Mark D. Turner, J Clin Cell Immunol 2012, 3:4
http://dx.doi.org/10.4172/2155-9899.S1.006

OMICS Group Conferences
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International Conference on
Clinical & Cellular Immunology

October 22-24, 2012 DoubleTree by Hilton Chicago-Northshore, USA

Emerging evidence for the role of CD40/TNFR5 in pancreatic β-cell death induced by glucolipotoxicity

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Diabetes is a multifactorial disease whose pathogenesis results from insulin deficiency caused by a reduction in pancreatic β-cell mass. In type 1 diabetes this is associated with autoimmunity, whereas type 2 diabetes (T2D) is due to premature aging and impairment of β-cell function. The latter is largely due to toxicity induced by high levels of glucose and lipid. T2D is also characterized by systemic inflammation, with pro-inflammatory cytokines produced by islet-infiltrating macrophages and lymphocytes contributing to β-cell destruction. In addition, glucolipotoxicity also activates the islet inflammasome, NALP3, triggering IL-1β activation and release from pancreatic β-cells. This then serves to activate the transcription factor NF-κB through an autocrine feedback loop that results in increased β-cell expression and release of cytokines and chemokines, with the former serving to trigger β-cell apoptotic cascades and the latter to induce islet immune cell invasion. In order to better understand the intracellular β-cell signaling mechanisms associated with glucolipotoxicity we performed Affymetrix microarray experiments to identify genes whose expression was sensitive to extracellular glucose and lipid environments. Importantly, of all the TNF receptor superfamily members that have been shown to be linked to NF-βB activation in other cell types, we found the greatest change in expression of TNFR5/CD40. Independent qPCR analysis confirmed >3-fold increase in TNFR5/CD40 expression, with Western blot data supporting these findings at the protein level. Ongoing studies are now underway to fully elucidate the signaling mechanisms associated with this novel pathway of glucolipotoxic islet cell death.

Biography

After completing his PhD in Medicine at the University of Liverpool, United Kingdom, Turner moved to the USA to undertake postdoctoral studies at The Scripps Research Institute, Harvard Medical School, and Albert Einstein College of Medicine. He then returned to the UK to take up a faculty appointment at Bart's and The London School of Medicine and Dentistry, before then moving to his current position of Associate Professor at Nottingham Trent University. He has published over 30 papers in reputed biomedicine journals and currently sits on the Editorial Board of *Biochimica Biophysica Acta* – Molecular Cell Research, Bioscience Reports, and Biochemical Society Transactions.

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