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Invited Commentary

Commentary on: Is the renal subcapsular space the preferred site for clinical porcine islet xenotransplantation? Review article (Int J Surg 2019 Jul 30;69:100-107. https://doi.org/10.1016/j.ijsu.2019.07.032. [Epub ahead of print])

Dear Editor,

In a recent issue of Int J Surgery, the group led by David Cooper at the University of Alabama, AL, together with Rita Bottino at the Institute of Cellular Therapeutics, Pittsburgh, PA, published a challenging review article advocating development of the renal subcapsular space as a site to implant islets, in treatment of diabetes [1]. This suggestion is based on the well-known disadvantages of administering islets by portal vein injection where they lodge along the liver sinusoids, which is presently most used in clinics. The review article presents the limited literature and thereafter compares the subcapsular space with the portal vein injection: addressing cellular/metabolic aspects, immune/inflammatory aspects, and mass transport/revascularization. Limited data gathered in the last decades do not allow an unequivocal conclusion: rather, these justify the recommendation to address the feasibility of the renal subcapsular space as site of xenogeneic islets in clinical transplantation.

The review is timely in view of progress in the field of xenotransplantation: first, clinical trials with porcine islets have been performed and are in progress, e.g., Ref. [2]. Noteworthy, a porcine islet product differs in many aspects from human islets, and this affects clinical application. At first this regards the quality: the review article mentions a higher purity in manufacturing porcine islets compared with human islets; also quality is much more consistent because of lower intra- and inter-product variation for porcine islets. Another feature regards the glucose-induced insulin production being lower for adult porcine islets than for human islets, and substantially lower for neonatal pig islets [3]. Hence, porcine islets differ from human islets regarding native metabolic function. The metabolic demand of the islet for oxygen and nutrients also differs: adult porcine islets are very susceptible to hypoxia, a major cause of islet failure. Neonatal islets are less sensitive to hypoxia.

Thus, in clinical development the site of administration for porcine islets is particular and separate from other cell therapies including human islets. A major advantage of porcine islets in respective studies is the availability of donors and low variability in quality of the manufactured product, enabling comparisons between sites in properly-sized studies. Important topics are not only graft survival and rejection, but even more, proper glucose-signaling at the site to stimulate graft insulin secretion and utilization. The anatomical environment of the transplant, i.e. the physiological compartment and metabolic function, is highly relevant for islet function and survival. Hence, efficacy outcome might not be diabetes reversal without need for exogenous insulin, but rather a basal stable insulin supply with a reduced need for exogenous insulin, reduced glycemic excursions, and a reduction in diabetes complications such as life-threatening hypoglycemia insults. In vivo studies with encapsulated islets, e.g. in the peritoneal cavity or omentum, increasingly demonstrate kinetic differences that demand novel functional assessments, one example being the so-called “transplant estimated function”. This is a composite functional parameter designed to overcome reliance on porcine C-peptide measures in the peripheral circulation, which alone may not accurately reflect the contribution of the graft [4].

Translational value of animal models is increasingly considered important, and this is evident for a feasibility comparison of administration sites (portal vein, renal subcapsule) for porcine islets. Models should be selected to mimic specific anatomical/physiological aspects of the intended site and the complexity of the clinical immune response [5].

In summary, this commentary is written to support the recommendation in the review article mentioned above to give attention to the renal subcapsular space as a potential administration site for adult or neonatal porcine xenogeneic islets in human diabetic patients, and to present some considerations in planning of nonclinical and clinical trials on the feasibility of this site. Such studies are of utmost importance since there is at present no preferred site that lacks the disadvantages identified thus far, either for islets that are not encapsulated (including devices) or for encapsulated islets.

Provenance and peer review

Invited commentary, internally reviewed.

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