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Subtle traps: Lessons from transplantation of pancreatic beta-precursor MSC

Transplantation of stem cells-derived beta cells has been a target of diabetes research for many years, but has yet to mature into a therapeutic option. We showed previously that proliferating human islet-derived de-differentiated cells (DIDs) exhibit many characteristics of mesenchymal stem cells (MSC). Dispersed DIDs, 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 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. Moreover, PDGF-BB-induced dispersal of ECCs was a more general phenomenon that occurred with bone marrow MSC and dermal fibroblasts (DFs). In DIDs, BM-MSC, and DFs, PDGF decreased the levels of DKK1 mRNA, suggesting involvement of the Wnt signaling pathway. PDGF-BB stimulated a significant increase in S473 phosphorylation of Akt and the PI3K specific inhibitor (PIP828) partially inhibited PDGF-BB-induced ECC dispersal. Lastly, the PDGF-receptor (PDGF-R) antagonist JNJ-10198409 inhibited both PDGF-BB and serum-induced ECC dispersal. Epidermal growth factor (EGF), which shares most of the PDGF signaling pathway, did not induce dispersal and only weakly stimulated Akt phosphorylation. Hence, PDGF-BB mediated serum-induced DIDs dispersal correlated with the activation of the PI3K-Akt pathway. In conclusion, although we may manipulate cells to change their physiology, the ultimate result 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.

Biography

Yoram Oron is currently a Professor Emeritus at the Department of Physiology and Pharmacology, Sackler Faculty of Medicine, Tel Aviv University, Israel. He received his BSc in Chemistry and his MSc and PhD in Biochemistry from the Hebrew University in Jerusalem. He further trained in diabetes research at the University of Virginia in the laboratory of Professor 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 12 years he has changed the focus of his research to studying the biology of diabetes and pancreatic adenocarcinoma. In the past he served as Department Chair and as a Head of the Office of International Academic Relations at Tel Aviv University. He has authored and co-authored more than 110 peer-reviewed publications in quality journals, including Nature, Science, PNAS, and J Physiol.

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