From feast to famine: Biology and pharmacology of Fibroblast Growth Factor 1

Jae Myoung Suh

KAIST, Graduate School of Medical Sciences and Engineering

The ability to adapt to cycles of feast and famine is critical for survival. Communication between multiple metabolic organs must be integrated to properly metabolize nutrients. By controlling networks of genes in major metabolic organs, nuclear hormone receptors (NHRs) play central roles in this process.

As part of a screen to identify genes that respond to feast and famine cues, we discovered that in white adipose tissue (WAT) PPARγ induces FGF1 in response to high-fat-diet (HFD) and it is repressed during a fast. Thus, FGF1 participates in both fed-state and fasted-state responses in a PPARγ dependent fashion. Because FGF1-deificient mice are normal, it was thought to be a nonessential gene. However, on HFD, FGF1 deficient mice develop an aggressive diabetic phenotype, with adipose progressively becoming dysmorphic, fibrotic and necrotic and unable to adapt to nutrient stress. Thus, though seemingly dispensable under standard laboratory rearing conditions, within the context of feast and famine FGF1 is critical for survival.

As FGF1 knockout mice on HFD are insulin resistant and diabetic, we wondered if synthetic FGF1 could restore insulin sensitization. As a proteoglycan binding protein, endogenous FGF1 acts in a paracrine fashion and has no detectable levels in blood. Nonetheless, 'endocrinization' of FGF1 by simple injection restores insulin sensitivity in obese diabetic mice. This effect is rapid, robust and does desensitize as most other medications used to lower glucose. Structure function studies show that mitogenicity can be eliminated while retaining full glucose lowering action. Thus, 'endocrinized' FGF1 is a potent metabolic regulator and offers a new class of therapeutic modality in the management of Type II diabetes.