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Cadherins in Islet β -Cells: More Than Meets the Eye



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In 1975, Orci et al. (1) reported that human islet cells contain specialized membrane domains that are compatible with the ultrastructural features of two types of intercellular junctions: tight junctions and gap junctions. Since then, numerous reports have demonstrated critical functions for these cell–cell junctional complexes in islet cells (2–8). Eventually, a number of proteins were identified that regulated cell aggregation, islet cell–type segregation, architectural organization within islets of Langerhans, and state of differentiation, cell growth, and hormone secretion (9–16). Hints that direct islet cell-to-islet cell interactions are required for proper insulin secretion were uncovered in the 1980s when it was observed that single (isolated) β -cells are unresponsive to glucose unless they are given the opportunity to reaggregate into small clusters (17). Even more interesting, it was observed that islet cell types harbor specific cell-to-cell recognition signatures that drive their reaggregation into organoids that have architectural organization indistinguishable from that of native islets (18). These earlier observations have inspired numerous investigations that have led to a more complete understanding of mechanisms regulating islet cell development, architectural organization, and function. In a time of considerable interest in the development of cell-based replacement therapies for diabetes, lessons learned over the past three decades on the function of cell adhesion molecules in islet cells harbor significant translational implications. Hence, promoting the function of select members of the cadherin and integrin families of adhesion receptors plays an important role in the derivation of β -cells from multipotent stem cells; in the isolation, culture, and survival of organ donor–derived islets; and in the successful engraftment and function following transplantation.

This article focuses on adhesion receptors of the cadherin superfamily (19,20), which were referred to as uvomorulin in early work by Kemler et al. (21). Over the past three decades, the function of cadherins in epithelia has evolved from simple cell–cell adhesion molecules that

populate subcellular domains called “adherens junctions” to biochemical transducers of signaling processes that contribute to the development, homeostasis, and function of multiple tissues (22–24). Interestingly, cadherins can also function as mechanosensors that affect cell phenotype and function in a dose-dependent manner (25,26). It appears that the transmission of forces from cellular domains occupied by E-cadherin to F-actin filaments is regulated by the intracellular recruitment and accumulation of a number of effector proteins at sites of cell–cell adhesion (27,28). As a result, cells that are in contact with each other through cadherin-mediated junctions sense tension forces that are directly proportional to the degree of actin-anchored cadherin adhesions. In turn, these forces elicit mechanosensory signals from cadherin complexes that ultimately impact on cell phenotype and function in multiple cell types (29,30), including pancreatic islets (31).

In this issue of *Diabetes*, Parnaud et al. (32) uncover direct involvement of E- and N-cadherin in the control of β -cell secretory function in response to glucose. The authors used an elegant approach in which recombinant E-, N-, or P-cadherin ectodomains fused to the Fc of immunoglobulin (E-cad/Fc, N-cad/Fc, or P-cad/Fc) were used for protein mimicry to support islet cell attachment (Fig. 1). This approach allowed them to emulate cadherin-mediated adhesions in single β -cells adherent to a substrate that presented high concentrations of recombinant E-cad/Fc, N-cad/Fc, or P-cad/Fc as if presented by another cell (Fig. 1). Insulin secretion was monitored using a powerful hemolytic plaque assay developed by Salomon and Meda in 1986 that allows probing of the secretion of single β -cells (33–35). This reductionist experimental environment showed a surprisingly close to normal insulin secretory behavior even in single-adherent β -cells.

Essential findings of the new report include the demonstration that cadherin-mediated adhesion in single β -cells, but not α -cells, is positively regulated by glucose and that it is associated with increased insulin secretion.

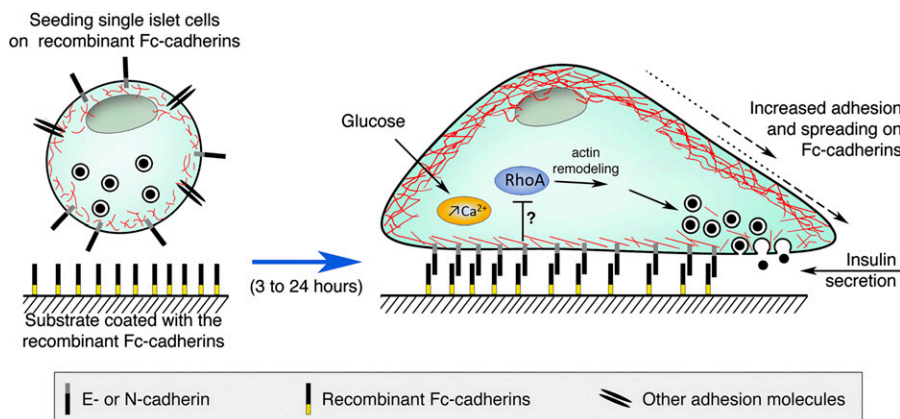


Figure 1—Islet β -cell adhesion to recombinant Fc-cadherins emulates cell-cell interactions and positively regulates glucose-dependent insulin secretion. Seeding of single islet cells on substrates precoated with either E-cad/Fc, N-cad/Fc, or P-cad/Fc (left) leads to cell attachment and spreading over a culture period of 3–24 h (right). Glucose stimulation results in an increased islet cell spreading and insulin secretion. Blockade of Rho-associated kinase further enhances β -cell attachment and spreading onto E-cad/Fc and N-cad/Fc, a phenotype that positively correlates with enhanced glucose-induced insulin secretion.

As glucose did not affect cadherin gene expression per se, a likely mechanism responsible for this glucose-dependent increase in β -cell adhesion and insulin secretion is the redistribution or reorganization of cortical actin. This has been previously shown to be crucial for proper insulin secretion (36–40). Although the authors let islet cells adhere to recombinant Fc-cadherins for up to 24 h in some experiments, the possible participation of integrin-mediated adhesion to the islet cell-deposited matrix during this short-term culture period, even if present (41,42), may have been minimal as function-blocking antibody treatment to cadherins obliterated the observed effects on adhesion and insulin secretion. This will need to be investigated further because it is possible that cooperation between cadherins and integrins may play a role in the regulation of islet cell polarity and function (43,44).

Collectively, the observation by Parnaud et al. that glucose-induced insulin secretion in individual β -cells can be directly linked to specific cadherin-cadherin ligation offers a new perspective on mechanisms regulating the complex secretory machinery of these endocrine cells. Surely, coupling of insulin secretion with cadherin-mediated cell adhesion is not coincidental or stochastic. Rather, it is likely that these two important processes have coevolved in β -cells to share common signaling mechanisms, one of them being calcium mobilization. Hence, calcium is not only required to elicit glucose-induced insulin secretion but also crucial for the stabilization of cadherin Ca^{2+} -binding ectodomains. Thus, functionally, it activates cell-to-cell adhesion. Finally, in line with the notion that inhibition of Rho-associated kinase, a major effector of RhoA, increases cadherin-mediated adhesion complexes (45), the authors noted that inhibitors of Rho-associated kinase caused a significant increase in β -cell adhesion to recombinant E-cad/Fc (Fig. 1). This observation further adds to a model in which the coordinated regulation and stabilization of cadherin-mediated adhesion complexes, in concert

with complementary extracellular signaling cues (46,47), are likely to occur in synergy during glucose-induced insulin secretion. Although the molecular mechanisms that drive glucose-induced enhancement of cadherin ligation and stabilization of adhesions remain to be further elucidated, the new study by Parnaud et al. (32) offers unique opportunities to further delve into the biology of cell-adhesion molecules as regulators of β -cell physiology. Results from this study also open exciting new prospects for the molecular engineering of biocompatible scaffolds that would support islet cell survival and function in islet transplantation settings. Hence, it is only a matter of time before we learn more from the β -cell and its microenvironment.

Acknowledgments. This article is dedicated to the memory of Dominique Guido Rouiller, who first demonstrated the expression and functional requirement of E-cadherin (also known as uvomorulin) in pancreatic islet cell aggregation.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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