Guest Editorial

THE MOLECULAR DETAILS OF GESTATIONAL DIABETES MELLITUS: BEHAVIORAL PATTERNS OF PANCREATIC CELLS

Increasingly, it is being realized that insulin resistance is one among the most widely studied biological mechanism that frequently occurs during pregnancy. Data obtained through high-throughput technologies have started to shed light on the fact that insulin resistance and pancreatic β-cell insufficiency are underlying factors for development of gestational diabetes and epidemiologic evidence associates gestational diabetes mellitus (GDM) with increased perinatal morbidity. This editorial provides mechanistic insights of signaling cascades, which are identified to be associated with GDM, and highlights the considerable advancements in our understanding of role of genetic factors in the pathogenesis of GDM. Studies have shown that there is a considerable expansion of the maternal population of insulin-producing β-cells. Data obtained through laboratory investigations are continuously improving our knowledge related to cell signaling cascades and communication between cells and microenvironment.

Overwhelmingly, increasing laboratory data have highlighted the role of signaling pathways in metabolic homeostasis and its implication in gestational diabetes. Genome-wide association studies have shown that downstream effectors of the linear signaling cascades are implicated in metabolic homeostasis and the development of diabetes mellitus. There is sufficient evidence related to role of signaling and diabetes, but there are knowledge gaps related to how pancreatic cells behave during gestational diabetes and which pathways are overexpressed and underexpressed. Here, we expand our views regarding the cross talk between insulin signaling and modulators of different signaling cascades, which further illustrates the complexity of the insulin signaling pathway during GDM.

INSULIN SIGNALING

Various downstream effectors of insulin signaling are misrepresented that leads to GDM. It has been shown that nutrient-sensitive mTOR/S6K1 pathway is activated in GDM.[1] Insulin and insulin-like growth factor 1 (IGF-1) are well-studied and well-appreciated stimulators of placental nutrient transporters and fetal growth. However, it has been indicated that full-length adiponectin attenuates placental insulin signaling in primary human trophoblast cells.[4] The membrane-type matrix metalloproteinase 1 is controlled by insulin signaling and is upregulated in GDM.[3] Insulin signaling stimulates cell surface expression of TRPM6 via PI3K and Rac1. Surprisingly, insulin did not activate genetic variants of TRPM6, as phosphorylated levels of TRPM6 were not enhanced in cells stimulated with insulin.[8] Gestational diabetes mellitus is interconnected with reduced adenosine transport and increased fetal plasma adenosine concentration in placental macrovascular endothelium. Direct piece of evidence substantiated the fact that Akt inactivation resulted in a decline in mRNA expression and hENT1 protein abundance and its availability at the plasma membrane to take up adenosine.[10] Contemporary evidence suggests that effects of IGF-I signaling are attenuated in insulin-resistant conditions in extravillous trophoblast (EVT) cells. Moreover, restoration of insulin sensitivity by pioglitazone alters IGF signaling, resulting in the promotion of EVT cell migration. Both αVβ3-integrin and α5β1-integrin promote EVT cell migration and IGF-1 activates the integrin signal pathways in EVT cells.[7]

Insulin Signaling Cross Talks with Other Signaling Cascades

HGF/c-Met-mediated intracellular signaling is vital for maternal β-cell adaptation during pregnancy and its loss leads to GDM. Laboratory findings suggested that knock down of c-MET resulted in considerably reduced β-cell replication. Moreover, there was a significantly enhanced apoptotic cell death of β-cell at gestational day 15.[2] It has been convincingly revealed that inhibition of serotonin synthesis also inhibited β-cell expansion in pregnant mice. Cellular studies have substantiated the fact that expression of G α(q)-linked serotonin receptor 5-hydroxytryptamine receptor-2b (Htr2b) was noted to be remarkably enhanced in maternal islets during pregnancy. Paradoxically, normalization of Htr2b was noted just before parturition. Likewise, β-cell expansion was also inhibited upon targeted inhibition of Htr2b signaling in pregnant mice and caused glucose intolerance.[5]

Apelin is an endogenous ligand of the G protein-coupled receptor; however, no relationship between circulating apelin or apelin/APJ mRNA expression and GDM is reported.[11] Chemerin is an adipokine involved in insulin signaling; however,

it is not dysregulated in GDM.[9] SOCS1 and SOCS3 mRNA expression did not vary in adipose and placental tissue in pregnant women with and without GDM.[6]

It was reported that serum miRNAs expressed differentially in GDM women as evidenced by marked decrease in expression of miR-222, miR-132 and miR-29a in GDM women.[12] Enhanced expression of miR-518 also played a key role in development of GDM as expression of miR-518 was notably enhanced in placentas taken from patients with GDM.[13]

We have developed a deeper understanding of GDM, but how patients with different genetic make up respond during pregnancy is incompletely understood, because we do not have previously documented studies aimed at genetics of GDM patients in Pakistan. Future studies must converge on a better knowledge of the GDM-associated genes, so that patients can be treated in best possible manner.

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Talha Abdul Haleem
Associate Professor, Department of Obstetrics and Gynecology
Rashid Latif Medical College, Lahore, Pakistan
e-mail: talhaayubi@hotmail.com

Rubina Sohail
Professor, Department of Obstetrics and Gynecology (Unit II)
Services Institute of Medical Sciences, Lahore, Pakistan
e-mail: rubina95@gmail.com