OMICS Group Conferences
Accelerating Scientific Discovery

International Conference on
Regenerative & Functional Medicine

November 12-14, 2012 Hilton San Antonio Airport, USA

Macrophage-derived TGFβ1 promotes BIGH3 secretion and BIGH3-mediated renal cell apoptosis

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The ECM protein BIGH3 (Transforming Growth Factor Beta-Induced Gene Human Clone 3), also called TGFBIp, beta-ig and keratoepithelin, is an adhesion-class protein that supports integrin-mediated cell attachment and migration. In a wide range of mesenchyme-derived tissues in developing and adult organisms the cytokine TGFβ1 upregulates the BIGH3 gene (TGFβI). BIGH3 is proapoptotic when up regulated in disease states such as diabetes. Using our mouse model of diabetic complications, we found that BIGH3 expression in kidney cortex is upregulated when compared to nondiabetic kidney. When TGFβ1 induces BIGH3 synthesis and secretion in human renal proximal tubule epithelial cells (RPTEC), then the proapoptotic BIGH3 is processed to its apoptotic form, bringing about a significant increase in renal cell apoptosis. Adding recombinant BIGH3 back to renal cells is sufficient to induce apoptosis, indicating that the cellular secretory pathway per se is not involved in the cells' demise. Growth medium conditioned by human macrophages cultured in a diabetic stress environment (i.e., high glucose and LDL) induces a significant increase in BIGH3 expression and renal cell apoptosis, indicating that macrophages secrete soluble factors that activate TGFβI.

Inhibiting TGFβ1 signalling and BIGH3 greatly diminish apoptosis. These data indicate that an axis of macrophage, macrophage-derived TGFβ1 and BIGH3 protein is involved in cell adhesion and apoptosis in tissue injury and regenerative processes.

Biography

Richard LeBaron completed his Ph.D. at the University of Alabama-Birmingham and postdoctoral studies at the Sanford-Burnham Medical Research Institute, La Jolla, CA. At Advanced Tissue Sciences (La Jolla, CA) he helped engineer human dermis and cartilage equivalents. Next he joined Biology Department faculty at UT San Antonio, where he continues his research on ECM and cell adhesion, and teaches undergraduate and graduate Cell, Molecular, and Cancer Biology courses. He has published papers, reviews and chapters on ECM in tissue homeostasis and disease states. He is a Board Member of AL Phahelix Biometrics, a company developing diagnostic tools.

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