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β -Cell replacement therapy –What do we do wrong? Some lessons from transplantation of pancreatic Beta-precursor MSC

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Transplantation of stem cell-derived beta cells has been a target of diabetes research for many years but has yet to mature into a therapeutic option. Dispersed islet-derived mesenchymal-like cells, induced by serum deprivation to undergo mesenchymal-to-epithelial transition, aggregate into epithelial cell clusters (ECCs). ECCs implanted under kidney capsules of SKID mice tend to differentiate into β -cell colony. Albeit, in a large proportion of mice the implanted cells de-differentiate back to stem-like phenotype. As ECCs disperse and undergo epithelial-to-mesenchymal transition by re-addition of sera, we postulated that the differentiation failure in vivo may have been due to an agent in the host serum. We found that PDGF-BB alone mimics serum-induced ECCs' dispersal accompanied by accumulation of cytoplasmic b-catenin and a decrease in the levels of insulin

and glucagon mRNAs. Hence, PDGF-BB mediated serum-induced DID dispersal correlated with the activation of the PI3K-Akt pathway. In conclusion, we did fail like many others. In the second part of my talk, I will attempt to analyze the causes of the manifest failure to provide effective and reliable β -cell replacement for the last sixty years. Obviously, we may manipulate cells to change their physiology; the ultimate result, however, depends on many uncontrolled and/or unknown factors. Our understandings of the complexity of inter- and an intracellular interaction in vitro and in vivo is still too sketchy to allow prediction of therapeutic outcomes. Another detrimental factor may be our present system of publishing and funding of basic research.

Biography

Yoram Oron is the Professor Emeritus of the Department of Physiology and Pharmacology at Sackler Faculty of Medicine, Tel Aviv University, Israel. He has received the degree of BSc in chemistry and the MSc and PhD in biochemistry from the Hebrew University in Jerusalem. Further, he was trained in diabetes research at the University of Virginia in the laboratory of Prof. Joseph Larner and continued to study signal transduction pathways at Tel Aviv University, utilizing mainly the *Xenopus* oocyte system and electrophysiology and microscopic imaging techniques as read-outs. In the last fifteen years Dr. Oron changed the focus of his research to studying the biology of diabetes and pancreatic adenocarcinoma. In the past, he had served as Department Chair and as a Head of the Office of International Academic Relations at Tel Aviv University. He has been an author and co-author of more than 110 peer-reviewed publications in highly reputed journals, including Nature, Science, PNAS, and J Physiol.

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