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The Future of TZD, from Lab Bench to Bedside

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The metabolic syndrome is strongly associated with insulin resistance and consists of a constellation of factors such as hypertension and hyperlipidemia that raise the risk for cardiovascular disease (CVD) and diabetes mellitus. Emerging data suggest that peroxisome proliferator-activated receptor-γ (PPARγ) is a critical determinant that may provide functional links between diabetes and CVD. PPARγ binds diverse ligands to transcriptionally regulate lipid metabolism and energy balance implicated in the development of insulin resistance and obesity. Activators of PPARγ include lipids and anti-hyperglycemic drugs such as thiazolidinediones (TZDs). Recently, TZDs have raised concern after being linked with increased risk of peripheral edema, weight gain, and adverse cardiovascular events. The concept of selective PPARγ modulators (SPγm) for the better treatment of diabetes and CVD is recently emerged. Previously, we have found that nitrated oleic acid (OA-NO2) and linoleic acid (LNO2), nitroalkenes formed by reaction with NO-derived reactive nitrogen species, have been structurally characterized and quantified in human blood. Of significance, we have shown that both OA-NO2 and LNO2 activate PPARγ at physiological levels. Our recent analyses of the co-crystal structure of LNO2/PPARγ have identified that LNO2 binds to PPARγ in distinct manners to the ligand-binding pocket of PPARγ, leading to alternative receptor conformations. We have also documented that LNO2-activated PPARγ recruits/displaces differential cofactors leading to different gene expression ultimately with different biological responses in comparison with TZD (e.g., rosiglitazone)-activated PPARγ. Taken together, we expect that novel nitroalkene derivatives can be developed that can display more favorable pharmacologic impact than current TZD-based synthetic PPARγ ligands.

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