Designing and Testing a Novel Drug Targeting the Distinct Metabolic Roles of the Isoforms of PPARGamma

Li, Dylan

The obesity pandemic affects 36.5% of the US adult population and exacerbates the risk for deadly comorbidities including Type II Diabetes (T2DM). Current obesity and T2DM therapeutics are nonviable because they are ineffective or toxic. One class of T2DM drugs called TZDs improves insulin-sensitivity by augmenting the activity of PPARGamma, a transcription factor regulating fat function and metabolic homeostasis. However, TZDs cause side effects ranging from weight gain to osteoporosis due to the overactivation of PPARGamma. It was shown last year that the two versions of PPARGamma have distinct roles in regulating adipocyte plasticity. PPARGamma1 upregulates beneficial catabolic genes, while PPARGamma2 potently induces lipid synthesis and TZDs' side effects, suggesting developing isoform-specific therapies for obesity and T2DM. In the present study, these results were further expanded with QPCR analyses and RNA-sequencing analyses for two human cohorts that identified the role of PPARGamma2 in obesity and the beneficial role of PPARGamma1 in lipid catabolism. Thus, limiting PPARGamma2 function may deter obesity and alleviate TZDs' poor therapeutic viability. Subsequently, a novel small molecule was designed to act as a competitive inhibitor for only PPARGamma2 activity. Oil-Red-O staining and QPCR analyses revealed that the drug reduced PPARGamma2 activity but minimally affected PPARGamma1 activity. It was able to effectively reduce adipogenesis and modify adipocyte morphology while simultaneously decreasing the activity of deleterious genes. This study, therefore, further distinguishes PPARGamma's isoforms. It also showcases a therapeutic design limiting only PPARGamma2 function that may prove effective in improving T2DM treatments and combating obesity.

Awards Won: