International Journal of Pharmaceutics 521 (2017) 346–356

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Cell based therapeutics in type 1 diabetes mellitus

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ARTICLE INFO

Article history:
Received 7 February 2017
Received in revised form 21 February 2017
Accepted 22 February 2017
Available online 27 February 2017

Keywords:
Diabetes
Cells
Encapsulation
Immunoprotection
Gene therapy

ABSTRACT

This review focuses on Type 1 diabetes mellitus (T1DM) and the role of bioengineering, nanotechnology and cell therapy in its treatment. T1DM is discussed in terms of its prevalence as well as the role of the extra cellular matrix (ECM) of the pancreas in its development and mode of action. Surface engineering strategies and the chemistries behind important cell encapsulation techniques, which are emerging from recent research in immunosuppression, are described. Key enabling technologies such as therapeutic agent immobilization on cells, oxygen releasing systems, gene delivery and bio imaging are assessed with respect to T1DM. These latest cell surface technologies provide unlimited possibilities for control of cell/cell and cell/ECM interactions, allowing the ability to confer "immune camouflage". Finally, we provide an outlook to the future of cell-based technologies for T1DM treatment and their likely deployment in clinical trials.

1. Introduction

Since the discovery of insulin in 1921, type 1 diabetes mellitus (T1DM) has been effectively treated through the control of blood glucose levels. However, exogenous insulin replacement therapy, by multiple daily injections or by continuous subcutaneous insulin pump, still does not mimic the physiological pancreatic insulin secretion pattern, allowing the occurrence of life threating hypoglycaemic episodes leading to the occurrence of macro and microvascular complications, such as heart disease, retinopathy, neuropathy and nephropathy (Fig. 1). T1DM arises from loss of pancreatic β cells in response to an autoimmune reaction and this results in a state of absolute insulin deficiency (Watkins, 2003). It is estimated that 5% of all cases of diabetes are T1DM (Hilal-Dandan et al., 2014).The International Diabetes Federation (IDF) has estimated that the global prevalence of diabetes mellitus in 2015 is 8.8% with over 414.7 million people being affected with the disease. By 2040 this is expected to increase to 642 million people (IDF, 2015) due to increasingly unhealthy eating habits, sedentary lifestyles and obesity (Patterson et al., 2014).The estimated number of people with diabetes by the IDF region classification is presented in Table 1. The United States is the country with the highest number of children with diabetes (84,100 children) and Finland is the country with the highest number of new cases of T1DM in children (62.3 new cases per 100.000 population per year), see Table 2 for demographics. The susceptibility to T1DM (not the disease itself) is transmitted genetically through Human Leucocyte Antigen (HLA) genes (Atkinson and Eisenbarth, 2001). In addition to genetics, environmental factors such as viral infections, nutritional factors, vaccinations, toxins (N-nitroso derivatives), drugs, psychological stress, maternal and intrauterine factors, sunshine (vitamin D) and climatic influences are also sought to trigger T1DM (Tuomilehto, 2013).

Latest trends in T1DM treatment are shifting towards pancreatic beta cell replacement, in order to restore responsive insulin secretion to blood glucose variations. Beta cell replacement strategies include human whole pancreas or islet transplantation, genetically engineered insulin secreting cells, bio-artificial pancreas and automated insulin delivery devices (Fig. 2). Pancreatic islet transplantations infused through the portal vein of the liver as described by the Edmonton protocol has demonstrated improved glucometabolic control, reduced hypoglycaemic episodes and cessation of complications resulting from diabetes (Maffi and Secchi, 2015) and insulin independence could be achieved for up to 10 years (Brennan et al., 2016; Shapiro et al., 2006). However, the shortage of donors in association with the dangers of pharmacological immunosuppression, makes it an unlikely approach for T1DM, generally reserved for people undergoing renal transplantation from DM end-stage renal failure (Scharp and Marchetti, 2014; Vrabelova et al., 2014). To overcome the shortage of donors and the use of systemic immunosuppressant drugs, encapsulation of cellular grafts has been proposed by different processing

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http://dx.doi.org/10.1016/j.ijpharm.2017.02.063
0378-5173/

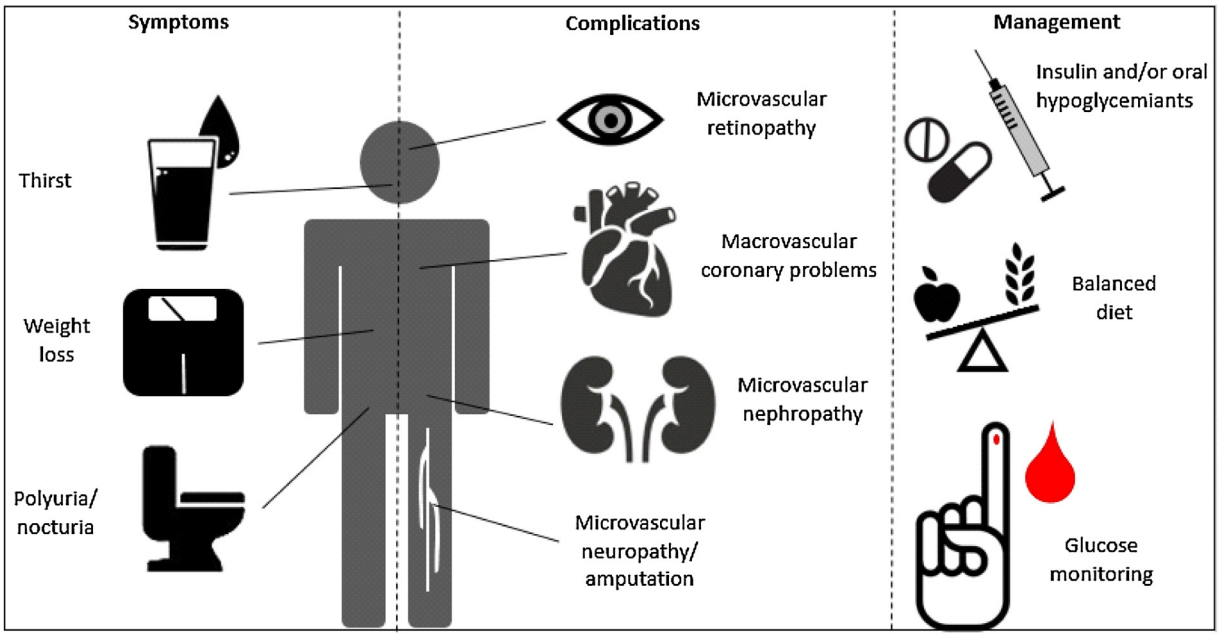

Fig. 1. Diabetes Infographic outlining symptoms, associated complications and current management strategies.

methods in tissue engineering (Souness et al., 2017). In this landscape, we review emerging technologies that are being used in cell therapy for T1DM in order to create a biofunctional engineered immunoprotective environment with the ambition of restoring insulin competence.

2. The extra cellular matrix (ECM) of the pancreas and its role in T1DM

Pancreatic islets consist of five distinct cellular types, α cells, β cells, δ cells, ε cells and PP cells, which are responsible for the synthesis and secretion of peptide hormones. For example, insulin is secreted by β cells, in response to high blood sugar. Glucagon is produced by α cells and it is known to counteract the effects of insulin, by raising the blood glucose concentration. (Wu et al., 2015). The extra cellular matrix (ECM) of the pancreas can be classified as pericellular or interstitial. The pericellular (such as basement membrane) is located surrounding each acinar cell, pancreatic islet and blood vessel while the interstitial matrix is located as a thin layer subjacent to the *peri*-islet basement membrane. The interstitial matrix confers tensile strength and elasticity to tissues mainly due to the presence of fibrillar collagens, whereas the basement membrane is a highly crosslinked sheet-like layer that provides an anchoring platform for epithelial cells to stay in place preventing them from rupture via the formation of hemidesmosomes (Bogdani et al., 2014). The basement membrane is composed of collagen (type IV), laminins (*in the pancreas,* laminin 511) and proteoglycans. Laminins provide

Table 1
The number of people (aging from 20 to 79 years old) with diabetes in the year 2015 and a prediction for 2040 (IDF, 2015).

	2015			2040		
IDF region	Population (million)	Diabetes (million)	Prevalence (%)	Population (million)	Diabetes (million)	Prevalence (%)
Africa	441	14.2	3.2	926	34.2	3.7
Europe	660	59.8	9.1	663	71.1	10.7
MENA[a]	387	35.4	9.1	635	72.1	11.4
NAC[a]	344	44.3	12.9	413	60.5	14.7
SACA[a]	315	29.6	9.4	411	48.8	11.9
Southeast Asia	926	78	8.5	1,310	140	10.7
Western Pacific	1,600	153	9.3	1,800	215	11.9
Total	4,720	414.7	8.8	6,160	642	10.4

[a] ABBREVIATIONS: Middle East and North Africa (MENA); South American and Central America (SACA); North America and the Caribbean (NAC).

Table 2
Rank of countries for number of children with T1DM and rank of countries for number of new cases of T1DM per 100,000 children per year.

Top 5 countries for number of children with T1DM			Top 5 countries for new cases of T1DM in children		
Rank	Country	Number of cases	Rank	Country	Number of new cases/100000 children/year
1	USA[a]	84,100	1	Finland	62.3
2	India	70,200	2	Sweden	43.2
3	Brazil	30,900	3	Kuwait	37.1
4	China	30,500	4	Norway	32.5
5	United Kingdom	19,800	5	Saudi Arabia	31.4

[a] United States of America.