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Cross talk between the extracellular matrix and the immune system in the context of endocrine pancreatic islet transplantation. A review article

Interactions entre la matrice extracellulaire et le système immunitaire dans le contexte de la transplantation d'îlots pancréatiques endocriniens. Une revue de la littérature

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ABSTRACT

This review aims to highlight the importance of the bidirectional influence of the extracellular matrix (ECM) and immune cells in the context of type 1 diabetes mellitus (T1DM) and endocrine pancreatic islet transplantation. We introduced the main classes of molecules and proteins constituting the ECM as well as cells and cytokines of the immune system with the aim to further examine their roles in T1DM and islet transplantation. Integrins expressed by immune cells and their functions are detailed. Finally, this article reviews the roles of the ECM and the immune system in islet transplantation as well as ECM-related cytokines and their influence on the ECM and immune cells.

RÉSUMÉ

Cette revue de la littérature a pour but de mettre en évidence l'importance des interactions bidirectionnelles de la matrice extracellulaire (MEC) et des cellules du système immunitaire dans le contexte du diabète de type 1 (DT1) et de la transplantation d'îlots pancréatiques endocriniens. Nous faisons un survol des grandes classes de molécules qui composent la MEC ainsi que les protéines, cellules et cytokines impliquées dans le système immunitaire. Cet article examine aussi les rôles de la MEC et du système immunitaire dans la transplantation d'îlots pancréatiques et plus particulièrement les effets des intégrines exprimées par les cellules du système immunitaire et leurs fonctions. Finalement, les cytokines liées à la MEC et leur influence sur les cellules immunitaires et la MEC sont abordées.

1. Abbreviations

APC	antigen-presenting cells
bFGF	basic fibroblast growth factor
BM	basement membrane
DC	dendritic cells
ECM	extracellular matrix
FN	fibronectin
GAG	glycosaminoglycans
IBMIR	instant blood-mediated inflammatory reaction
IFN	interferon

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IL	interleukin
LFA	leukocyte function-associated antigen
LPS	lipopolysaccharides
MHC	major histocompatibility complex
MMP	matrix metalloproteinase
NK	natural killer cells
RGD	Arg-Gly-Asp
T1DM	type 1 diabetes mellitus
TGF	transforming/tumor growth factor
TNF	tumor necrosis factor
VCAM	vascular cell adhesion molecule

2. Introduction

The extracellular matrix (ECM) was long considered to be solely the non-cellular connective tissue and served mainly as mechanical support for the surrounding cells. Now it is known that apart from a structural support, the ECM is fulfilling functions, such as tissue segregation, regulation of intercellular communication, storage and activation of growth factors and cytokines, as well as mediation of cell development, growth, survival, adhesion and migration [1]. The immune system was long believed to act on its own but it emerges now that interactions with other cells, integrins, growth factors, cytokines and the ECM play a pivotal role in immune cell development, maturation, and function [2]. In this review, the specific role of the ECM in the immune system is investigated. A highlight will be set on type 1 diabetes mellitus (T1DM) and pancreatic islet transplantation.

3. The extracellular matrix

There are two major categories of ECM, the basement membrane (BM) and the interstitial or stromal ECM. The BM is a thin layer, between 50- and 100-nm thick, of a specialized ECM made up of collagen, laminin, and fibrillin (microfibrils), separating the epithelial or endothelial tissue from the connective tissue. Besides providing a structural support to cells, the BM modifies the cellular behavior via outside-in signalling. The structure, composition, and function of the BM is organ-specific [3].

The interstitial or stromal ECM is a tissue of high complexity and variety. It constitutes a network of many proteins and polysaccharides. Those are secreted by local cells and stay closely associated to the surface of those cells that produced them. After secretion, the ECM proteins and polysaccharides are assembled into a highly organized meshwork [4]. There is a great diversity in ECM organization and different types of matrix proteins and polysaccharides. This diversity results in different types of ECM, each formed depending on the function of the particular tissue e.g., hard, mineralized structures for bone or teeth, soft ECM in internal organs, transparent layers in the cornea, and strung ECM in tendons [4].

3.1. ECM components

The two main classes of extracellular macromolecules that make up the matrix are namely:

- polysaccharide chains of glycosaminoglycans (GAGs), which are usually found covalently linked to proteins in the form of proteoglycans;
- fibrous proteins, including collagens, elastin, fibronectin (FN), and laminins.

Whereas proteoglycans constitute the basic substance of ECM by forming a gel-like hydrated network, the fibrous proteins embedded within provide the structural and functional cues for cells [4,5].

3.2. Glycosaminoglycans

GAGs are long, unbranched, mostly high molecular weight polysaccharides (also mucopolysaccharides) with a backbone of repeating disaccharide units incorporating an amino sugar and a uronic acid. There are two main types of GAGs, heparan sulphate and chondroitin sulphate. Proteoglycans occur when one or more GAGs are attached to a core protein at specific sites. Proteoglycans are found throughout the extracellular matrix and attached to the cell membrane. Chondroitin sulphate chains are mostly found on matrix proteoglycans (aggrecan) whereas membrane proteoglycans contain mostly heparan sulphate chains (syndecan, glypican) [6]. Proteoglycans form a gel-like ground substance of the connective tissue and fill most of the extracellular space because of their hydrophilic nature. Other functions are to interact with signalling molecules, to modulate ligand-receptor interactions, and to play a role in development, migration, and enzyme activity. Proteoglycans are furthermore involved in several signalling pathways, like TGFß, FGF, Hedgehog, etc. Additionally, proteoglycans form networks by linking to collagen fibres [7].

3.3. Collagens

Collagens represent the most abundant fibrous proteins in vertebrates, constituting 30% of the total body protein. To date, 28 types of collagens have been identified and described with the five most common types of collagens being collagen I (skin, tendon, vascular ligature, organs, bone), collagen II (main component of cartilage), collagen III (main component of reticular fibers, commonly found alongside collagen I), collagen IV (basal lamina) and collagen V (cell surfaces, hair and placenta) [8].

Ubiquitously expressed in all mammals, type I collagen is the most abundant type, constituting more than 90% of all collagens. It is one of the largest and most complex macromolecules. Some of the proposed functions of collagen I include mediation of cell adhesion, binding to other matrix molecules, interactions with tissue calcification factors, but also glycation. Glycation occurs when reducing sugars bind to protein, forming adducts. Those glycation products are believed to contribute to diabetes development and pathologies of aging [9].

3.4. Fibronectin

Another essential ECM molecule is the ubiquitously cell-mediated expressed glycoprotein fibronectin (FN), found in blood as soluble FN and in interstitial connective tissue as insoluble FN [10]. The dimeric protein, consisting of two nearly identical monomers linked by a pair of disulfide bonds, is organized into a fibrillar network through direct interactions with cell surface receptors called integrins [10–12]. FN plays a pivotal role during embryogenesis, guiding cell migration and adhesion. Being part of the ECM network, FN is essential for cell growth, attachment, migration, and development [11]. Soluble FN is also very important in wound healing, contributing to the initial blood clot formed at the site of injury together with fibrin [13]. FN can bind and interact with other ECM components, such as collagens and proteoglycans, especially heparin, and fibrin. Within the cell-binding domain of FN, a specific adhesion sequence called RGD is found [14]. RGD is a tripeptide composed of L-arginine, glycine, and L-aspartic acid (Arg-Gly-Asp). This sequence constitutes the best-known integrin-binding region in FN. Other integrin-binding minimal sequences can be found in the cell-binding domain of FN, such as LDV (Leu-Asp-Val), REDV (Arg-Glu-Asp-Val), IDAPS (Ile-Asp-Ala-Pro-Ser)