigens, critical for preventing autoimmunity. What is less understood are the complex interactions between DCs and the ECM in maintaining this balance between steady-state tissue residence and DC activation during inflammation. DCs are finely tuned to inflammation-induced variations in fragment length, accessible epitopes and post-translational modifications of individual ECM components and correspondingly interpret these changes appropriately by adjusting their profiles of cognate binding receptors and downstream immune activation. The successful design and composition of novel ECM-based mimetics in regenerative medicine and other applications rely on our improved understanding of DC-ECM interplay in homeostasis and the challenges involved in maintaining it.

Key words: Dendritic cells; Extracellular matrix; Tolerance; Biomaterials; Homeostasis; Regenerative medicine;

Biointeractive implants

Core tip: The extracellular matrix (ECM) provides an essential framework for tissues in the body as well as actively orchestrates diverse cellular functions. Professional antigen presenting cells namely dendritic cells (DCs) are uniquely positioned to distinguish between self and non-self and accordingly regulate systemic immunity or tolerance. DCs and the ECM participate in finely-tuned, dynamic exchanges that ultimately impact the equilibrium between steady-state DC tissue residence or DC-instigated inflammation. To design biointeractive, ECM-inspired implants for regenerative medicine applications that retain functionality and undergo successful integration long-term, it is critical to understand the challenges involved in maintaining DC-ECM immune homeostasis under normal conditions.

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INTRODUCTION

Dendritic cells (DCs) are professional antigen presenting cells (APCs) that differentiate self from non-self and play crucial roles in determining the balance between tolerance and immunity. They were first discovered in mouse spleen by Steinman and Cohn[1] in a seminal paper published in 1973. Since this initial finding, the dogma that DC maturation is essential for the initiation of immunity has been well established. Immature DCs are typically distinguished by high levels of intracellular major histocompatibility complex class II (MHCII), low expression of adhesive and costimulatory receptors, strong endocytic, pinocytic and phagocytic abilities and weak capacities for T cell stimulation[2,3]. Immature DCs mount an immune surveillance program mediated in part by extracellular or cytoplasmic pattern recognition receptors (PRRs) expressed by DCs that identify evolutionarily conserved pathogen associated molecular pattern motifs on bacteria, viruses and on other foreign bodies or endogenous damage-associated molecular patterns (DAMPs). These recognition events trigger their transformation from rounded immature DCs into terminally differentiated mature DCs with enhanced motility, that exhibit extended dendritic processes and upregulate expression of co-stimulatory (CD80, CD86), MHCII molecules and adhesion molecules which bind T cells[2]. Ingested antigens processed intracellularly and presented as spliced peptides are loaded on to MHC complexes on mature DCs. The interactions between MHC and T cell receptors [MHCI: cytotoxic T cells (T_C) and MHCII: helper T cell (T_H) subsets] expressed on T cell surfaces drive antigen-specific cellular immunity. Notably, DCs are unique in their capacity to trigger T cell immunity. Taken together, DC-driven generation of cytokines, chemokines and other factors together orchestrate downstream host protective antigen-specific adaptive immune responses, as reviewed in[2]. DCs have three broad functions - mounting an immune response, maintaining immune tolerance and regulating immune memory, underscoring their critical roles in maintaining the balance between immunity and homeostasis[2].

This review discusses the growing body of evidence that the extracellular matrix (ECM) orchestrates DC interactions at different sites both in homeostasis and in inflammation. These interactions are highly complex and have many redundancies since DCs possess numerous receptors capable of binding the multicomponent ECM and are capable of upregulating and downregulating the expressions of PRRs in response to alterations in the ECM, thereby making it essential to better understand this interchange. Many questions remain incompletely elucidated: Why DCs are selective in terms of residing in certain tissues but not in others. For instance, what roles do tissue specific cytokines, chemokines and other factors associated with and released by the ECM play in regulating DC behaviour? To what extent are other tissue resident cells responsible for maintaining DC homeostasis, *e.g.*, hepatic stellate cells (HSCs) in the liver[4], epithelial cells in intestine[5], or keratinocytes in skin[6]. Finally, how do alterations in the ECM affect the DC steady-state and are these alterations reversible?

DC SUBSETS

Over the last few decades several groups have contributed to the large body of work performed in characterizing DCs present in tissues and in blood and their *in vitro* generated counterparts. DCs are identified by the expression of MHCII and costimulatory markers, and the absence of lineage markers such as CD3 (T cell), CD14 (monocyte), CD19 (B cell), CD56 (natural killer cell) or CD66b (granulocyte)[2]. DCs are described as two types: Conventional DCs (cDCs) and plasmacytoid DCs (pDCs). The cDCs are a principal DC subset and are sub-divided into migratory and non-migratory. Migratory DCs arise from the tissues and reach secondary lymphoid organs (SLO) *via* the lymphatics. Tissue resident conventional migratory DCs are broadly classified as $CD103^+$ $CD11b^-$ and $CD11b^+$ cDCs and have been described in intestine, liver, lung, kidney and skin as reviewed in[7,8]. The specific locations and roles of the different DC subsets vary in different tissues. For instance, lung DC subsets include migratory $CD103^+$ $CD11c^{high}$ $CD11b^-$ DCs in the intra-epithelial network, $CD103^-$ $CD11c^{high}$ $CD11b^+$ DCs in the lamina propria (LP) and non-conventional pDCs[8]. Intestinal DCs in Peyer's Patches (PP), LP and mesenteric lymph nodes exhibit varied expression of CD103 and CX3CR1 of which migratory, conventional $CD103^+$ DCs have been

assigned both immunogenic and tolerogenic roles[8]. Liver DCs consist of $CD11c^+$ $B220^-$ DCs (further divided into $CD103^+$ and $CD103^-$), both linked to regulatory T cells (T_{reg}) induction as reviewed in[8] and $CD11c^+$ $B220^+$ pDCs, the latter playing a role in maintaining steady state tolerance and the resolution of inflammation after liver injury[8]. Kidney DCs comprise $CX3CR1^+$ $CD11b^+$ DCs, $CX3CR1^+$ $CD11b^-$ DCs and $CD103^+$ DCs, while $CD103^+$ cells are thought to play a tolerogenic role as opposed to other subsets as reviewed in[8]. Skin DCs include dermal DCs which are Langerin+ ($CD207^+$) $CD103^+$ DCs and are categorized as cDCs with bone marrow precursors, as well as Langerin- $CD103^-$ DCs (with unknown precursors)[8].

Conventional DCs also include lymphoid DCs that are distinct from myeloid DCs, lack expression of CD11b, CD13, CD14, and CD33 and are derived from precursors that have the ability to differentiate into T cells and NK cells as reported in[3] as opposed to monocyte/macrophage lineages[9]. While cDCs sample tissue antigens and migrate to present the processed peptide(s) to T cells in LNs, in contrast, non-migratory cDCs previously considered as "lymphoid" DCs reside in thymus, spleen, LNs or PP[3,10]. Lymphoid DCs include $CD4^-CD8\alpha^+$ DCs that cross present antigen to $CD8^+$T cells, while $CD4^+CD8\alpha^-$ DCs in spleen or $CD4^-CD8\alpha^-$ DCs in mucosal associated lymphoid tissue, activate $CD4^+$ T cells. Non-migratory lymphoid DCs regulate thymic negative selection, drive T_H2 responses in humans and stimulate regulatory responses overall[3].

The pDCs are found mostly in lymphoid tissues and secrete IFN-α upon exposure to viral antigens. Phenotypically, pDCs, the second principal DC subset express CD45RA, CD123, CD303 and CD304 as well as low levels of MHCII, costimulatory molecules and CD11c, while myeloid DCs express CD11c, CD13, CD33 and CD11b[11]. The pDCs are highly secretory, exhibit plasma cell-like morphologies and display properties of both cDCs and lymphocytes. Importantly, pDCs express endosomal TLR7 and TLR9 that detect viral single stranded RNA and unmethylated CpG-containing DNA and respond by rapid and substantial production of type Ⅰ IFN (IFN-α/β)[12]. Plasmacytoid DCs start in bone marrow and enter lymphoid tissues where they mainly reside, through blood[7]. Plasmacytoid DCs are important for mediating differentiation of B cells to plasma cells for antibody production and have been linked to immunogenic and tolerogenic responses in the liver and lung as reviewed in[8]. Most DCs [apart from yolk sac derived - Langerhans cells (LCs)] are generated in bone marrow from myeloid progenitor cells[13] with some *in situ* proliferation in spleen. Another class of non-conventional DCs namely monocyte-derived "inflammatory" DCs have been detected in the skin and kidneys and intestine and have been implicated in the progression of inflammation in colitis and as $CD103^-$ $CX3CR1^+$ DCs in maintaining gut homeostasis. In the lung, $CD103^-$ $CD11c^{high}$ $CD11b^+$ DCs play crucial roles in reacting to allergens and triggering T_H2-mediated immunity. Finally, self-renewing DC-like cells such as slow turnover LCs and microglia are specialized dendritiform cells derived from the yolk sac and reside in the squamous epithelium and in CNS parenchyma respectively and mediate tolerance in the resting states[8,11].

It is clear that DCs are not narrowly defined as a single type of cell but instead represent a diverse assortment of cells derived from different lineages[10,14-17]. The generally accepted theory is that hematopoietic DC progenitors from the bone marrow circulate through the body and are receptive to specific combinations of cytokines and signals, resulting in DC subsets with specialized homing properties and roles. *In vitro* DCs have been generated from $CD14^+$ monocytes in blood and $CD34^+$ bone marrow precursors[2]. "Classical" myeloid DCs have been generated from myeloid committed $CD34^+$ progenitor cells and monocytes treated with granulocyte macrophage colony stimulating factor (GM-CSF) and tumour necrosis factor-α (TNF-α) ± interleukin-4 (IL-4) *in vitro*[7,8,11,18,19]. Myeloid DCs regulate responses of CD4 and CD8 T cells and are involved in B cell differentiation into plasma cells. In addition, $CD34^+$, $CD14^-$ cells differentiate into LCs in the presence of transforming growth factor-β (TGF-β)[7,8,11,18,19]. Also, lymphoid committed $CD34^+$ cells become pDCs in the presence of IL-3[20]. Myeloid DCs are sometimes referred to as DC1 and express toll-like receptor 2 (TLR2), TLR3, TLR4, TLR7 and activate naïve T cells along T_H1, T_H2 pathways[7,8,11,18,19]. In contrast, lymphoid DCs or DC2 express TLR7 and TLR 9 and secrete IFN-α in response to invading viruses. Notably, high numbers of DCs have been generated in mice and in humans by recurrent injections with hematopoietin flt-3L, thought to act on DC precursors in the bone marrow[2,21,22].

Interestingly however, when tissue residence is discussed there is little reference to how the tissue might affect or even permit the DCs to migrate into tissue matrices and egress from it *via* the lymphatics. Furthermore, changes in the tissue which occur during inflammation will affect not only the resident DCs but also newly recruited DCs. For instance, the retina in normal mice has a small population of $MHCII^+$ $33D1^+$ DCs located mainly at the periphery while tissue resident microglia are macrophage-like cells. However, during inflammation, *e.g.*, uveoretinitis, there is a marked increase in the numbers of antigen-presenting cDCs[23]. Microglia mostly maintain tolerance in non-inflamed retina but can become activated during degenerative disease such as age-related macular degeneration (AMD) or inherited retinal degeneration[24]. Dysregulated clearance/accumulation of debris result in microglial activation accompanied by elevated production of pro-inflammatory chemokines and cytokines. Similarly, bone and cartilage do not have DCs under steady state conditions[25], although activated DCs can trigger cartilage degradation by producing TNF-α. It is not clear why certain tissues restrict DCs from being present in steady state or why others permit their entry. It would

be fascinating to gain an understanding of what the microenvironmental cues provided by the ECM towards this are as well as how these signals are altered in pathological conditions to pave the way for DC infiltration and subsequent immune responses.

FUNCTIONAL DICHOTOMY OF ECM

It has been well established that the ECM plays critical roles in regulating cellular differentiation, survival, shape and function including adhesion, motility, apoptosis and tissue specific alignment[26,27]. The ECM is a three dimensional mixture of triple helical collagens, complex proteoglycans composed of glycosaminoglycans covalently linked to protein, glycoproteins, proteases, growth factors and cytokines that respond actively to microenvironmental conditions[28,29]. Notably, dysregulation or mutations in the ECM have been linked to developmental, degenerative, malignant, and pathological states such as cancer and inflammatory arthritis[26], while oxidative impairment of ECM components by enzymatic or non-enzymatic pathways has been associated with progression of kidney disease, lung disease, arthritis, and chronic inflammation[30]. Protein fragmentation has been proposed to form site-specific focusses for free radicals and reactive species as suggested in this review[31].

Remarkably, the ECM displays functional dichotomy. Besides forming a supporting mesh to stabilize cells, the ECM plays active roles in regulating normal or pathological states of inflammatory cells[27]. Degradation of intact steady state high molecular weight proteins to low molecular weight fragments has been directly linked to initiating and contributing to the progression of inflammation as demonstrated for major constituents of the ECM such as collagen, elastin, laminin, hyaluronan (HA) or fibronectin, based on their effects on neutrophils, monocytes, macrophages[27,32-34]. In chronic lung neutrophil-mediated diseases that affect the matrix such as chronic obstructive pulmonary disease or in cystic fibrosis, evidence suggests that the products of protease degradation of matrix proteins (elastin, collagen fragments) are active triggers of inflammation (chemotactic for neutrophils)[35]. Interestingly, the degradation of interstitial matrix components such as collagen can induce peripheral blood mononuclear cells (PBMC) activation *via* IL-1β production, and to different extents depending on the nature of the collagen peptide[33]. In homeostasis, matrix components such as fibronectin play essential roles in mediating tissue cell adhesion and stabilize the ECM by interactions with fibrinogen. In contrast, fibronectin fragments detected in synovial fluid in rheumatoid arthritis (RA) display pro-inflammatory characteristics such as enhanced monocyte chemoattraction, phagocytosis of polymorphonuclear leukocytes and complement engagement as compared to intact fibronectin[34]. Similarly, ECM components can play dual roles, one during cardiac development and second in healthy recovery or persistent heart failure after myocardial infarction as indicated by the diverse expression of ECM factors in different physiological states (foetal, neonatal, adult)[28,36]. Importantly, ECM interactions with cytokines including fibroblast growth factor, TGF-β, interferon-γ (IFN-γ), macrophage inflammatory protein-1β, ILs or TNF-α and enzymes such as heparanase, urokinase-type plasminogen activator, elastase or matrix metalloproteinases (MMP) regulate the increase or decrease of inflammation at sites of tissue injury[37]. Blocking heparanase activity helps counteract early ECM degradation by controlling early inflammation[29]. Heparan sulfate in ECM binds chemokines and cytokines such as IL-2 and IFN-γ in steady state and when freely available, IL-2 triggers immune responses underscoring the point that ECM channels the host response towards or away from homeostasis[29]. Taken together, the picture emerging is that contrary to earlier concepts, the ECM is not a passive bystander but actively participates in the overall immune response. Indeed, the notion that the tissue regulates the immune response has been proposed by Matzinger[38] although precisely how awaits discovery. At the microenvironmental level, the matrix is dynamic and attuned to the stage of the immune/inflammatory response, prompting factors that are pro-inflammatory early on in the response to have anti-inflammatory effects during wound resolution[29].

TISSUE MATRICES AND DCS IN HOMEOSTASIS

DCs occupy diverse matrices in different tissues. The matrices assist in preserving DC tolerance through unique interactions and support their immune surveillance program. Some of these examples have been briefly reviewed here namely for skin, intestine, liver, retina, cornea and spleen. Although this is not a comprehensive list, immune privilege at different sites has been exhaustively reviewed elsewhere[39]. Long-lived LCs reside in skin epidermis (Figure 1) and maintain homeostasis by forming E-cadherin junctions with keratinocytes and by TGF-β mediated events *via* suppression of pro-inflammatory factors IL-1, and TNF-α[6,40,41]. Resting epidermal LCs in normal adult human skin importantly have the capacity to preserve immune homeostasis by stimulating tolerogenic skin resident T_{reg} responses to self-antigens and can also elicit activation of T_{eff} cells in response to foreign pathogens[42]. Interestingly, $CD1a^+$ and Birbeck granule expressing LCs also express neuronal receptors and communications between LCs and nerves suggest bidirectional signalling towards sustaining homeostasis[43]. Homeostasis and development of specialized DCs such as LCs and microglia rely on IL-34 secreted by epidermal keratinocytes and brain neurons respectively[44] Neuropeptides have been shown capable of regulating DC function. Interestingly, the neurotransmitter neurokinin A activates bone marrow-derived DCs to drive type 1 immune responses by targeting the neurokinin-2 receptor on

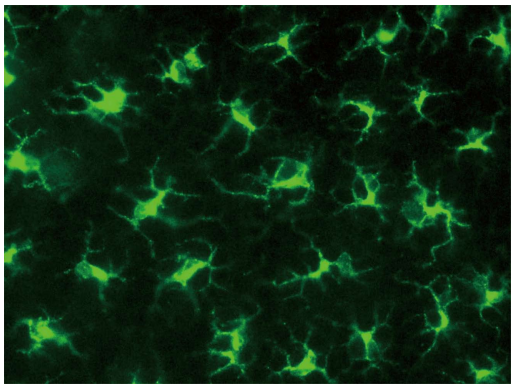


Figure 1 Murine Langerhans cells in ear skin reside in the epidermis, stained here for major histocompatibility complex class Ⅱ (green). Reprinted from Jakob T, Ring J, Udey MC. Multistep navigation of Langerhans/dendritic cells in and out of the skin. *J Allergy Clin Immunol* 2001; 108: 688-696 Copyright (2001), with permission from Elsevier.

DCs[45], while other neuropeptides such as Substance P, calcitonin gene-related peptide (CGRP) and somatostatin importantly can be secreted by DCs and regulate T cell activation[46]. Further, signalling *via* type 1 CGRP receptor on human DCs downregulates expression of MHCII and CD86 as well as decreases DC-associated T cell proliferation[47].

Similar to the skin, intestinal mucosa represent large surface areas exposed to the outside environment. It is therefore critical to maintain DC tolerance under steady state conditions. Intestinal $CD103^+$ $CD11b^+$ migratory DCs in LP, PP, gut-associated lymphoid tissues or solitary intestinal lymphoid tissue are key regulators of homeostasis[48] and are capable of inducing anti-inflammatory T_{reg} differentiation[5]. Also, $CX3CR1^+$ and $CD103^+$ mucosal DCs in the LP are important in maintaining gut immune homeostasis[49]. Furthermore, DCs in PP and mucosal DCs in LP are involved in generating oral tolerance to collagen Ⅱ in collagen-induced arthritis models, mediated by TGF-β, T_{regs} and tipping the balance towards T_H2 cytokines (IL-4)[50].

Liver resident professional and non-professional APCs including Kupffer cells (KCs), liver sinusoidal endothelial cells and DCs are crucial in maintaining hepatic tolerance under non-inflammatory conditions[51,52]. The HSCs located in perisinusoidal spaces of the liver have the ability to present antigen under tolerogenic conditions and exhibit cytoplasmic interactions with a broad range of functionally diverse cells such as hepatocytes, sinusoidal endothelial cells and KCs[4]. Specifically, HSCs coexist with murine liver DCs *in vivo* under homeostatic conditions and were shown to downregulate DC activation *via* tryptophan-catabolizing enzyme indoleamine-2,3-dioxygenase expression, towards establishing an anti-inflammatory phenotype[4]. Specifically, resident immature DCs operating in the microenvironment of anti-inflammatory IL-10 and TGF-β are tolerogenic and block the activation of liver penetrating lymphocytes *via* interactions of cytotoxic T lymphocyte associated antigen receptor-4 and PD-1, both of which are potent negative regulators of T cells[51].

The transparent, avascular cornea at the anterior of the eye is comprised of the epithelium, the highly stratified layers of collagen types Ⅰ and Ⅲ that form the stroma and the innermost endothelial layer. Towards sustaining homeostasis in the normal healthy state, $CD11b^+$ $CD11c^+$ DCs present in the stroma act as sentinels, maintaining an $MHCII^{low}$ $CD80^{low}$ $CD86^{low}$ immature phenotype in the centre of corneas *vs* at the periphery where immature and mature DCs coexist[53,54]. Following inflammation, infection or corneal trauma, resident B220+ $CD11c^{low}$ pDCs, $CD34^+$ MHCII myeloid precursors and $CD11b^+CD11c^-$ macrophages, as well as infiltrating DCs recruited from the bone marrow permeate the corneal collagen matrix as part of the protective response[55-57].

In the spleen, the largest secondary lymphoid organ, several resident DC populations including lymphoid DCs, myeloid DCs and pDCs have been identified in both humans[58] and mice[59]. However, relatively little is understood about the complex interactions between the matrix components and DCs occupying different splenic zones that are responsible for the crucial task of maintaining tolerance to self-components. Interestingly, splenic stroma has been shown capable of supporting hematopoiesis of dendritic-like cells from splenic or bone marrow precursors[60]. Within the bone marrow, specialized tissue microenvironments or niches crucial for homeostasis of resident hematopoietic stem cell DC progenitors have been described at vascular sites mediated by associations with endothelial cells or at osteoblast sites[61]. Furthermore, while cellular mechanisms responsible for DC tolerance in certain tissues have been elucidated, the specific nature of the ECM ligands and counterparts that form an important part of this "homeostasis handshake" remain poorly characterized.

Markedly, DCs are absent or at least their presence is debated in certain tissues such as the brain[62], while others have contradicted this finding[63]. It is important to mention that isolations of brain DCs have been contaminated with DCs from the meninges which are themselves very rich in DCs[64], analogous to the retina which has few, if any DCs as opposed to the uvea which is abundantly populated with DCs. Under steady-state conditions normal brain parenchyma was found to have resident $CD11c^+$ $MHCII_{neg}$ ramified cells, possibly differentiated from microglia[63]. Also, brain resident DCs could be removed and differentiated into immature DCs with GM-CSF and to mature DCs with CD40 ligation as shown in[65]. It is important to elucidate how DCs maintain homeostasis and also why they are absent in bone, cartilage and other tissues, yet these tissues are flooded with DCs during inflammation. What are the cues from the ECM that keeps DCs away during homeostasis? How does the ECM contribute towards this diversion/chemorepulsion event? Or do DCs gain entry but then undergo apoptosis? Finally, how is this phenomenon relevant to enhancing the immunocompatibility of artificial stroma utilized in regenerative

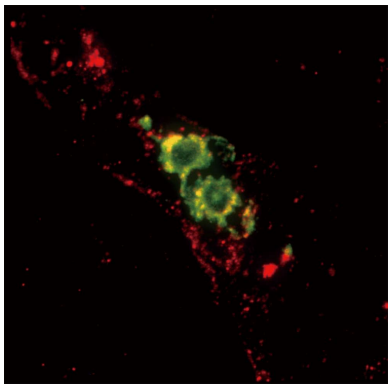


Figure 2 Mature skin dendritic cells egress *via* lymphatics that display secondary lymphoid tissue chemokine (SLC/CCL21) constitutively. Shown here are two mature DC expressing MHC class Ⅱ (green) located within a lymphatic vessel that presents SLC (red). Reprinted from Jakob T, Ring J, Udey MC. Multistep navigation of Langerhans/dendritic cells in and out of the skin. *J Allergy Clin Immunol* 2001; 108: 688-696 Copyright (2001), with permission from Elsevier. Courtesy of Saeki H and Hwang S, National Cancer Institute, Bethesda, MD.

medicine?

IT WORKS BOTH WAYS: DC MODULATION OF MATRICES

Communication between DCs and the ECM is bi-directional. The DCs signal out to the ECM and actively modulate the matrix which affects their ability to migrate, adhere, traffic into lymphatics, or cross the vascular endothelium. Specifically, epidermal LCs migrate towards skin-draining LNs after antigen encounter, a complex transmigration event mediated by C-C chemokine receptor type 7 (CCR7), selectins, integrins and MMP activity to cleave ECM components (Figure 2)[6,40,41]. In the LNs, LCs present antigens in the context of self/non-self to T cells to drive tolerance or immunity, as seen in T_H2-driven atopic dermatitis[66,67]. Markedly, in heparanase deficient mice that are incapable of cleaving heparan sulfate in the ECM and on cell surfaces, the loss of heparanase results in critical defects in facilitating DC migration from skin to lymphatics. Intriguingly, immature DCs in these mice transition to mature DCs and appear more activated. Increased DC activation is possibly due to the compensatory elevation of CCR7 expression and CCR7-CCL19-driven DC activation[68]. Furthermore, DCs co-cultured with fibroblasts in the presence of TNF-α/IL-1β enhanced MMP-9 expression on DCs, important for DC migration *via* degradation of collagen type Ⅳ in basement membranes[6], underscoring the important role played by the ECM in maintaining DC homeostasis and controlling DC localization within tissue. Tissue migratory cDCs display heterogeneity depending on their microanatomical location. For instance skin epidermal migratory LCs are distinct from dermal DC subsets (Langerin+CD11b^{low}, Langerin-CD11b^{-}, and Langerin-CD11b^{low}) and display differential migratory characteristics depending on the nature of the antigen[69]. Following skin infection with HSV, epidermal LCs migrated swiftly away from the epidermis, likely towards skin draining LNs in contrast to dermal DCs which collected in the dermis together with monocyte-derived DCs[70]. On the other hand, skin painting with contact sensitizing substances resulted in differential migration kinetics within different dermal DC subsets and as compared to LCs, suggesting that dermal DCs arrive earlier in cutaneous LNs and are involved in the early response to skin immunization[71]. This observation is supported by another study that demonstrated a vital role for tissue migratory dermal DCs rather than migratory LCs in response to contact hypersensitivity induced by 2,4-dinitro-1-fluorobenzene in terms of their abilities to elicit antigen-specific T cell proliferation. Taken together, these studies highlight the exquisite complexity that tissue migratory DCs demonstrate in their direction of response, migration kinetics and role depending on the specific properties of the matrix that they occupy. In other words, the DC subset that migrate initially to the site of an insult and therefore help shape the overall adaptive response may be profoundly impacted by the anatomical and microenvironmental location of the injury and the resident DC populations present there.

MAJOR ECM COMPONENTS IMPINGING ON DC

Individual constituents of the ECM have been associated with differential impacts on inflammation and immunity. Distinct contributions of the various classes of ECM macromolecules have been reviewed in this section with special emphasis on their unique interactions with DCs to highlight how the specific biology, site in the body, phase of response, form (soluble or particulate), fragment length, post-translational adaptations and enzymatic modifications may vary in healthy *vs* pathological conditions (Table 1). While by no means a comprehensive list, we highlight that ECM components are crucial factors and play distinct roles in directing innate/adaptive responses, focusing on DC/cellular/humoral-orchestrated downstream homeostasis or inflammatory consequences.

Collagen

Collagens represent a major component of the ECM and connective tissue with characteristic Gly-Pro-X repeats, providing support and tensile strength[72]. Collagen type Ⅰ (skin, tendon, bone, interstitial tissues, ligaments, cornea), type Ⅱ (cartilage, vitreous humour) and type Ⅲ (skin, muscle, blood vessels) account for the majority of collagens present in the body[72]. While collagen types Ⅰ, Ⅱ and Ⅲ are present as covalently crosslinked fibrils, notably, type Ⅳ collagen forms a two dimensional reticulum (basal laminaes)[73]. The type and form (soluble or particulate) of collagen appear to be important determinants of their abilities to stimulate DC activation. Soluble collagen types Ⅰ, Ⅱ, Ⅲ coated onto

Table 1 Dendritic cells and the maintenance of homeostasis in different tissues

Tissue	Location	Resident DC in naïve tissue	Resident associated cells/ naïve tissue	Stromal/cellular interactions in immune homeostasis	Ref.
Skin	Epidermis	Cd1a$^+$ Langerin+ Langerhans cells expressing Birbeck granules	Keratinocytes	E-cadherin junctions with keratinocytes, TGF-β production, tolerogenic T_{reg} responses	[6, 40-42]
	Dermis	CD1c$^+$ DC-SIGN+ DEC205$^+$ dermal DC subsets (Langerin+ CD11b^{low}, Langerin-CD11b-, and Langerin-CD11b^{low})	To be elucidated (presumed dermal matrix, fibroblasts)	Pluripotent dermal DC may present antigen, migrate or reside in tissue depending on local interactions	[69, 144]
Intestinal mucosa	LP, Peyer's patches, GALT, SILT	CD103$^+$CD11b$^+$ or CD103$^+$ CD11b- migratory DC, CD103$^+$Sirpα- DC, pDC, CX3CR1$^+$ DC	Macrophages, B cells	Maintain immune homeostasis, induce T_{reg} differentiation, oral tolerance (TGF-β, T_{reg}, T_H2 factors) Gut: Retinoic acid, T_H17 cells LP: indoleamine 2,3-dioxygenase CD83 on DC regulates mucosal tolerance	[5, 48-50, 145, 146]
Liver	Portal tracts, interstitial DC	CD103$^+$DC, CD103$^-$DC, CD103$^-$ CD11b$^+$DC, CD141$^+$ DC (high in healthy liver)	Hepatic stellate cells, sinusoidal endothelial cells, Kupffer cells, hepatocytes	Inhibit DC activation (indoleamine-2,3-dioxygenase expression), repress T cell activation (IL-10, TGF-β) *via* CTLA-4, PD-1	[4, 51, 52,147,148]
Cornea	Central/peripheral corneal stroma	CD11b$^+$ CD11c$^+$ DC, B220$^+$ CD11c^{lo} pDC, CD34$^+$ MHCII myeloid precursors	Stromal Collagen Ⅰ, CD11b+ CD11c- macrophages, keratocytes	Maintain MHCII^{low} CD80^{low} CD86^{low} phenotype under normal conditions	[54-57]
Spleen	Marginal zones	Lymphoid, myeloid and pDC	Macrophages, T cells, B cells (zone dependant)	To be elucidated	[58-60]
Bone marrow	Osteoblastic or vascular niches	Resident hematopoietic stem cell DC progenitors	Osteoblasts, stromal cells and sinusoidal endothelial cells	-	[61]
Retina	Peripheral margins and juxtapapillary areas	Presence of DCs is debated. Few MHCII$^+$ 33D1$^+$ DC observed in naïve brain	Likely migrated in from choroid, ciliary body and meninges	Perivasulcar - around retinal venules (initial site of immune disruption), but not arterioles.	[149]
Brain	Regions of synaptic plasticity and neurogenesis	Presence of DCs is debated. Brain-derived CD11c$^+$ DC	-	-	[62,63,150]
Bone/ cartilage/ vitreous	Not detected	-	-	-	-

DC: Dendritic cell; TGF-β: Transforming growth factor-β; LP: Lamina propria; GALT: Gut-associated lymphoid tissues; SILT: Solitary intestinal lymphoid tissue; MHCII: Major histocompatibility complex class Ⅱ; IL: Interleukin-4.

dishes activated murine/human BMDCs and resulted in elevated costimulatory receptor expression, pro-inflammatory cytokine secretion and allostimulatory capacities[74-76], demonstrating that ECM components can trigger DC activation locally. In contrast, extracted dermal hydrogels composed of basement membrane constituents such as particulate collagen type Ⅳ, collagen type Ⅶ and laminin β3 improved dermal wound healing in a rodent model and mitigated granulation tissue thickness by assisting with wound contraction[77]. Furthermore, in a study comparing the effects of individual matrix components on DC maturation, DCs cultured on plates coated with ECM components fibronectin, collagen, gelatin, or on poly-lysine or polystyrene surfaces were observed to upregulate CD80, MHCII in the presence of pro-inflammatory factors. Interestingly however, on Matrigel (collagen type Ⅳ, laminin, entactin, heparan sulfate proteoglycans)-coated surfaces, the ECM components were able to inhibit DC maturation even in the presence of activating factors[78], suggesting that gelatinous Matrigel derived from murine tumour stroma and mimicking basement membranes promotes DC tolerance to maintain homeostasis under normal conditions.

Glycoproteins - fibronectin, vitronectin, laminin and fibrillin

Glycoprotein constituents of ECM play well defined roles during inflammation. In injury, fibronectin draws cells towards repopulating the wound by exploiting cell surface integrins, while laminin helps in the formation of blood vessels[72]. Interestingly, fibronectin and laminin have been implicated in inhibiting DC maturation. Specifically, human monocyte-derived DCs cultured in the presence of pre-adsorbed fibronectin and laminin retained a less mature phenotype with enhanced endocytic capacities (Figure 3)[79]. On the other hand, modified presentation of Arg-Gly-Asp (RGD) integrin-binding sequence of the ECM glycoprotein fibrillin in microfibrils disrupted murine pDC adherence and increased its activation (IFN-α, IL-6), plasma cell and B cell accretion and autoantibody secretion, skewing of

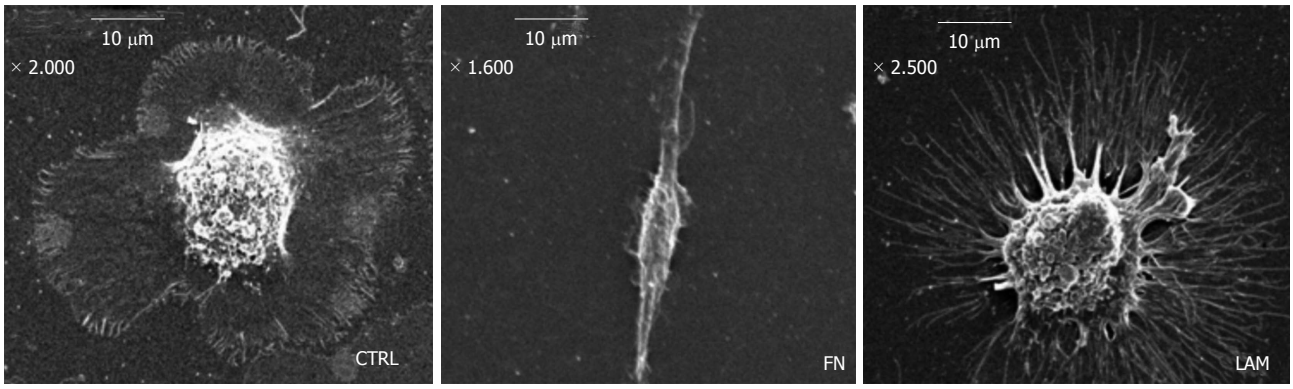


Figure 3 Scanning electron microscope images demonstrate that dendritic cells cultured on fibronectin or laminin for 48 h exhibit widely differential morphologies. Taken in part from García-Nieto S, Johal RK, Shakesheff KM, Emara M, Royer PJ, Chau DY, Shakib F, Ghaemmaghami AM. Laminin and fibronectin treatment leads to generation of dendritic cells with superior endocytic capacity. *PLoS One* 2010; 5: e10123. Copyright (2011), published under the Creative Commons Attribution (CC BY) license. FN: Fibronectin; LAM: Laminin.

T_H subsets and ultimately enhanced dermal fibrosis, showing a role for fibrillin in instigating pro-inflammatory, pro-fibrotic programmes[80].

Non-proteoglycan polysaccharides

HA: HA a copolymer of GlcNAc and GlcUA plays dual roles both as supporting meshwork of lymphatics as well as that of a potent danger signal, based on the fragment length[81]. Breakdown of long glycosaminoglycan HA resulting in the formation of small HA fragments activated skin DCs. Higher serum and lymphatic HA levels have been associated with reduced DC maturation and feeble tumour responses correlating to higher HA in tumour ECM[82]. Hyaluronic acid is a significant non-immunogenic component of healthy ECM linked to wound healing, inhibition of inflammation and angiogenesis. Hyaluronic acid hydrogels enhanced healing after myocardial infarction in rats by decreasing collagen production and increasing vascular endothelial growth factor levels[83].

Modulators: Periostin plays an anti-inflammatory role in IgE-mediated airway hyperresponsiveness and allergy *via* upregulating active TGF-β and therefore inducing differentiation of T_{regs}[84]. Tenascin C is an ECM glycoprotein not normally detectable in healthy adult tissues but is present in pathological conditions such as arthritis[85] and myocarditis[86]. In tumours, tenascin C has been implicated in epithelial mesenchymal transition and migration of cancer cells[87]. Secreted protein acidic and rich in cysteine is a Ca^{2+} binding matrix glycoprotein involved in organization of germinal centres of LNs and essential for follicular DCs to receive necessary cues to induce T_H17 differentiation as shown in a model of experimental autoimmune encephalomyelitis[88]. Thrombospondin 1-DC axis is a negative regulator of inflammation associated with elevated levels of anti-inflammatory mediators (PGE-2, TGF-β). It is critical towards maintaining homeostasis and serves to resolve inflammation during wound healing[89].

MMPs

In injury, enzymes are involved in matrix turnover and remodelling, needed for cell entry and egress and proliferation, vasculogenesis and angiogenesis[72]. Tumour enlargement and dissemination involve interplay between tumours, immune cells and ECM. Active MMP-2 acts as an endogenous anti-inflammatory mediator as evidenced by anti-inflammatory T_H2 profile of MMP-2-expressing $CD4^+$ T cells that infiltrate tumours and the roles of MMP-expressing DCs in inducing this profile *via* OX40L and inhibition of IL-12p70 production[90,91].

Post-translational modifications of ECM components and effects on DC homeostasis

Post-translational modifications including glycation, carbamylation and citrullination have implication in diabetes, kidney fibrosis and inflammatory conditions such as rheumatoid arthritis respectively[92], *via* interactions with DC C- type lectin receptors (CLRs), a class of PRRs[2]. Alterations of the ECM are strongly linked to altered ligand binding and cellular interactions[93]. Inhibition of terminal fucosylation alters macrophage phenotype from pro- to anti-inflammatory, demonstrating how immune homeostasis can be compromised by altered glycosylations of ECM components[94]. Altered fucosylation and exposure of glycans normally "buried" on serum IgG have been implicated in systemic lupus erythematosus progression[95], while changes in sialylations may transform it from being pro- to anti-inflammatory[96]. Interestingly, mucosal surfaces of the human female reproductive tract display glycation patterns analogous to those seen on metastatic cells or on efficacious pathogens in order to promote anti-inflammatory responses for survival of placenta and human sperm[97], reinforcing the observations that host proteins can be altered to present tolerizing or activating glycosylation patterns as reviewed in[98].

DC RECEPTORS FOR ECM

DCs express many receptors which interact with tissue

or matrix components during homeostasis as well as with their breakdown products[78], some of which have been reviewed here and summarized in Table 2. Immature DCs express adhesion complexes to bind different structural ECM components: CD49a/CD29 and CD49b/CD29 to collagen and laminin; CD49c/CD29 to collagen, laminin, fibronectin and thrombospondin; CD49d/CD29 and CD49e/CD29 to fibronectin; CD49f/CD29 to laminin; CD41, CD51 and CD61 to fibrinogen, fibronectin, vitronectin and thrombospondin[78]. Besides expressing adhesion molecules to direct their migration and localization within tissues, DCs express extracellular and cytoplasmic PRRs such as TLRs, RIG-I-like receptors (RLRs) and NOD-like receptors (NLRs) that respond to pathogens[99,100]. Major PRRs such as TLRs bind bacterial and viral nucleic acids, lipopetides, and lipopolysaccharide and initiate signalling cascades triggering DC maturation[101]. Cytoplasmic RLRs recognize bacterial and viral nucleic acids while NLRs such as NOD1 and NOD2 bind bacterial peptidoglycans[102]. Endocytic scavenger receptors recognize modified and unmodified lipoproteins[103].

Another class of PRRs, endocytic CLRs bind glycosylated moieties in a Ca^{2+} dependant manner, and internalize and present both self and non-self on MHC molecules[104,105]. CLRs recognise glycations on ECM constituents - N-linked glycans present on glycoproteins as well as O-linked glycans on collagens[105]. Importantly, antigen uptake by CLRs resulting in TLR ligation results in the generation of antigen-specific immunity, while in contrast, CLR-mediated recognition alone facilitates homeostasis and tolerance to tissue antigens, as discussed in this review[105]. There is growing evidence that CLRs play significant roles in regulating immune tolerance in the gut[106]. Dectin-1 and galectin-3 maintain tolerance to gut mucus by repression of NF-κB[107]. Tolerogenic DCs recognize GalNAc on tumours by MGL (macrophage galactose/N-acetylgalactosamine-specific C-type lectin) binding[105] and mannose receptor expressed by DCs has been implicated in maintaining immune homeostasis[108]. Furthermore, $MGL1^+$ and $MGL2^+$ cells were detected in various tissues under normal conditions suggesting that they play an active role in tightly controlling DC homeostasis in tissues regularly exposed to antigens including thymus, intestine, stomach, trachea and skin[109]. Modified glycosylation patterns alter CLR binding and contribute towards immune evasion by impacting CLR-TLR cross talk[105].

"Homeostatic danger signals" were defined in a recent review as disruptions in tissue steady-state that stimulate DC activation, typically occurring during inflammation[110]. Endogenous DAMPs released or activated during injury or surgical trauma include degraded ECM constituents such as fibronectin, fibrinogen, HA[111,112] heparan sulfate[113], biglycan[114,115], versican[116] activate DCs mediated by TLRs resulting in pro-inflammatory outcomes[117,118]. Heparan sulfate, TLR4 agonist stimulates DC activation and enhanced allostimulation *in vitro*[113]. Blocking heparan sulfate serum levels with alpha-1-antitrypsin reduced extent of graft *vs* host diseases in mice[119]. Biglycan is released from ECM during tissue damage or may be produced by inflammatory cells and activates DCs *via* TLR2/4[115], MyD88, TRIF as shown in myocardial matrix[120]. Chondroitin sulfate proteoglycans regulate immunity in the CNS[121]. Breakdown of long glycosaminoglycan HA resulting in the formation of small HA fragments activated skin DCs in a TLR4-mediated manner[122]. Another ECM component, tenascin C initiates TLR4-mediated DC activation and generation of T_H17 cells[85,86].

DC receptors that recognize collagen, a major constituent of the ECM, may be activating (discoidin domain receptors[74,75], mannose family receptors, glycoprotein Ⅵ) or tolerogenic [CD305/leukocyte-associated Ig-like receptor 1 (LAIR-1)[123]]. LAIR-1 binds soluble adsorbed collagen (hydroxyproline in Gly-Pro-Hyp) and interferes with DC differentiation in an immunoreceptor tyrosine-based inhibitory motifs -mediated manner[124]. LAIR-1 may play an important role in maintaining homeostasis and has been shown to be upregulated on tumour-associated DCs[125]. On the other hand, soluble adsorbed collagen types Ⅰ, Ⅱ, Ⅲ, ligands of osteoclast-associated receptor were shown to activate human monocyte-derived DCs and triggered upregulation of maturation markers, TNF and TLR signalling demonstrating that ECM components can trigger DC activation locally, important in the context of DC differentiation into bone-degrading osteoclasts in the synovial tissues of rheumatoid arthritis patients[76].

INTELLIGENT BIOMATERIAL DESIGN TO MIMIC ECM IN TISSUE REGENERATION

In recent years, tissue engineering strategies have been proposed to address the shortfall of utilizable donor tissues for transplantation. The main objective is to generate functional, viable tissue substitutes that are well-integrated long-term in a site-specific manner. Several regenerative medicine approaches are ECM-based and some include the use of processed whole tissues such as decellularized stroma or human amniotic membrane where the intrinsic mechanical and functional properties of the matrix can be exploited to promote tissue regrowth. Other strategies employ ECM-derived biopolymers from mammalian and other sources including collagen, fibrin, chitin and chitosan, taking advantage of the dynamic, flexible nature of these scaffolds in directing cellular engineering of skin, cartilage, bone and nerve[126]. As a next step, bio-interactive implants comprising polymers coated with ECM proteins such as laminin, fibronectin, collagen or with grafted or tethered cell adhesive peptides have been proposed[127].

Overcoming the host immune/inflammatory response remains a significant challenge to the long-term success of ECM-based implants. Most of this work

Table 2 Dendritic cell interactions with extracellular matrix components

Class of component	ECM component	DC responses	DC receptors	Overall impact
Collagen	Soluble collagen Ⅰ [74]	Murine BMDC upregulated CD86, IL-12, antigen uptake	DDR2	Pro-inflammatory
	Soluble collagen Ⅰ [75]	Human MDDC increased IL-12p40, TNF-α, IFN-γ	DDR2	Pro-inflammatory
	Adsorbed collagen Ⅰ, Ⅱ, Ⅲ[76]	Human MDDC increased maturation markers, pro-inflammatory cytokines, allostimulation	OSCAR	Pro-inflammatory
	Dermal hydrogel (laminin β3, collagen Ⅳ, Ⅶ)[77]	Decreased width of granulation tissue	-	Skin regeneration, anti-infl.
	Adsorbed fibronectin, collagen Ⅰ, gelatin, Matrigel[78]	Murine myeloid DC on Matrigel were less mature (maturation marker, cytokines, morphology)	Adhesion complexes (CD29, CD49a-f, CD41, CD51, CD61)	Differential effects – Matrigel less inflammatory *vs* collagen Ⅰ
	Collagen-like motifs in complement C1q[124]	Inhibits MDDC differentiation, TLR activity of pDC	LAIR-1	Anti-inflammatory
Glycoproteins	Pre-adsorbed laminin, fibronectin[79]	Human MDDC remained immature (maturation marker, high endocytosis)	Mannose receptor, DC-SIGN	Anti-inflammatory
	Modified Arg-Gly-Asp (RGD) on fibrillin[80]	Murine pDC adherence, TGB-β secretion increased in systemic sclerosis model	Integrins	Pro-fibrotic
Proteoglycans	Heparan sulfate[113,119]	DC maturation increased (morphology, costimulatory factors, T cell stimulation)	TLR4	Pro-inflammatory
		In GVHD blocking HS with alpha-1-antitrypsin limited alloreactive T cells	-	Pro-inflammatory
	Chondroitin sulfate[121]	Impact immunity in CNS pathologies	-	Pro- and anti-inflammatory
	DAMPs[111-113,117,118]	Activate DC	TLRs	Pro-infl.
Non-proteoglycan polysaccharides	Hyaluronan[82]	Increased hylauronan corresponds to decreased murine DC activation	-	Anti-inflammatory (tumours)
	Natural polymer hyaluronic acid[129,130]	Decreased DC maturation (maturation markers, cytokines, allostimulation)	-	Anti-inflammatory
Modulators	Secreted protein acidic and rich in cysteine[88]	Organization of germinal centres in LNs for T_H17 by follicular DC	-	-
	Thrombospondin-1[89]	DC-derived thrombospondin inhibits resolution of inflammation	CD47, CD36	Anti-inflammatory
Enzymes	Matrix metalloproteinases[90]	Endogenous MMP-2 prime DC to T_H2 (IL-12p70)	-	T_H2 profile
	Tissue transglutaminases[151]	Influence DC activation (concentration-dependant)	-	Pro- and anti-inflammatory
Glycosylation modifications	Gut mucous[107]	Decrease in DC activation by inhibition of NF-κB	Dectin-1, galectin-3	Anti-inflammatory
	Tissue matrix in skin thymus, trachea[109]	Steady state homeostasis	$MGL1^+$ $MGL2^+$	Anti-inflammatory

DC: Dendritic cell; ECM: Extracellular matrix; OSCAR: Osteoclast-associated receptor; DDR: Discoidin domain receptors; IL: Interleukin-4; TNF-α: Tumour necrosis factor-α; IFN-γ: Interferon-γ; LAIR-1: Leukocyte-associated Ig-like receptor 1; TLR: Toll-like receptor; MGL: Macrophage galactose/N-acetylgalactosamine-specific C-type lectin.

addresses the effect of various biomaterials on the inflammatory response and particularly macrophage behaviour and its effects on the ECM. However, little work has been done on how biomaterials affect DC behaviour and function. Information is needed in this area since biomaterials may not only act as allo and xenoantigens but can directly behave like DAMPS (see Introduction) and thereby promote autoimmune responses through host tissue damage. Since tissue *via* the ECM tightly regulate DC homeostasis and inflammation, this directly impinges on how artificial matrices affect DC behaviour and hence the balance between immunogenicity and tolerance. Artificial stroma and their components may activate or suppress DCs, induce DC differentiation, promote or inhibit fibrosis or change DC interactions with other cells, *e.g.*, other inflammatory cells or activate the adaptive immune response *e.g.* as an "autoimmune" response when human altered matrices are implanted in humans (or mouse into mouse, *etc.*). Studies have compared the individual effects of natural polymers on DC responses. Human monocytes differentiated to DCs in the presence of the natural, biocompatible polymer chitosan, a polysaccharide derived from the exoskeleton of crustaceans or cell walls of fungi, were activated to a pro-inflammatory state (higher CD86, TNF-α, IL-

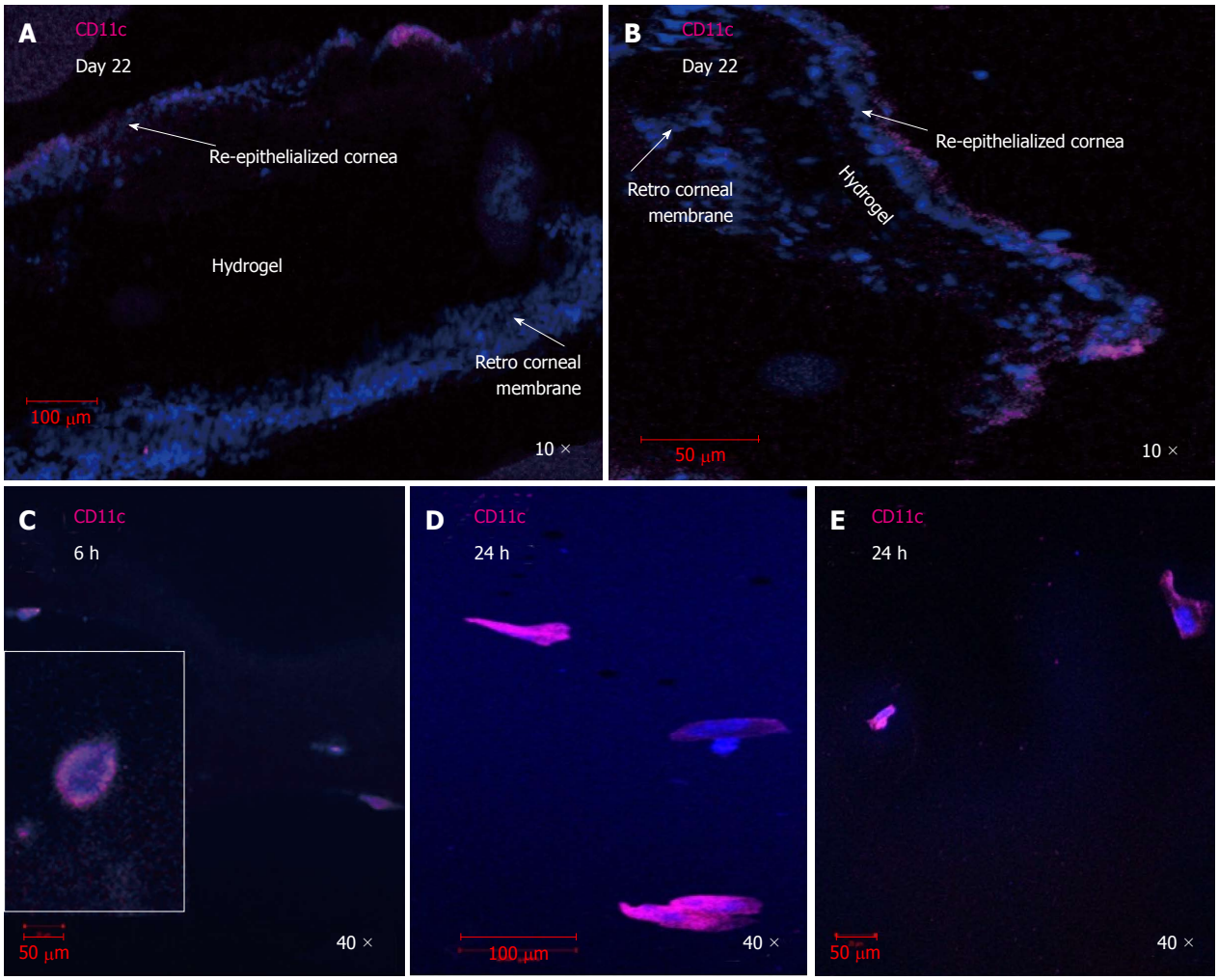
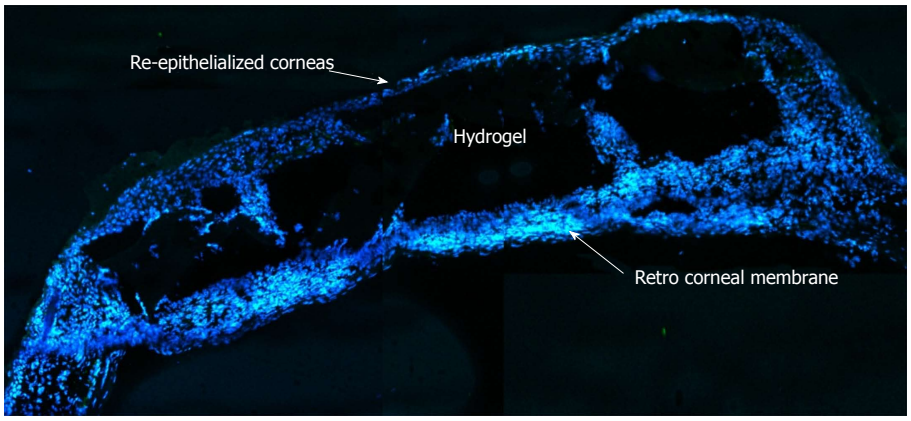


Figure 4 CD11c$^+$ dendritic cells are involved in the host response to transplanted hydrogels. CD11c$^+$ DC were detected in re-epithelialized layers surrounding RHCIII hydrogels transplanted in murine corneas, 22 d post transplantation (A, B). CD11c$^+$ dendritic cells infiltrated hydrogels transplanted into murine corneas as early as 6 h (C) or 24 h (D, E) after transplantation and showed a transformation in morphology from rounded immature DC to well-differentiated DC at the latter time point after interacting with the three dimensional crosslinked collagen matrix. Images were taken within the hydrogel in (C-E) as shown in the schematic. DAPI: Nuclear staining shown in blue; CD11c in magenta; DC: Dendritic cell.

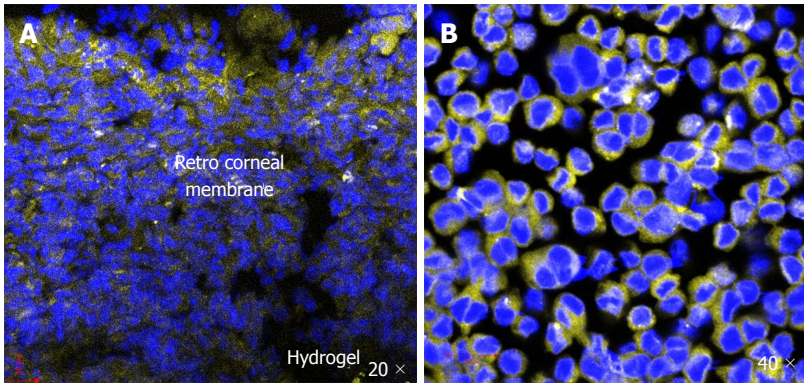
1β and lower IL-10 levels)[128]. Also, it was observed that while alginate and hyaluronic acid were less maturing to DCs, the opposite effect was observed with chitosan or agarose[129,130], implying that specific ECM mimetics can have applications in vaccine delivery or in tissue engineering whether host immune responses are desired or not, as suggested in[129]. Surprisingly, regenerative medicine approaches to reconstruct heart valves using xenogeneic porcine or bovine collagen and elastin, did not induce human DC maturation (low CD83 expression and TNF-α secretion)[131]. Hydrogels fabricated from lyophilized constituents of porcine dermal ECM were coated onto polypropylene meshes as a means of reducing the inflammatory responses associated with these non-biodegradable materials. The presence of ECM hydrogels facilitated decreased recruitment of CD86$^+$ CD68$^+$ M1 macrophages by day 14 post implantation in rats and decreased collagen type Ⅰ deposition related to wound healing responses[132]. HA was electrospun into nanofibers to assist the adherence and survival of NIH-3T3 fibroblasts to mimic ECM properties to support cell adhesion[133].

ECM-based scaffolds have been developed to boost tissue repair and reconstruction. Since collagen is a major ECM component in most tissues, different strategies have been employed to generate three dimensional fibrillary collagen matrices, including plastic compression of hydrated polymerized collagen and fluid expulsion, using contractile properties of activated fibroblasts, as discussed in[134]. Regenerative biomaterial scaffolds composed of clinical grade recombinant human collagen hydrogels crosslinked with water soluble carbodiimides have been fabricated to mimic the type Ⅰ and Ⅲ collagens predominantly present in natural corneas that are crosslinked with glycosaminoglycans[135]. These ECM mimetics are cell free, chemically well characterized, resistant to biodegradation and mimic natural corneas in terms of optical and mechanical properties of corneas. They retained optical clarity in partial[136] or full-thickness[137] corneal transplants in animal models



Day 22 post transplantation
aSMA, DAPI, 10 ×

Figure 5 Merged images showing the formation of dense retro-corneal membrane separating corneal hydrogel from lens and posterior areas of eye, shown on day 22 after transplantation of murine corneas with RHCIII hydrogels. Newly generated membrane exhibits presence of alpha smooth muscle actin, likely produced by myofibroblasts recruited during the wound healing process. Tissue ingrowths into the RHCIII hydrogel are evidence of active remodelling of the artificial matrix scaffold by immune/inflammatory cells and ECM components, towards long-term integration with natural tissue. DAPI: Nuclear staining shown in blue; Alpha smooth muscle actin in green; ECM: Extracellular matrix.



Day 22 post transplantation
Tenascin C, DAPI

Figure 6 Murine corneas transplanted with RHCIII hydrogels stained positive for extracellular matrix constituent tenascin C in the retro-corneal membrane, a marker of epithelial to mesenchymal transition, indicative of active wound healing (A) and WEHI-164 murine fibrosarcoma cell line cultured with 5 ng/mL transforming growth factor-β1 for 48 h also produced tenascin C (positive control) (B). DAPI: Nuclear staining shown in blue; Tenascin C in yellow.

and promoted corneal cellular and nerve regrowth. ECM scaffolds have also been fabricated to elucidate mechanisms underlying cell-matrix interactions in physiologically relevant settings. DCs were recruited to murine corneas transplanted with RHCIII hydrogels and could be detected surrounding and within the artificial matrix, demonstrating their involvement in the host response (Figure 4)[138]. Also, RHCIII hydrogels implanted in murine corneas underwent remodelling by cellular and ECM components as part of the wound healing process (Figures 5 and 6)[138]. A three dimensional model composed of epithelial cells, fibroblasts generating ECM components such as tropoelastin, vimentin, collagen type Ⅳ and laminin and DCs was developed to recapture the complexity and architecture of DC interplay with lung tissue mucosa towards maintaining homeostasis[139]. Lung epithelial cells are no longer considered mere physical barricades against foreign allergens but key players in mediating DC responses and T_H2 responses as reviewed in this paper[140].

Three dimensional ECM mimetics have shown promise in the transition from bench to bedside. Notably, RHCIII scaffolds were employed as partial thickness corneal transplants in a 4-year clinical study in 10 patients and demonstrated minimal rejection, enhanced stability, epithelial, stromal cell and nerve regeneration (human allografts) (Figure 7)[141]. Remarkably, DCs were not recruited into transplanted RHCIII hydrogels but in contrast were present in donor human allografts[141]. In another study, bone substitute P-15 comprising bone mineral calcium phosphate and cell-interactive peptide of collagen type Ⅰ acted as a promising alternative to allografts in its ability to repair non-union fractures as exhibited in a pilot clinical study with 22 patients, an example of an ECM mimetic that has successfully reached the bedside[142]. A randomized clinical trial with 120 patients showed that natural tissues derived from

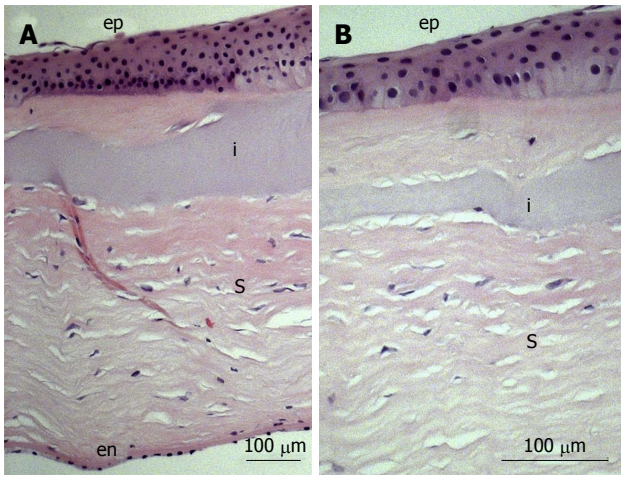


Figure 7 Immunohistochemistry image of biointeractive RHCIII hydrogel in a lamellar keratoplasty and removed after 4 years, upon regrafting of the patient. Notably, regrowth of characteristically stratified corneal epithelium (ep), layered stroma (s) and endothelial monolayer (en) left intact during transplantation, can be observed (A). A portion of the RHCIII implant (i) is visible in a higher magnification image (B), displaying a uniform assimilation with the native stroma in a dynamic, ongoing remodelling process. Reprinted from Fagerholm P, Lagali NS, Ong JA, Merrett K, Jackson WB, Polarek JW, Suuronen EJ, Liu Y, Brunette I, Griffith M. Stable corneal regeneration four years after implantation of a cell-free recombinant human collagen scaffold. *Biomaterials* 2014; 35: 2420-2427. Copyright (2014), with permission from Elsevier.

porcine small intestinal mucosa consisting mainly of collagen along with other macromolecules, active forms of basic fibroblast growth factor and TGF-β, enhanced healing[143]. While promising strides have been made, several challenges remain including gaining successful integration of scaffolds into host, retaining long-term stability and functionality and obtaining immune acceptance. Exploiting our knowledge of DC-ECM interactions would be an important way forward.

CONCLUSION

We have reviewed the body of evidence describing interactions between DCs and the ECM and the constantly changing role of the latter in directing DC responses in normal conditions *vs* in inflammation. These mechanisms may be active or reactive. While they offer us a glimpse of the numerous ways that the ECM restrains DCs to play very precise, context-dependant roles, there are probably many more aspects as yet undiscovered. It is possible that the decisions made by individual tissues in allowing DC to enter and reside in them or not and how and why this changes when the tissue is under attack will offer important insights into optimal design of artificial stroma.

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