Integrin linked kinase (ILK) modify blood glucose homeostasis by regulating striated muscle GLUT4 expression.

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Abstract

Introduction: diabetes mellitus type 2 (DM2) and metabolic syndrome are defined by insulin resistance and hyperglycemia. In this context, the membrane glucose transporter type 4 (GLUT4) is the only insulin-sensitive member of their family that finally maintain the euglycemia after the nutrients have being absorbed. Thus, the decrease in GLUT4 functionality drives to cardiovascular and metabolic malfunctions. Insulin binds to its receptor (IR) and initiates a cascade where several kinases, as AKT (aka PKB) and GSK-3β, participate in the expression and intracellular location of GLUT4. However, the role of the extracellular matrix (ECM) in the mediation of insulin resistance is still unknown. ECM regulates the cellular phenotype via AKT and GSK-3β through upstream kinases such as Integrin Linked Kinase (ILK). **Objective:** to study the role of ILK in blood glucose homeostasis by analyzing GLUT4 protein levels in striated muscle, in vivo and in vitro. **Methods:** Adult male mice with a transgenic depletion of ILK protein (cKD-ILK) and Wild-Type (WT) [1,2] were fed with a chow diet for 1 month after ILK depletion. All the measurements were performed in randomly fed conditions ("ad libitum"). Blood glucose levels were measured via tail bleeding using a glucometer. To determinate the levels of insulinaemia, the blood was collected from submandibular vein and was analyzed by a ELISA kit. In cardiac tissue, the protein total levels of ILK and GLUT4 and the phosphorylation rates of GSK-3β (ser9) and AKT(ser473) were determinated by inmunoblot. Same proteins were analyzed in cultured C2C12 cell line differentiated in myotubes (an in vitro model of skeletal muscle), which were transfected with small interfering RNA to deplete ILK (siRNA-ILK) or scrambled siRNA as control (CT). **Results:** cKD-ILK have basal hyperglycemia (200 mg/dl) compared with WT, but not differences were observed in insulin blood levels between groups. We confirmed ILK depletion in the cardiac tissue in cKD-ILK. The ILK downstream pathway was diminished in cKD-ILK hearts, since phosphorylation of ILK substrates and GLUT4 regulators AKT (Ser473) and GSK-3β (Ser9) were reduced as well as protein levels of cardiac GLUT4. Similar expression pattern behaviour was observed in siRNA-ILK myotubes compared with CT. Conclusions These results suggest for the first time the importance of the ECM intracellular mediator ILK in the regulation of insulin sensitivity in the striated muscle. The ILK-dependent GLUT4 expression modification alters the blood glucose homeostasis.

1. Cano-Peñalver J. L, Griera M, García-Jerez A, Hatem-Vaquero M, Ruiz-Torres M. P, Rodríguez-Puyol D, Rodríguez-Puyol M. 2015. Renal integrin-linked kinase depletion induces kidney cGMP axis upregulation: Consequences on basal and acutely damaged renal function. Molecular Medicine 21:873-88
2. Cano-Peñalver J.L, Griera M, Serrano I, Rodríguez-Puyol D, Dedhar S, de Frutos S, Rodríguez-Puyol M. 2014. Integrin-linked kinase regulates tubular aquaporin-2 content and intracellular location: a link between the extracellular matrix and water reabsorption. The FASEB Journal 28(8): 3645-3659.

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