Stem Cell Biology and Regenerative Medicine

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Stem Cell Therapy for Diabetes
Regenerative medicine is an old human dream, and for the first time in human history its realization is within reach. Diabetes ranks high on the priority list of diseases that can benefit from regenerative medicine interventions. β-cell function is lost in both type 1 and type 2 diabetes. In type 1 β-cell loss results from autoimmune destruction. In type 2 the exact mechanisms of β-cell functional deterioration remain poorly understood, but they likely involve exposure to agents such as islet amyloid polypeptide and free fatty acids, coupled with cell “exhaustion” owing to increased demands for insulin and insufficient β-cell renewal. The incidence of both types of diabetes is on the rise, and the supply of human donor pancreatic tissue for β-cell replacement falls far short of the demand.

Stem cells hold a promise for providing an abundant source of cells for cell therapy for diabetes. The generation of human embryonic stem cell lines created expectations for an imminent unlimited supply of all cell types needed in regenerative medicine. A decade later, harnessing the potential of embryonic stem cells remains an attractive prospect, but the initial optimism was replaced by a more realistic appreciation of the difficulties involved in realizing this potential. As a result, the alternative source of tissue stem cells has also become a topic of intense investigation. Tissue stem cells possess a more limited proliferation capacity and offer fewer differentiation choices compared with embryonic stem cells, but it may be easier to realize their therapeutic potential.

This book reviews the three main approaches for the generation of sufficient numbers of insulin-producing cells for restoration of an adequate β-cell mass: β-cell expansion, stem cell differentiation, and nuclear reprogramming. The first section, Beta-Cell Expansion and Regeneration, opens with a description of our current knowledge of β-cell development, which can be utilized in the stimulation of β-cell renewal by replication or neogenesis. This is followed by a review of the updated status of β-cell replacement through pancreas and islet transplantation, which forms the clinical framework in which surrogate β cells can be evaluated as they become available. The next three chapters assess the prospects of generating β cells from pre-existing β cells or their normal progenitors. Assuming that residual β cells exist in patients with type 1 diabetes leads to the possibility that their renewal can be stimulated in vivo. Alternatively, donor islet expansion in vitro may serve as a source
for allogeneic β-cell transplantation. These prospects rely on a detailed understanding of the regulation of β-cell replication and differentiation under normal and pathological conditions.

The second section, *Beta Cells from Non-Beta Cells*, considers alternative cell sources for deriving insulin-producing cells and opens with an overview of the intricate makeup of normal β cells. Although insulin administration cannot avoid diabetic complications, it represents a safe treatment, thereby posing a high bar for the quality and safety of surrogate β cells. Thus, β-cell function must be understood in detail to allow its mimicking to a close approximation in surrogate β cells, primarily with respect to accurate release of insulin in response to physiological signals. The following four chapters evaluate the potential of embryonic and tissue stem/progenitor cells, as well as mature cells from pancreatic and nonpancreatic tissues, to be differentiated or reprogrammed into β-like cells. This might be achieved using soluble factors to effect changes in gene expression in target cells, or, alternatively, by transfer of genes encoding transcription factors capable of inducing such changes. Once sufficient numbers of differentiated cells are generated, they will likely have to be assembled into a miniorgan structure to be fully functional and protected from immune rejection following transplantation.

The third section of the book, *Tissue Engineering and Immune Protection*, discusses cell interaction with matrix scaffolds, compares the merits of employing autologous or banked allogeneic cell sources for generation of surrogate β cells, and evaluates ways for protecting both endogenously generated and transplanted cells from recurring autoimmunity and graft rejection. Among possible approaches, cell encapsulation may help solve both the structural and immunological issues; however, it faces a number of difficult technical problems that have to be tackled before clinical application can be considered.

I hope that this book will be of interest to investigators, clinicians, and students interested both in stem cell application in regenerative medicine and cell therapy of diabetes. These are rapidly evolving research areas, but the contributions collected herein from leading experts in both fields capture the state of the art. They represent essential reading for those interested in tracking the progress in application of one of the most exciting new developments in biomedicine toward a cure for diabetes.

Tel Aviv, Israel

Shimon Efrat, Ph.D.
Contents

Part I  Beta-Cell Expansion and Regeneration

1 Pancreas and Islet Development .......................... 3
   George K. Gittes, Krishna Prasadan, and Sidhartha Tulachan

2 Islet and Pancreas Transplantation .......................... 41
   Davide Mineo, Gaetano Ciancio, George W. Burke,
   Rodolfo Alejandro, and Camillo Ricordi

3 Cell Cycle Regulation in Human Pancreatic Beta Cells .......... 85
   Nathalie Fiaschi-Taesch, George Harb, Esra Karsiloglu,
   Karen K. Takane, and Andrew F. Stewart

4 Islet Regeneration ........................................... 105
   Xiaobo Xu, Joke D’Hoker, Nico De Leu, Xiangwei Xiao,
   Yves Heremans, Mark Van De Casteele, and Harry Heimberg

5 Beta-Cell Expansion in Vitro .................................... 123
   Shimon Efrat

Part II  Beta Cells from Non-beta Cells

6 What Does It Take to Make a Beta Cell? .......................... 137
   Gordon C. Weir and Susan Bonner-Weir

7 Generation of Beta Cells from Acinar Cells ...................... 153
   Luc Baeyens, Ilse Rooman, and Luc Bouwens

8 Generation of Beta Cells from Pancreatic Duct Cells
   and/or Stem Cells ........................................ 167
   Susan Bonner-Weir and Arun Sharma

9 Adult Cell Reprogramming: Using Nonpancreatic Cell Sources to Generate Surrogate Beta Cells for Treatment of Diabetes ......................... 183
   Irit Meivar-Levy, Vered Aviv, and Sarah Ferber
10 Embryonic Stem Cells as a Potential Cure for Diabetes 203
Michael A. Bukys and Jan Jensen

Part III Tissue Engineering and Immune Protection

11 Functional Tissue Reconstruction with the Use of Biologic Scaffolds 223
Stephen F. Badylak, Jennifer B. Ogilvie, and Thomas W. Gilbert

12 Immunoisolation in Cell Transplantation 241
Riccardo Calafiore and Giuseppe Basta

13 Prevention of Islet Graft Rejection and Recipient Tolerization 263
Eitan M. Akirav and Kevan C. Herold

Index 281
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