The dark side of islet vasculature

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Abbreviations

ROS Reactive oxygen species
VEGF-A Vascular endothelial growth factor-A

Pancreatic islets are highly vascularised and contain about five times more capillaries than exocrine pancreatic tissue [1, 2]. In addition, the islets receive 5–15% of the entire pancreatic blood supply, even though they represent only 1–2% of the pancreatic mass [3]. Moreover, as determined by beta cell- or pancreas-specific deletion of vascular endothelial growth factor-A (VEGF-A), the islet microvasculature is required for normal insulin release and physiological blood glucose levels [4, 5], indicating that a dense islet vasculature is needed for proper islet function. In addition, VEGF-A is necessary for proper islet revascularisation following islet transplantation [5, 6].

Interestingly, Carlsson and colleagues recently suggested that there are two populations of islets within a healthy rodent pancreas: (1) a large islet population that is well blood-perfused and oxygenated, contains a dense vascular network and has a high beta cell proliferation rate and strong secretory function, and (2) a small population of islets representing

about 20–25% of all islets within a rat pancreas that are not well perfused or well oxygenated, contain only very few proliferating beta cells and have a low secretory function [7, 8]. The authors employ fluorescent microspheres that they inject into the arterial blood stream to discriminate between microsphere-containing, well-perfused islets and non-perfused islets harbouring no microspheres [9]. Importantly, the latter islets can be recruited on demand into the well-perfused and functional islet population, as evidenced by the conversion of all islets into well-perfused ones following partial pancreatectomy [7].

The correlation between vascular density and islet function can be partially explained by the fact that islet beta cells metabolise glucose almost exclusively via aerobic glycolysis, making them heavily dependent on a high and continuous supply of oxygen [10]. Moreover, the blood vessels within the islets also contribute to islet function by supplying paracrine factors, such as components of the vascular basement membrane or hepatocyte growth factor [11, 12].

In their present study, reported in this issue of *Diabetologia* [13], Ullsten and colleagues report that highly perfused islets are more susceptible to cell death induced by the inflammatory cytokines $\text{TNF}\alpha$, $\text{IFN}\gamma$ and $\text{IL-1}\beta$ or hypoxia in vitro. In addition, despite being better vascularised and oxygenated in the host, the highly perfused, microparticle-containing islets were found to be more prone to cell death and fibrosis. Therefore, the findings reveal for the first time the other side of the vascularisation coin: strongly vascularised islets seem to be more susceptible to cell death following islet transplantation. This finding could be explained by the highly perfused islets being more accessible to inflammatory cytokines and immune cells. Alternatively, or additionally, these islets are metabolically more active and therefore more prone to the induction of cell death. A high glycolytic flux in islets that are more metabolically active, in combination with the relatively limited capability of islet cells to remove reactive oxygen

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species (ROS), could lead to higher levels of ROS accumulation, oxidative stress and apoptosis—a situation that may be compounded by the effect of inflammatory cytokines. Finally, increased levels of protein biosynthesis (in particular of pro-insulin) in the metabolically more active islets may also be more prone to develop cytokine-mediated endoplasmic reticulum stress [14].

What is the relevance of these observations for islet transplantation? The current report did not address the question of whether the histopathological signs of islet damage were accompanied by decreased graft function and diminished potential for the normalisation of blood glucose values. Experiments in which perfused and non-perfused islets are transplanted into diabetic recipients could shed light on this aspect. However, previous studies have shown that islet vascularisation promotes normoglycaemia following islet transplantation [15, 16], suggesting that an enhanced islet vascular density outweighs the increased islet cell death and fibrosis observed in the highly vascularised islets reported here. An alternative, but less likely, explanation for the increased cell death in the highly perfused islet population might be the presence of microparticles that, in combination with other stress factors, induce beta cell death. In vivo, such particles could conceivably stimulate local inflammation and thus explain the observed islet damage in perfused islets.

Clearly, we are only at the beginning of this story. Many further steps need to be taken before we can fully appreciate the implications of these findings. Is the heterogeneity of islet perfusion and the size of the populations of both functionally ‘dormant’ islets with a low perfusion rate on the one hand and highly perfused, highly active and highly vulnerable islets on the other hand, anything that can be pharmacologically modulated? Are changes in the size or function of these populations directly related to abnormal glycaemic control in diabetes? More importantly, is the heterogeneity observed in rodents also present in the human pancreas?

Heterogeneity in the islet microvasculature has previously been described in rodents, with vascular differences associated with differences in islet size and localisation [1]. More recent studies have pointed to the large variation in islet cell composition between individual islets [17, 18], and to the different flow patterns observed in the islet vasculature [19].

If islets with the highest perfusion rate are also the islets that have the highest sensitivity to cytokines and hypoxia, as suggested by Ullsten and colleagues [13], this has many implications for our understanding of islet endocrine function, islet transplantation and islet pathology. Heterogeneity with regard to perfusion, function and sensitivity to cytotoxic conditions could conceivably help explain some of the histopathological observations that have until now had no clear explanation. In young recent-onset (<1 year) human type 1 diabetic patients, only a low fraction (<10%) of islets show a clear

inflammatory infiltration [20]. It would be of interest to investigate whether such inflamed islets correspond to the damage-prone, highly perfused islets described in the present study. The pancreases of the recent-onset diabetic patients also contain a substantial fraction (20–30%) of normal insulin-containing islets that show no insulinitis or other pathological islet changes [20]. Is it possible that such islets correspond to ‘dormant’ islets with low perfusion and low function, protecting them from autoimmune destruction? In this respect, the link between low perfusion and low islet function [8] is of interest as ‘dormant’ islets could explain the somewhat puzzling observation of large numbers of fully granulated beta cells in most recent-onset type 1 diabetic patients [20]. In the context of type 2 diabetes, it would be of interest to investigate whether the variable fraction of islets showing amyloidosis in elderly patients [21] represents the highly perfused islet subgroup.

The concept of functional heterogeneity of islets may also lead to new strategies for the treatment of type 1 diabetic patients if highly perfused islets turn out to be preferentially targeted during the progression of type 1 diabetes. In this case, therapies could be aimed at improving vascularisation/perfusion to (re)activate ‘dormant’ islets for improved glycaemic control. Similarly, in type 2 diabetic patients, the disease might be caused through an imbalance between the two islet populations, possibly with an excessive fraction of ‘dormant’ islets being responsible for a relative insulin deficiency.

As the authors point out, their observations in rodents may also have important implications for clinical islet transplantation programmes. One of the problems associated with human islet transplantation is that in many transplanted patients there is a gradual decrease of graft function with time post-transplantation, ultimately leading to graft failure. The degree of beta cell loss in the peri-transplant period may be critical, as it is estimated that the functional beta cell mass in transplanted patients is, on average, only 20–30% of that in normal age-matched controls [22]. In addition to the substantial beta cell loss that probably occurs immediately after transplantation as a result of an instant blood-mediated inflammatory reaction, the present observations in rodents suggest an additional risk, with the islets that are most metabolically active being preferentially destroyed after transplantation; if this also applies to human islets, such a destructive mechanism would further diminish the functional capacity of an already borderline beta cell mass.

Many of the possibilities discussed above are speculation, and more data on human islets are needed. Unfortunately, we know very little about islet perfusion and vascularisation in the human pancreas, as the number of studies on the intact human islet is extremely limited. Additional studies, possibly in the perfused human donor pancreas, should lead to a better insight into the heterogeneity of the human islet population

and the existence of islet subpopulations with different perfusion rates, vascular densities and endocrine functions.

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