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Current Opinion in Immunology

Extracellular matrix and the maintenance and loss of peripheral immune tolerance in autoimmune insulitis

Carlos O Medina, Nadine Nagy and Paul L Bollyky

There is a growing appreciation that the extracellular matrix (ECM) contributes to both the maintenance of immune tolerance in healthy tissues and to its loss at sites of autoimmunity. Here, we review recent literature on the role of ECM and particularly the glycosaminoglycans hyaluronan and heparan sulfate in the development of autoimmune, type 1 diabetes (T1D). Data from transplant models suggest that healthy islets are embedded within an intact ECM that supports beta-cell homeostasis and provides physical and immunoregulatory barriers against immune infiltration. However, studies of human insulitis as well as the non-obese diabetic (NOD) and DORmO mouse models of T1D indicate that autoimmune insulitis is associated with the degradation of basement membrane structures, the catabolism of the islet interstitium, and the accumulation of a hyaluronan-rich, pro-inflammatory ECM. Moreover, in these models of autoimmune diabetes, either the pharmacologic inhibition of heparan sulfate catabolism, the reduction of hyaluronan synthesis, or the targeting of the pathways that sense these ECM changes can all prevent beta-cell destruction. Together these data support an emerging paradigm that in healthy islets the local ECM contributes to both immune tolerance and beta-cell homeostasis while in chronic inflammation the islet ECM is permissive to immune infiltration and beta-cell destruction. Therapies that support ECM-mediated 'barrier tolerance' may have potential as adjunctive agents in combination regimens designed to prevent or treat autoimmunity.

Address
Division of Infectious Diseases and Geographic Medicine, Dept. of Medicine, Stanford University School of Medicine, Beckman Center, 279 Campus Drive, Stanford, CA, 94305, United States

Corresponding author: Bollyky, Paul L (pbollyky@stanford.edu)

Current Opinion in Immunology 2018, **55**:22–30

This review comes from a themed issue on **Autoimmunity**

Edited by **Daniel Stetson**

https://doi.org/10.1016/j.coi.2018.09.006

Introduction

The extracellular matrix (ECM) surrounds cells and tissues throughout the human body and it has long been known that these structures contribute to local homeostasis and function. However, there is a growing appreciation that the ECM also provides barriers against immune infiltration in healthy tissues.

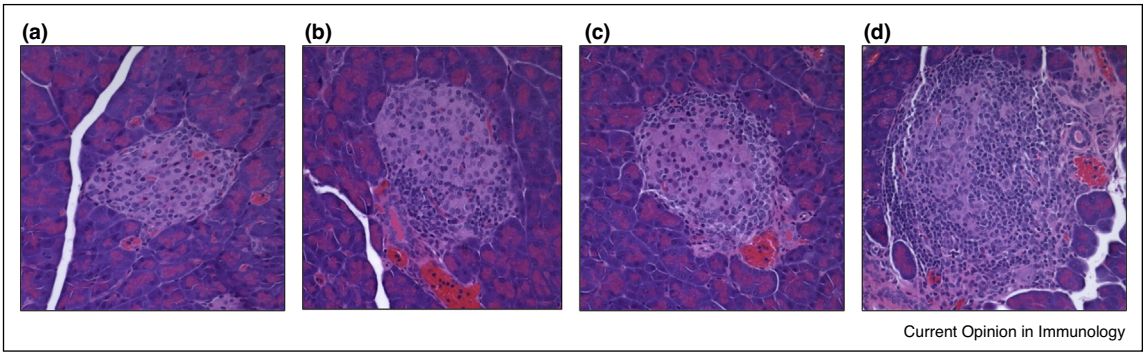
The contributions of the ECM to tissue homeostasis and peripheral tolerance are perhaps best understood for type 1 diabetes (T1D), an autoimmune disease characterized by lymphocyte-mediated destruction of insulin producing beta-cells within the pancreatic islets [1]. Most current models of the pathogenesis of T1D invoke the progressive, sequential loss of B-cell and T-cell tolerance to islet auto-antigens as well as a failure of immunoregulatory mechanisms that normally control potentially auto-reactive lymphocytes [1–3]. Alongside mechanisms of central and peripheral tolerance that are presumably interrupted in this progression, there are suggestions that tissues may themselves provide barriers against immune-mediated destruction and that these are likewise lost in T1D. This can be inferred from histologic data from human T1D [4] as well as experimental models of the disease, including the Non-Obese Diabetic (NOD) [5] and DORmO mouse models (Figure 1).

Here, we review recent literature on the role of ECM and particularly the glycosaminoglycans hyaluronan (HA) and heparan sulfate (HS) in the development of T1D. We first briefly review what is known about the ECM in healthy islets as well as data suggesting that it supports beta-cell homeostasis as well as providing physical and immunoregulatory barriers against immune infiltration. Next we review studies indicating that autoimmune insulitis is associated with the degradation of basement membrane structures, the catabolism of the islet interstitium, and the accumulation of a HA-rich, pro-inflammatory matrix and that these changes are permissive to immune infiltration and beta-cell destruction. Finally we propose that agents that support ECM integrity may have therapeutic potential for prevention or possibly treatment of T1D.

The ECM in healthy pancreatic islets

In pancreatic islets, as in all tissues, cells exist within an ECM – a complex network of proteins, polysaccharides, and proteoglycans that constitute basement membrane (BM) and interstitial matrix structures. The detailed biochemistry and histologic distribution of islet ECM components are the subjects of several excellent recent studies and reviews [6,7•,8].

Figure 1



Autoimmune insulitis in the DORmO mouse model of T1D is associated with the progressive, sequential loss of local tissue barriers against autoimmunity.
H&E staining of islets from DORmO mice at various ages and stages of progressive insulitis: **(a)** no infiltration (3–4 weeks of age), **(b)** peri-insulitis (4–5 weeks), **(c)** insulitis (8 weeks), and **(d)** islet destruction (12 weeks).

In brief, the BM that surrounds capillaries and encases each islet mostly comprises tightly interconnected networks of type IV collagen and laminin. These are interwoven with lesser amounts of heparan sulfate proteoglycans (HSPGs) such as perlecan, glycoproteins such as nidogens, and glycosaminoglycans such as HA [7•,8–10]. The islet BM differs somewhat between species, being continuous in mice and discontinuous in humans [11]. In contrast to the BM matrix, the islet interstitial matrix present within the islet stroma is more diffuse and mostly contains collagens I, II, and IV, and fibrillin-2 [10,12]. HSPGs are present as well, including HS polymers attached to the core proteins collagen type XVIII, versican, and syndecan-1 [8,13•].

Together these ECM components provide critical structure and support to islet-resident cells. In particular, transplant studies indicate that the islet ECM communicates chemical and mechanical signals that mediate key aspects of islet physiology including survival [14–18], differentiation [19–22], proliferation [23–25], and insulin secretion [14,15,23,26,27]. The ECM signals that support these cells are communicated in part via interactions between cell membrane receptors, such as integrins, and ECM polysaccharides and proteins, such as laminin, that contain the peptide signaling sequence arginine-glycine-aspartic acid (RGD) [28,29]. In addition to providing structural support, the interstitial ECM modulates cellular behavior via the binding of growth factors to sulfated glycosaminoglycans such as HS [30,31] and it has been suggested that this may contribute to beta-cell homeostasis [32]. Capitalizing on these insights, ECM platforms are increasingly utilized to support islet transplantation efforts [33•] as well as the development of stem-cell derived beta-cells [34•].

ECM catabolism and the loss of tissue integrity in autoimmune insulitis

In comparison to healthy islets, the ECM at sites of insulitis is altered in multiple ways. These include the loss of BM integrity, the catabolism of interstitial matrix, and the deposition of a pro-inflammatory matrix dominated by HA.

The transition between non-destructive peri-insulitis (Figure 1b) and destructive insulitis (Figure 1c) is accompanied by a breakdown in the islet BM, as demonstrated conclusively by Dr Lydia Sorokin and her colleagues. In particular, there is a loss of laminin and perlecan staining within the BM in both humans with T1D [10] as well as in the NOD [9,10] and DORmO mouse models of the disease (Figure 2). This catabolism occurs in association with increased expression of cathepsins S, W, and C, and heparanase [9,10,35]. In transplant studies, loss of islet BM integrity has major, adverse effects on islet function and viability [36•] while inhibition of BM degradation can preserve islet function [37]. Modeling studies suggest that the balance between degradation and repair of the BM may be a critical determinant in the progression to clinical diabetes [38•]. Perhaps consistent with the pathophysiology observed in T1D, disruption of the BM structures that maintain the blood-brain barrier is likewise seen in Multiple Sclerosis (MS) and in the experimental autoimmune encephalitis (EAE) model of that disease [39,40]. Together, these data suggest that the islet BM functions as a physical barrier against leucocyte migration into islets and that degradation of this barrier is a critical step in progression to diabetes (Figure 3).

The subsequent infiltration of leukocytes into the islet stroma (Figure 1c) is also associated with the catabolism of the interstitial matrix, in particular the loss of HS content, as demonstrated in beautiful work by Dr Charmaine Simeonovic and her colleagues. They demonstrated that intra-islet HS is lost in both NOD mice [35] as well as in humans with T1D [13•] in association with expression of heparanase by leukocytes [41]. We observe similar findings in DORmO mice (Figure 2). This catabolism of HS has been reported to contribute to local