metabolism, it is not entirely clear how obesity compromises the metabolic function of bone and whether deregulated energetics in bone play a causal role in declining bone quality. Transforming growth factor-beta (TGFβ), a key mediator of bone homeostasis, was recently shown by us to play a positive role in osteocytes, where its ablation ($T\beta RII^{ocy-/-}$) compromised bone quality. TGFβ signaling has been previously implicated in etiologies of obesity and type 2 diabetes. Also, our unpublished unbiased transcriptomic analysis in $T\beta RII^{ocy-/-}$ mouse bones (osteocyte-enriched RNA) has shown that osteocytic ablation of TGFβ signaling causes profound changes in the expression of genes implicated in glucose and fatty metabolism. Together these observations led us to hypothesize that osteocytic TGFβ plays an integral role in regulating obesity impacted bone architecture and function in metabolism.

Using hyperglycemia to model the metabolic milieu of obesity in vitro, we found that hyperglycemia upregulated TGFβ signaling in osteocytes. We also found that TGFβ acts similarly to hyperglycemia in reprogramming osteocyte cellular metabolism to promote glycolysis at the expense of oxidative phosphorylation. Thus, TGFβ may be a crucial mediator of hyperglycemia-induced metabolic reprogramming in osteocytes.

In $T\beta RII^{ocy-/-}$ mice, inhibition of osteocyte-intrinsic TGFβ signaling reduced age-dependent weight gain and improved glycemic control relative to littermate controls. When subjected to a high-fat diet (HFD, 18 weeks), $T\beta RII^{ocy-/-}$ mice continued to be leaner, with lower food intake, and higher levels of activity and fatty acid metabolism in the liver compared to HFD fed littermate controls. This implicates osteocyte-intrinsic TGFβ signaling as a crucial regulator of systemic energy metabolism. $T\beta RII^{ocy-/-}$ mice on HFD also showed increased trabecular and cortical bone mass, increased bone mineral density, and protection against reduced bone strength compared to littermate controls on a similar diet.

Overall, our study identifies a novel role for osteocytic TGFβ signaling in regulating energy metabolism and bone health in obesity.

Diabetes Mellitus and Glucose Metabolism

DYSREGULATED METABOLIC RESPONSE

Preclinical Characterization of Once Weekly Basal Insulin Fc (BIF)

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Weekly basal insulin injections may increase treatment adherence in subjects with diabetes and an appropriately engineered weekly basal insulin may reduce daily pharmacokinetic (PK)/pharmacodynamic (PD) fluctuations compared to currently available daily basal insulins. Therefore, a weekly insulin has the potential to not only ease the burden of insulin therapy, but also improve outcomes for subjects with diabetes in a real-world setting. Basal insulin Fc (BIF, LY3209590) is an insulin Fc-fusion protein in clinical testing as a once weekly treatment for type 1 and type 2 diabetes mellitus (T1DM, T2DM). BIF is comprised of a human single-chain insulin fused to a human IgG2 Fc domain through a peptide linker. The *in vitro* evaluation determined that BIF exhibited reduced insulin receptor (IR) potency with full agonism, selectivity against human insulin-like growth factor-1 receptor (hIGF-1R), and functional properties similar to native human insulin. The binding affinity of BIF for hIR isoform A, Ki = 25 nM (SEM = 4, n=10), and hIR isoform B, Ki = 26 nM (SEM = 4, n=10), was more than two orders of magnitude weaker than human insulin. BIF stimulated IR phosphorylation in cells with reduced potency, but full agonism, and showed a significantly faster hIR dephosphorylation profile than either human insulin or AspB10 insulin. BIF stimulated *de novo* lipogenesis in 3T3-L1 adipocytes and cell proliferation in SAOS-2 and H4IIE cells with at least a 70-fold reduction in potency compared to human insulin. BIF possessed markedly reduced binding and activation of hIGF-1R making definitive mitogenic measurements unattainable. In preclinical *in vivo* pharmacology studies using streptozotocin (STZ)-treated diabetic rats, a statistically significant decrease in blood glucose compared to vehicle-treated animals was seen 24 hours post-injection and persisted through 336 hours post-injection following a single subcutaneous administration (30 nmol/kg) of BIF. In STZ-treated rats, BIF reached a T_{max} at 48 hours, possessed an apparent clearance rate of ~0.85 mL/hr/kg, and $t_{1/2}$ of ~120 hrs. Collectively, these results demonstrate that BIF possesses selective IR agonism with a pharmacological profile similar to native insulin, however with a significantly reduced potency, and a significantly extended time action profile in preclinical animal models supporting once weekly testing in the clinic.

Diabetes Mellitus and Glucose Metabolism

DYSREGULATED METABOLIC RESPONSE

Tgm2-p62-p53 Complex May Function as an Autophagic Regulator Through Fyn and Involve in Diabetic Kidney Disease.

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Diabetic kidney disease (DKD) is one of the major diabetic complications and the leading cause of the end stage renal disease. Recently autophagy was shown to regulate DKD. Previously we reported that Fyn regulates muscle mass by suppressing autophagy through Fyn-STAT3-VPS34 signaling pathway. More recently, we demonstrated that Fyn also down-regulates autophagy in HK2 cells, an *in vitro*cell model of renal proximal tubular epithelial cells (RPTC). Phospho-proteomic analysis revealed that Fyn phosphorylates Transglutaminase 2 (Tgm2), a known autophagic inhibitor, at Y369 and Y617. Moreover,