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Identifying novel therapeutic targets for diabetes through improved understanding of islet adhesion receptors

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Short title

Islet adhesion receptors

Key words

Diabetes, islets, extracellular matrix, integrins, cadherins, adhesion GPCRs

Abstract

Adhesion receptors are transmembrane proteins that mediate cell-cell and cell-matrix communications. In addition to their adhesive role in maintaining islet architecture, they are also important for promoting islet cell survival, proliferation and secretory function. Their capacity for improving β-cell mass and insulin secretion suggest that they may be suitable targets for pharmacological intervention, and their interactions with extracellular matrix proteins hold promise in improving islet transplantation outcomes. In this review, we have focused on integrins, cadherins and adhesion GPCRs, and highlight recent advances in their roles in islet function and discuss whether they could be targeted for diabetes therapy.

Highlights

- Adhesion receptors expressed by islets include integrins, cadherins and adhesion GPCRs.
- Endogenous ligands of adhesion receptors are mainly proteins of the extracellular matrix.
- Adhesion receptors are essential for maintaining islet architecture, survival and function.
- Islet adhesion receptors are unexplored targets for type 2 diabetes therapy and they also offer potential for optimising cell replacement therapy for type 1 diabetes.

Introduction

Islets of Langerhans are heterogeneous cell clusters in the pancreas, consisting mainly of insulin-secreting β-cells, glucagon-secreting α-cells and somatostatin-secreting δ-cells, and there are also minority endocrine cell types that express the peptides pancreatic polypeptide and ghrelin. These cells are arranged in compact three-dimensional clusters and they work synchronously to maintain euglycemia. Earlier observations in which isolated β-cells secreted less insulin than β-cells within intact islets point to the importance of intercellular contacts and cellular organisation in islet function [1]. Moreover, there are several reports that islets exposed to extracellular matrix (ECM) proteins exhibit increased survival and improved insulin secretion [2–5], which is suggestive of an important role for islet-matrix interactions in appropriate regulation of glucose homeostasis.

The ECM consists of a fibrous mesh that contains proteins such as collagens, elastins, fibronectins and laminins, which provide structural support to cells and facilitate cellular elasticity, motility and adhesion. These ECM proteins can regulate cellular function by interaction with families of cell surface adhesion receptors that include integrins, cadherins and adhesion G-protein-coupled receptors (GPCRs). Islets express members of these adhesion receptors, which allow them to sense signals from the ECM and the islet microenvironment (Figure 1). This is of potential therapeutic interest for diabetes since drugs targeting adhesion receptors are in current use or are undergoing clinical trials to treat diseases such as multiple sclerosis, inflammatory bowel disease, cancer and asthma (Table 1) [6]. However, despite the important roles that adhesion receptors play in islet function they have not yet been investigated as potential targets for diabetes therapy. This article reviews recently published data on islet adhesion receptors and considers the therapeutic implications for diabetes.

Diabetes epidemic: a case for additional therapeutic options

Diabetes is rapidly becoming a global epidemic, with a current incidence of 425 million people worldwide (International Diabetes Federation; URL: https://www.idf.org/). With the current trend of globalisation, physical inactivity, obesity and increased longevity, diabetes will continue to have

significant human and financial consequences for the foreseable future: the number of people affected is predicted to increase by 48% by 2045 (International Diabetes Federation; URL: https://www.idf.org/) and the global cost of diabetes is set to rise to $2.5 trillion by 2030 [7]. There are currently a range of drugs available to treat type 2 diabetes (T2D), which accounts for approximately 90% of all diabetes cases, but approximately 50% of younger T2D patients cannot achieve their glycaemic target with the available drugs despite a good history of adherence [8]. Potential T2D therapies targeting GPCRs such as GPR40 and GPR119 have largely had unsatisfactory outcomes in clinical trials [9], and there is still a pressing need to identify additional therapeutic targets that may be used for appropriate glucoregulation in T2D.

Islet adhesion receptors

Adhesion receptors are plasma membrane proteins consisting of a 'sticky' extracellular domain, a transmembrane component and a cytosolic terminal domain, and the adhesion receptor superfamily consists of integrins, cadherins, immunoglobulin-like cell adhesion molecules, selectins and the more recently described adhesion GPCRs (aGPCRs). Selectins are not included in this short review because they are not expressed by islets *per se*, but by infiltrating lymphocytes in type 1 diabetes (T1D) [10].

Defective communication between islet endocrine cells has deleterious consequences and contributes to the islet dysfunctions seen in T2D and neonatal diabetes mellitus [11, 12]. In addition, impaired islet function has been observed following deletion or inhibition of adhesion receptors. For example, reduced β1 integrin expression in islets results in impaired glucose tolerance and reductions in insulin secretion and islet mass [13], while inhibition of E-cadherin prevents the formation of pseudoislets, which are β-cell clusters that have been configured to resemble native islets and show improved insulin secretion compared to dispersed cells [14]. All adhesion receptors are involved in cell-cell or cell-ECM interactions. It is known that the ECM plays a key role in islet differentiation and maintenance of a mature phenotype, since ECM collagen gene deletion in mice leads to reduced islet mass and impaired glucose-induced insulin secretion [15]. Additional studies have established the importance of ECM in islet survival, insulin secretion and proliferation [16–18], and there is now a good understanding of the molecular receptors mediating these functions.

Integrins

Integrins are integral membrane glycoproteins that exist as heterodimers of α- and β-subunits, with at least 24 different heterodimers identified in mammals, formed from eighteen α- and eight β-subunits [19]. Integrins bind to a range of ECM components with varying affinity. Thus, α1β1, α2β1, and α10β1 preferentially bind to multiple collagen subunits, α5β1 binds to fibronectin, while α6β1 and β4 interact with laminins [4, 20, 21]. There are at least five integrin heterodimers in islets (Table 2), with rodent islets expressing α3, β1 and β4 integrin subunits [22], while human islets express α3, α5, αv, β1 and β5 subunits [23, 24]. Integrins have been implicated in β-cell processes such as differentiation, expansion, migration, survival and function [25–29] and they also participate in pancreas development by regulating morphogenesis, adhesion and migration of progenitor cells [25, 26, 28].

Integrin over-expression has been observed in the retina of people with long term diabetes [30], but there is currently no information on the expression pattern of integrins in islets from people with T2D. The multiplicity of integrin subunits and promiscuity in ligand binding has thus far confounded

attempts to translate the understanding of β-cell integrin-ECM interactions into novel therapeutic targets. In addition, integrin-based therapies for T2D would require integrin activation to optimise β-cell mass and function, which could have deleterious effects as some integrin family members are up-regulated in cancer where they promote invasion and progression of metastasis. Drugs that antagonise integrin function, mainly by inhibiting heterodimers consisting of α4, α5 and β1 subunits, have been used in clinical trials for the treatment of cancers (Table 1), suggesting that integrin-based agonist therapies for T2D would only be feasible if they could be targeted to non-α4/α5-β1 islet cell heterodimers. The observation that α3β1 integrins are abundantly expressed by islet cells [22] may provide some specificity, since this heterodimer is not currently targeted for cancer therapies.

Cadherins

Cadherins are calcium-dependent transmembrane glycoproteins that form adherens junctions between cells. Their extracellular N-terminal domain is used for homophilic adhesion by binding to cadherins on neighbouring cells and this is important in tissue morphogenesis. The intracellular domains of cadherins are linked to the actin cytoskeleton via α- and β-catenins [31], indicating that they can also initiate signalling rather than simply functioning to form stable adhesive complexes. The expression of some members of the classical cadherin subfamily such as epithelial (E-) and neural (N-) cadherins has been reported in human islets, whereas placental (P-) cadherin expression has not been detected [32]. N-cadherin is reported to be preferentially expressed by islet β-cells while E-cadherin is expressed at similar levels by α- and β-cells [32].

Cadherins play important roles in regulating islet structure and function. Thus, E-cadherin is necessary for the proper three-dimensional configuration of islets, and in the clustering of β-cells to form pseudoislets [14, 33] and it also influences various islet functions such as proliferation, survival and insulin secretion [34, 35]. Disruption of islet architecture by dispersal into single cells leads to poor secretory outcomes and increased apoptosis, but association of islet cells with E- and N-cadherins reduces apoptosis in isolated human β-cells [32]. The specific involvement of E- and N-cadherins in promoting insulin secretion from human β-cells was demonstrated using recombinant E- and N-cadherin peptides fused with Fc immunoglobulin to mimic the homophilic adhesion of cadherins that occurs in vivo [36].

Other adhesion receptors belonging to the immunoglobulin-like cell adhesion molecules, such as N-CAM, have also been implicated in islet function. Deletion of N-CAM in mice impairs glucose tolerance and reduces insulin secretion as a result of defective F-actin reorganisation [37]. Connexin 36, ephrin-As and their EphA receptor tyrosine kinases are also involved in islet cell-cell interactions, where they allow rapid electrical coupling and intercellular connectivity [38–40].

The therapeutic potential of cadherins is evident from the recent proposal that drugs targeting E-cadherin re-expression may be useful in diagnosing and treating cancer [41] (Table 1). Thus, developments in cancer pharmacotherapy may be beneficial in the search for new treatments for diabetes, but a tractable cadherin target that would be clinically viable as a therapy for T2D has not yet been identified.

Adhesion GPCRs

Adhesion GPCRs (aGPCRs) are the second largest group of the GPCR superfamily, with 33 human members identified to date [42]. Unlike the classical GPCRs, aGPCRs have complex structural features: they possess an unusually long extracellular N-terminal domain that is joined non-covalently with the seven-transmembrane C-terminal domain at a GPCR proteolytic site (GPS) within the evolutionarily conserved GPCR autoproteolysis-inducing (GAIN) domain (Figure 1). They are the least studied class of the GPCR family, despite the important roles they play in many physiological processes [42].

Mouse and human islets express approximately 60% of all known aGPCRs [43, 44] and recent advances are beginning to shed light on the biological roles of aGPCRs in islets and glucose homeostasis. The first evidence linking aGPCRs to metabolic function was provided by studies in which adipose tissue-specific deletion of GPR116 led to insulin resistance and glucose intolerance [45] while the absence of Celsr2/3 resulted in mice with severe deficiency in β-cell differentiation and glucose intolerance [46]. Another interesting member of the aGPCR family is GPR56. It is the most abundant islet GPCR [44], and it is expressed exclusively by the β-cells in islets [5]. Activation of islet GPR56 by its endogenous ligand, collagen III, has beneficial effects, including potentiation of glucose-stimulated insulin secretion and protection of islets against the deleterious effects of inflammation that occur in diabetes [5, 47]. Moreover, a recent study has shown that pre-treating human islets with mesenchymal stromal cell-derived ECM, which is rich in the GPR56 agonist collagen III, led to enhanced insulin output [2]. These observations, and others indicating improved islet function elicited by collagen and laminin ECM components, have led to the proposal that exposure of human islets to ECM molecules may improve the outcomes of islet transplantation therapy [48].

The unique structural features of the aGPCRs present excellent opportunities for therapeutic targeting. They usually contain an extracellular tethered agonist-containing ‘stachel’ sequence buried within the GAIN domain that becomes exposed upon ligand binding or detachment of the extracellular domain segment, and this activates downstream signalling. Synthetic peptides that mimic the stachel sequence have been shown to directly activate a range of aGPCRs including GPR56, GPR64, GPR110, GPR114, GPR133, GPR126 and latrophilin [49–52], but the similarity of aGPCR stachel sequences may result in agonist promiscuity that limits the ability to specifically target particular aGPCRs [53]. However, receptor activation and signalling varies between different aGPCRs [54], suggesting that specific pathways can be selectively targeted by biased ligands. Thus, the possibility of using synthetic peptides to activate desirable pathways downstream of adhesion receptors offers a promising prospect for drug development, which may be applicable for treating T2D.

Conclusions

There is a large body of evidence demonstrating that signalling via integrin, cadherin and aGPCR adhesion receptors has beneficial effects on islet function and these receptors might serve as novel targets for T2D therapy. However, unless specificity can be assured increased islet integrin signalling is unlikely to be an appropriate therapeutic strategy since integrins are involved in tumorigenesis. E-cadherin may be a suitable candidate for therapeutic intervention given its positive effects on islet function and the recent interest in development of drugs increasing expression of this cadherin for cancer treatment, but little progress has been made in further elucidating the role of E-cadherin in

islets in the past few years. The most promising adhesion receptor candidates for treating T2D are likely to be the aGPCRs since GPCRs are the targets of more than one-third of all prescription drugs in use, with GLP-1 receptor agonists being one of the most recent T2D therapies to be introduced. However, to date there have not been any clinical trials of aGPCR ligands. This apparent neglect might be a consequence of the majority of aGPCRs being orphans, and progress in this area is likely to be contingent on identification of the endogenous ligands.

In addition to providing potential targets for T2D drug development, islet adhesion receptors offer translational potential in islet transplantation therapy for T1D. For example, the loss of functional viability reported after islet isolation could be reduced by incubating isolated islets with agonists of islet adhesion receptors prior to transplantation. Islet transplantation outcomes could also be improved by co-delivery of ECM-derived products or other agonists of islet adhesion receptors to improve islet survival and function.

In summary, studies on the applicability of islet adhesion receptors as therapeutic entities are at a relatively early stage and much work is still required to identify the most appropriate receptor, activating ligand(s) and selectivity of effect before there is a prospect of clinical trials.

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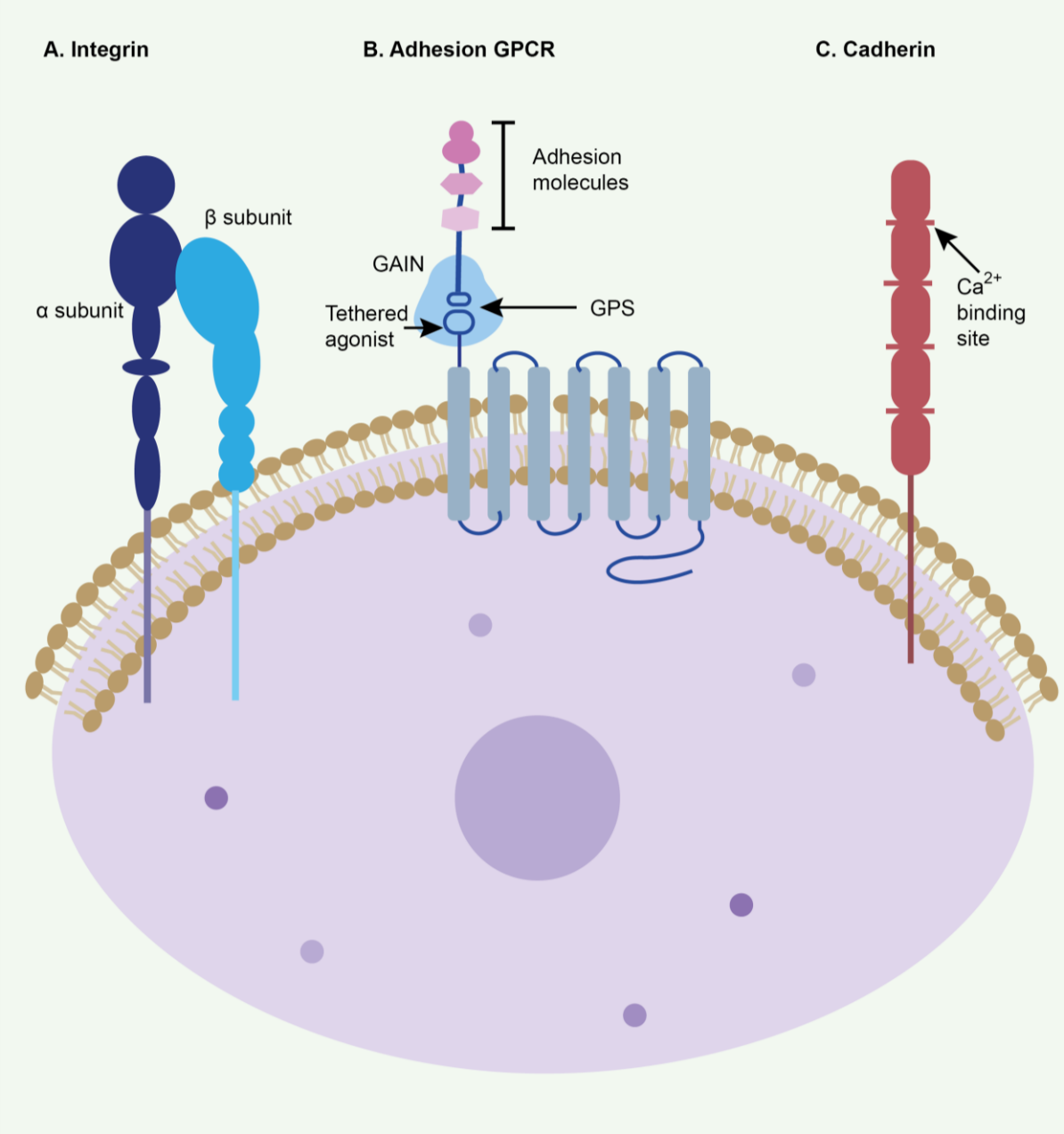

Figure 1: Islet adhesion receptors.

A) Integrins are transmembrane heterodimers composed of α and β-subunits. They provide adhesion through interaction of the extracellular domains with ECM molecules and they also recruit intracellular proteins that mediate cell signalling via their short cytoplasmic domains.
B) Adhesion GPCRs have adhesion molecules on their extracellular domain, which is joined non-covalently to the seven-transmembrane segment at the GPCR proteolytic site (GPS) within the GPCR autoproteolysis-inducing (GAIN) domain. Removal of the extracellular segment above the GPS exposes the embedded tethered agonist, which elicits downstream signalling.
C) Cadherins consist of five-extracellular repeats containing Ca^{2+} binding sites that enable them to participate in homophilic adhesion. The small cytoplasmic segment of cadherins regulates interaction with the actin cytoskeleton and intracellular signalling via binding to catenin proteins.

Table 1 Adhesion receptors antagonists that have been used in clinical trials.
The table includes a non-exhaustive list of drugs developed by a range of pharmaceutical companies that target adhesion receptors for clinical use. It also includes information on the highest development phase of clinical testing for each drug, or whether the drug is in current clinical use. Information was obtained from clinicaltrials.gov.

Drug	Adhesion receptor	Disease targets	Clinical trials status	Company
Anti-Integrins				
PF-04605412	$\alpha_5\beta_1$	Advanced non-hematologic malignancies	Phase I	Pfizer
Volociximab	$\alpha_5\beta_1$	Renal cell carcinoma, age-related macular degeneration	Phase II	PDL Biopharma
MEDI-522	$\alpha_5\beta_3$	Rheumatoid arthritis, metastatic melanoma, prostate cancer	Phase II	MedImmune
Ro 27-2441	$\alpha_4\beta_1$	Asthma	Phase II	Roche
Natalizumab	$\alpha_4\beta_1$	Multiple sclerosis	Clinical use	Biogen
Vedolizumab	$\alpha_4\beta_7$	Ulcerative colitis, Crohn's disease	Clinical use	Millennium Pharmaceut.
Anti-cadherin				
ADH-1	N-cadherin	Neoplasm	Phase I	Adherex Tech

Table 2 A summary of adhesion receptors expressed by islets and their effects on islet function.
The table summarises the adhesion receptor family members that have been identified in islets and provides information, where available, on the native ligand(s), signalling pathways downstream of receptor activation and effects on islet function.

Adhesion receptor	**Expression by islets**	**Ligand/binding partners**	**Signalling pathways**	**Effect of receptor activation on islet functions**
Integrins	$\alpha_1\beta_1$	Collagen IV	FAK, ERK	↑ insulin secretion, islet architecture [55]
	$\alpha_3\beta_1$	Unknown	Unknown	Unknown
	$\alpha_5\beta_1$	Unknown	Unknown	Unknown
	$\alpha_v\beta_1$	Unknown	Unknown	Unknown
	$\alpha_6\beta_1$	Laminin-5	Unknown	↑ insulin secretion [4]
Cadherins	E-cadherin N-cadherin	Homophilic interactions	Catenins, F-actin	↓ β-cell apoptosis [32], ↑ insulin secretion [36]
Adhesion GPCRs	ADGRG1 (GPR56)	Collagen III, TG2	$G_{\alpha12/13}$, $G_{\alpha q}$	↑ insulin secretion, ↓ β-cell apoptosis [5, 47]
	ADGRF5 (GPR116)	Surfactant protein	$G_{\alpha q}$	Unknown
	ADGRG3 (GPR97)	Unknown	$G_{\alpha o,}$ RhoA	Unknown
	ADGRG6 (GPR126)	Collagen IV	$G_{\alpha s}$	Unknown
	ADGRL1 (LPHN1)	α-latrotoxin, neurexins and tenuerins	$G_{\alpha o}$	Unknown
	ADGRL2 (LPHN2)	Tenuerins	Unknown	Unknown
	ADGRL4 (ELTD1)	Unknown	Unknown	Unknown
	ADGRA3 (GPR125)	Unknown	Unknown	Unknown
	ADGRD1 (GPR133)	Unknown	$G_{\alpha s}$, cAMP	Unknown
	ADGRC2 (CELSR2)	Unknown	Ca^{2+}	Unknown
	ADGRC3 (CELSR3)	Unknown	Ca^{2+}	Unknown