we found that Fyn-dependent phosphorylation of Tgm2 regulates autophagy. It has been reported that Tgm2 forms complexes with p53 and p62 (a known autophagy regulator) to mediate degradation of p53 at autophagosome in cancer cells and p53 functions as a DKD inducer. We found that p53 expression was decreased in Tgm2 knock-downed HK2 cells suggesting that Tgm2-p62-p53 complex also modulates autophagy in RPTC. We previously showed that Fyn and autophagy is regulated by energy status, therefore we next examined whether energy levels changed the subcellular localization of p53, p62 and Tgm2 in HK2 cells *in vivo*using the marker, Aquaporin 1. Confocal microscopic studies revealed that *ad libitum*-fed mice showed increased punctate of p62 in RPTC suggesting that autophagy was reduced. Fyn, Tgm2 and p53 shaped the dotted form mainly in the basement membrane of the cells. Interestingly, all these molecules moved to the cytoplasm in fasted state, where decreased p62 punctations were observed indicating increased autophagy. More importantly, in HFD fed mice, diet-induced rodent models of metabolic disorders, we found that protein expression of p53 was increased due to decreased levels of degradation with inhibition of autophagy implicated by decreased p62 punctations in RPTC. Taken together, these data suggest that the metabolic status may regulate Fyn to not only phosphorylate Tgm2 and modulates Tgm2-p62-p53 complex but also change their co-localizations of Fyn, p53 and Tgm2 in RPTC to regulate autophagy leading to pathogenesis of DKD.

Diabetes Mellitus and Glucose Metabolism

DYSREGULATED METABOLIC RESPONSE

The IgG Antibody Paradox in Insulin Resistance: Pathogenic and Therapeutic

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Chronic low-grade inflammation and mitochondrial dysfunction are hallmarks of insulin resistance. However, the mechanisms by which the immune system can propagate systemic insulin resistance remains poorly understood. IgG antibodies are a critical component of immunity and display paradoxical properties. IgG can propagate inflammation by crosslinking Fc receptors activating innate immune cells, and conversely, when given intravenously at high doses (1–2 g/kg intravenous immunoglobulin), actively suppress inflammation. Here, we demonstrate that IgG can exert similar paradoxical properties on glucose metabolism. IgG can elicit insulin resistance, and conversely, when given at high doses, promote insulin sensitivity in a diabetic mouse model. IgG, through its Fc-mediated interactions, suppresses insulin-induced mitochondrial function as well as insulin signaling. Modulation of insulin-dependent mitochondrial respiration by serum or purified IgG highly correlates (R2 = 0.70) with the quantitative measurement of insulin sensitivity accessed by the modified insulin suppression test. Our studies indicate that IgG antibody glycosylation is critically important to these conflicting actions. In mice and humans, the progression of insulin resistance is associated with reduced IgG Fc region sialylation, and administration of asialylated IgG is sufficient to cause insulin resistance in IgG null mice. On the other hand, a single administration of high-dose IgG significantly improved insulin and glucose tolerance as well as plasma glucose levels lasting over 72 days post-administration. These results demonstrate new insights into the systemic nature of insulin resistance, a novel mechanism of the disease, and an innovative therapeutic strategy for treating type 2 diabetes.

Diabetes Mellitus and Glucose Metabolism

DYSREGULATED METABOLIC RESPONSE

The Role of TGFβ Ligands and Signalling on Insulin Resistance in Skeletal Muscle in Women With PCOS

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Polycystic ovary syndrome (PCOS) is the most common female endocrinopathy affecting metabolic and reproductive health of 8–13% of reproductive-age women. Insulin resistance (IR) appears to underpin the pathophysiology of PCOS and is present in approximately 38–95% of women with PCOS. This underlying IR has been identified as unique from, but synergistic with, obesity-induced IR (1). Skeletal muscle accounts for up to 85% of whole-body insulin-stimulated glucose uptake; however, in PCOS this is reduced by about 27% when assessed by a euglycaemic-hyperinsulinaemic clamp (2). Interestingly, this reduced insulin-stimulated glucose uptake observed in skeletal muscle tissue is not retained in cultured myotubes (3), suggesting that *in vivo* environmental factors may play a role in this PCOS-specific IR. Yet, the molecular mechanisms regulating IR remain unclear (4). A potential environmental mechanism contributing to the development of peripheral IR may be the extracellular matrix remodelling and aberrant transforming growth factor beta (TGFβ) signalling. Previous work demonstrated that TGFβ superfamily ligands are involved in the increased collagen deposition and fibrotic tissue in the ovaries, and suggested that these ligands may be involved in the metabolic morbidity associated with PCOS (5). In this study, we investigated the effects of TGFβ1 (1, 5 ng/ml), and the Anti-Müllerian hormone (AMH; 5, 10, 30 ng/ml), a TGFβ superfamily ligand elevated in women with PCOS, as causal factors of IR in cultured myotubes from women with PCOS (n=5) and healthy controls (n=5). TGFβ1 did not have a significant effect on insulin signalling but induced expression of some ECM related genes and proteins, and increased glucose uptake via Smad2/3 signalling in myotubes from both groups. Conversely, AMH did not appear to activate the TGFβ/Smad signalling pathway and had no significant impact on insulin signalling or glucose uptake in any of the groups. In conclusion, these findings suggest that TGFβ1, but not AMH, may play a role in skeletal muscle ECM remodelling/fibrosis and glucose metabolism in PCOS but does not have a direct effect on insulin signalling pathway. Further