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Metformin reverses FOXO3-induced hyperactivation of hepatic gluconeogenesis and catabolic pathways

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Diabetes mellitus type 2 is a complex metabolic disorder that is often characterized by high glucose level and impaired insulin sensitivity (insulin resistance). Hepatic glucose production is essential for providing an energy source for other organs, but the inability of insulin to suppress glucose production in the liver (and regulate glucose catabolism in other organs) is a major reason for hyperglycemia in type 2 diabetes. Accordingly, metformin, one of the most widely used therapeutics for type 2 diabetes exerts its effect via suppressing hepatic glucose production, but the underlying molecular mechanism is still not clearly understood. Members of the FOXO family of forkhead transcription factors represent key downstream targets of insulin through PI3K/Akt. Here we demonstrate that among the FOXO transcription factor family members, FOXO3 is a key regulator of hepatic glucose as well as lipid metabolism. Using a novel mouse model where we express a constitutively active/Akt-insensitive allele of FOXO3 in hepatocytes we demonstrate that hepatic FOXO3 activation leads to hyperglycemia, hyperinsulinemia, as well as impaired insulin sensitivity. Furthermore, hepatic FOXO3 regulates lipid metabolism in that activation of FOXO3 leads to suppression of lipid anabolism and activation of lipid catabolism. Strikingly, administration of metformin rapidly and completely reversed FOXO3-induced metabolic alterations. These findings implicate FOXO3 as a critical metabolic regulator in the liver as well as a likely target of metformin, a widely used drug with a hitherto largely unknown mode of action.

Biography

Sarah Gul has completed her PhD at the age of 27 years from Institute of Physiolgical Chemistry Ulm University Germany. She is the Assistant Professor at Islamic International University Islamabad Pakistan. She has published more than 12 papers in reputed journals.