

ABSTRACT

Type 2 diabetes (T2D) is a multifactorial metabolic disorder characterized by impaired glucose homeostasis and systemic metabolic dysfunction. Increasing evidence implicates gut microbiota dysbiosis as a key contributor to T2D progression through altered microbial metabolism and host–microbe interactions. In this study, we applied genome-scale community metabolic modelling to investigate population-specific metabolic alterations in the gut microbiota of Indian and Chinese T2D patients. Genome-scale metabolic models (GEMs) were reconstructed and rigorously curated for gut microbial species exhibiting altered abundance in T2D cohorts, including *L. ruminis*, *P. copri*, *M. smithii*, and *F. prausnitzii* from the Indian population, and *A. rectalis*, *A. muciniphila*, *B. intestinalis*, *E. lenta*, *R. intestinalis*, and *S. salivarius* from the Chinese population. These curated GEMs were integrated into compartmentalized community models constrained by an average human diet and condition-specific microbial abundances. Comparative flux balance and variability analyses revealed pronounced metabolic dysbiosis in T2D, including reduced carbohydrate utilization, impaired short-chain fatty acid (SCFA) biosynthesis, altered amino acid metabolism, and disrupted inter-microbial cross-feeding. While the Indian T2D microbiota showed marked reductions in glucose consumption and acetate and butyrate production, the Chinese T2D microbiota exhibited impaired utilization of glucose, fructose, and mannose, along with reduced production of acetate, butyrate, propionate, and succinate. The model predicts that reduced glucose consumption may elevate blood glucose levels, while diminished SCFA production may impair insulin secretion and β -cell proliferation, collectively contributing to T2D progression. Microbial species such as *P. copri* and *A. rectalis* were identified as key contributors influencing human gut metabolism in T2D patients from Indian and Chinese populations, respectively. Despite these population-specific microbial signatures, conserved metabolic linkages between gut dysbiosis and T2D were observed. Although genome-scale community metabolic modelling elucidated population-specific alterations in gut metabolism associated with T2D, understanding how these microbiota-driven metabolic disruptions connect to disease pathology requires investigation on metabolic reprogramming within pancreatic β -cells, the primary regulators of insulin secretion in T2D.

T2D is characterized by impaired glucose homeostasis driven by pancreatic β -cell dysfunction. Elucidating the metabolic mechanisms underlying β -cell failure is essential for understanding T2D pathophysiology and developing effective therapies. In this study, context-specific genome-scale metabolic models of healthy and T2D pancreatic β -cells were reconstructed

using transcriptomics data. The models revealed substantial metabolic flux reprogramming in diabetic β -cells, including disrupted glucose sensing and utilization, impaired insulin biosynthesis, reduced ubiquinone synthesis, and enhanced fatty acid oxidation. These alterations highlight key metabolic drivers of β -cell dysfunction in T2D. Further, metabolically dysregulated reactions were leveraged to identify biomarker genes associated with β -cell dysfunction. Drug repurposing analysis identified 23 potential targets, including seven previously associated with T2D treatment, along with 341 FDA-approved drug candidates with therapeutic potential. Additionally, reduced gut microbiota-derived SCFA production was predicted to impair Free Fatty Acid Receptor 2/3 (FFA2/3) activation, leading to compromised insulin secretion and β -cell proliferation, thereby establishing a mechanistic link between gut microbiota dysbiosis and β -cell dysfunction. Overall, this integrated metabolic modelling framework provides a unified, systems-level view of gut microbiota- β -cell metabolic dysregulation in T2D, highlighting population-specific microbial signatures alongside conserved host metabolic impairments as promising targets for precision diagnostics and therapeutic interventions.

The integrative computational framework established herein can be further extended to map biochemical signatures and inter-microbial cross-talk, elucidating their impact on human health across various metabolic diseases. This modelling approach deepens our understanding of gut microbiota metabolism in disease and facilitates the identification of biomarkers and therapeutic probiotic targets.

Keywords: Gut microbiota, Community metabolic model, Metabolic interaction, Context-specific genome-scale model, Flux Variability Analysis (FVA), Genome-scale differential flux analysis (GS-DFA), Biomarker

Graphical abstract

