COMMENTARY

Cellular Senescence, Target of Interest to Optimize the Success of Pancreatic Islet Transplantation

Karim Bouzakri[1,2], Allan Langlois[1*]

[1]Department of Diabetes and Therapeutics, European Center for Diabetes Research, Boulevard René Leriche, 67200 Strasbourg, France

[2]ILONOV, Boulevard René Leriche, 67200 Strasbourg, France

DESCRIPTION

Pancreatic islet transplantation is a therapeutic option that has great potential for treating Type 1 Diabetes (T1D). However, the number of people with T1D who can benefit from it is limited by the need for 2 or 3 pancreas to treat a patient. In a recent publication, we reviewed the limitations and challenges of successful islet transplantation [1]. Although this information was insightful, it would have been interesting to discuss senescence, a process that can affect the physiology and function of pancreatic islets [2].

Senescence, also known as cellular aging, is a physiological process that causes slow degradation of cell functions. Specifically, it is an irreversible cell cycle failure associated with morphological and functional changes in the cell that induce, for example, insulin resistance and dysfunction of pancreatic β-cells [3]. Indeed, it is well accepted that a deficiency of insulin secretion in response to glucose stimulation (GSIS) and the process of β-cell senescence are distinctive signs of diabetes [2]. In addition, aging accelerates the senescence of β-cells by generating premature cellular senescence [4]. This suggests that the donor's age criterion should be considered to increase the chances of successful transplantation. Currently, the pancreas is proposed as a priority for an islet transplantation when the donor is 50 years old or older, while younger donors are used instead for a pancreatic transplant. This could mean that most of the organs proposed for pancreatic islet transplantation may already be altered by natural mechanisms of aging. However, in a recent study, Imamura et al. did not identify correlation between the donor's age and the expression of any of the senescence genes, while the authors found a correlation between donor age and the insulin gene [5]. This shows that there is indeed an age effect to consider for islet transplantation, but these underlying mechanisms have yet to be elucidated. Interestingly, senescence is mainly mediated by elevated glucose levels and may be promoted by metabolic stress in pancreatic islets [6]. This information is important to consider for the success of the transplant because pancreatic islets are subjected to stress both during isolation and post-transplantation such as Endoplasmic Reticulum (ER) stress, inflammatory reactions, hypoxia, oxidative stress or implantation in a hyperglycemic environment [1]. Therefore, one of the challenges would be to slow down the senescence of pancreatic islets at each stage of the transplant procedure (during isolation and post-injection) and/or to act on the stressors that potentiate it. To this end, it seems important to improve our knowledge of its mechanisms involved in order to develop strategies that will limit this deleterious phenomenon for pancreatic islets.

Some senescence markers have been found in human islets, such as the cycline-dependent kinase inhibitor 2A (p16) and the cyclin-dependent kinase inhibitor 1A (p21). Thus, it was shown that an increase in p21 indicates the entry of cells into early senescence and is responsible for the increase in p16 expression. This will then allow the maintenance of cells in senescence. As a result, a panel of proteins associated with senescence will be secreted such as chemokines, IL6, IL8 and remodeling factors of the extracellular matrix. These factors are known to be able to induce cell dysfunction and to precipitate their entry into the senescence process. Thus, these ranges of proteins could constitute interesting ways of action to limit deleterious effect of senescence. Other markers of were identified such as β-galactosidase and glutaminase 1 which is essential for the survival of senescent cells [5]. Recently, Yang et al. demonstrated that the deletion of the mitochondrial pyruvate carboxylase (PC) enzyme in β-cells alters the GSIS and induces their senescence in mice model [2]. The authors also showed that PC controls β-cell senescence via the MDM2 axis (a negative p53 regulator)-p53. Moreover, Sajiir H et al, [7] demonstrated that pancreatic β-cell IL-22 receptor

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Correspondence Allan Langlois

Department of Diabetes and Therapeutics, European Center for Diabetes Research, Boulevard René Leriche, 67200 Strasbourg, France

E-mail a.langlois@ceed-diabete.org

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(highly expressed in the pancreas) deficiency induces age-dependent dysregulation of insulin biosynthesis and systemic glucose homeostasis. This suggests that a therapeutic approach targeting IL-22 receptor could protect pancreatic islets from age-related dysfunction. Indeed, studies demonstrated that IL-22 can suppress β-cell stress, reduce local islet inflammation, restore appropriate insulin production, reverse hyperglycemia, and ameliorate insulin resistance in preclinical models of diabetes [8]. In this way, Sajiir et al. have recently developed and tested in vivo, on a mouse model, short-acting IL-22-bispecific biologic drugs (specific to liver and pancreas) targeting IL-22 receptor A1. The authors showed that their approach allowed to restore glycemic control, reduce hepatic steatosis, inflammation and fibrogenesis [8]. Thus, this strategy seems very relevant to rise against the adverse effects of senescence and protect the functional mass of transplanted pancreatic islets. In addition, mTOR signalling pathway is suggested to play a role in the promotion and progression of senescence and organismal aging [9]. In particular, in vitro mTOR inhibition in mouse islet cells using low concentration of Rapamycin, entirely prevents the glucotoxicity-mediated increase of senescence markers such as the senescence associated β-galactosidase and the p16INK4a protein [6]. These data are very interesting because Rapamycin is used to reduce instant blood-mediated inflammatory reaction which occur in the first few days after islet transplantation. However, the dosage will have to be rigorously controlled because it has been shown that mTOR inhibition can induce β-cell toxicity [1]. Finally, it was proposed that Extracellular Vesicles (EVs) could be used as candidate treatment strategy to increase the success rate of islet transplantation as shown in Figure 1. Indeed, Fang et al. shown that EVs derived from mesenchymal stem cells cultured in hypoxia condition improve apoptosis and senescence of pancreatic β-cells by activating YTHDF1 mediated autophagy [10].

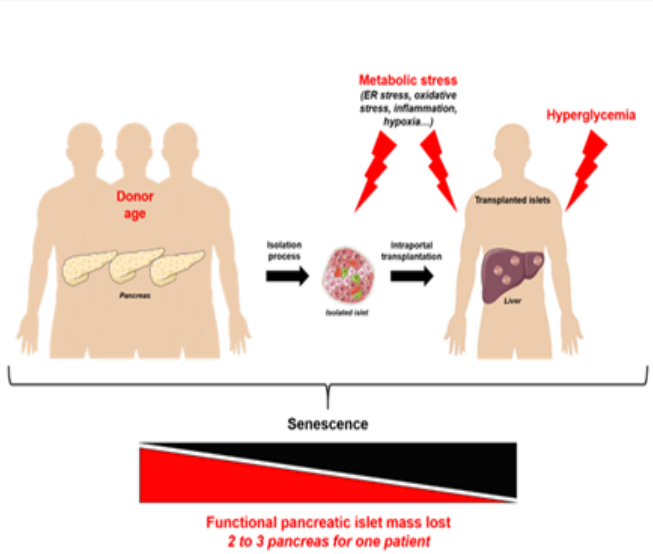

Figure 1. Senescence problem in successful pancreatic islet transplantation in a person living with T1D.

This case study demonstrates that a single session of OVT targeting the pancreas can effectively reduce cervical pain and improve CROM in patients with NS-NP of visceral origin. These findings support the potential of visceral manipulation in clinical practice, encouraging further research to elucidate the underlying mechanisms and broader applicability of this technique.

CONCLUSION

This review complements our previous work that aimed to present the limits and challenges to overcome to improve the success of the islet grafting. Through these few lines, we hope to show that it is also important to be interested in the issue of senescence and that this aging process is an interesting way of action to reduce the too high number of pancreas to be used to treat a single patient living with T1D.

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