Submitted for the Cell Transplant Society Congress 2009

The Anterior Chamber of the Eye Allows Studying Human Islet Cell Biology In Vivo

Alejandro Caicedo1, Rayner Rodriguez-Diaz1, R. Damaris Molano1, Camillo Ricordi1,2, Per-Olof Beggren1,2 and Antonello Pileggi1

1Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, FL, USA; 2Rolf Luft Research Center for Diabetes and Endocrinology, Karolinska Institutet, Stockholm, Sweden

The in vivo study of human islet cell biology relies mostly on cumbersome methods and generally islet cell function can only be inferred based on indirect measurements of plasma hormone concentrations. Unfortunately, functional imaging of islets in a living organism remains challenging, since non-invasive or minimally-invasive approaches to monitor islets at cellular resolution are not fully developed.

We have previously described that the anterior chamber of the eye (ACE) represents a valuable implantation site for the study of mouse islet structure and function in vivo. In the present study, we have extended the use of the ACE to study human islet cell biology in vivo. Human islets were transplanted into the ACE of streptozotocin-induced diabetic athymic nude mice. After transplantation of 500 islet equivalents per eye, recipient mice achieved and maintained normoglycemia for over 150 days. Tight control of plasma glucose concentrations by transplanted islets was observed during intraperitoneal glucose tolerance tests performed two months after implant. Longitudinal imaging of human islet revascularization was performed by confocal laser scanning microscopy following intravenous injection of fluorescein dextran. Islets were visualized with reflected light. Human islet neovascularization was completed within one month from implantation into the ACE. The time to diabetes reversal paralleled the progression of neovascularization.

In summary, our data indicates that human islets transplanted into the ACE of immunodeficient mice engraft and are fully functional, allowing to achieve tight metabolic control. The ACE acts as a natural window that allowing for real-time, repeated, noninvasive in vivo imaging of human islet cells in vivo. This can be performed on the very same islet(s) of individual animals multiple times during the follow-up period, which represents the uniqueness of this model when compared to other in vivo models.

While there is a wealth of information about the physiology of rodent and human islets in vitro, it is cumbersome to study islet cell biology in vivo; we can only infer their activity based on indirect measurements of plasma hormone concentrations. Unfortunately, functional imaging of islets in a living organism remains challenging, since non- or minimally-invasive technologies to monitor islet cell function are not fully developed. We have previously described that the anterior chamber of the eye (ACE) is a valuable implantation site to study mouse islet structure and function in vivo. In the present study, we have explored the value of this experimental platform to study human islet biology in vivo. We transplanted human islets into the ACE of streptozotocin-treated athymic nude mice. After transplantation of 500 islet equivalents per eye, animals achieved and maintained normoglycemia for over 150 days. Additionally, human islet grafts showed tight control of plasma glucose concentrations during intraperitoneal glucose tolerance tests performed two months after islet implant. Longitudinal imaging of human islet revascularization was performed by confocal laser scanning microscopy following intravenous injection of fluorescein dextran. Islets were visualized with reflected light. This allowed monitoring the progression of islet neovascularization that was completed within 30 days post-transplant. The time to diabetes reversal paralleled the progression of vascularization. Collectively, our results indicate that human islets transplanted into the ACE of immunodeficient mice engraft and are fully functional, allowing to achieve tight metabolic control. Importantly, the ACE acts as a natural window allowing for real-time, repeated, noninvasive in vivo imaging of human islet cells in vivo. This can be performed on the very same islet(s) of individual animals multiple times during the follow-up period, which represents the uniqueness of this model when compared to other in vivo models.