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Insulin Resistance in Type 1 Diabetes: An Integrative Transcriptomic Analysis of Insulin Signaling, Immunometabolic Dysfunction, and Peripheral Insulin Exposure-Related Pathways

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Abstract

Type 1 diabetes (T1D) is defined by autoimmune β-cell destruction and absolute insulin deficiency, yet a substantial proportion of patients develop clinically relevant insulin resistance (IR) that elevates exogenous insulin requirements, glycemic variability, and cardiovascular risk. The molecular architecture of this IR phenotype remains incompletely mapped and may involve coordinated dysregulation across insulin signaling, lipid metabolism, innate immune activation, mitochondrial function, and tissue-level energy homeostasis. Here we present a fully bioinformatic integrative framework that interrogates publicly available peripheral blood mononuclear cell (PBMC) transcriptomes from individuals with T1D (GSE9006, GSE55098, GSE72377, GSE156035) together with a subcutaneous adipose reference signature of insulin resistance (GSE245948). The analytic pipeline comprises differential expression modeling (limma), weighted gene co-expression network analysis (WGCNA), gene-set variation and single-sample enrichment scoring (GSVA/ssGSEA), protein–protein interaction network construction (STRING/Cytoscape), functional enrichment (clusterProfiler/Enrichr), and supervised molecular feature selection (LASSO and random forest). Five a priori biological axes guide the investigation: (1) intracellular insulin signaling, (2) lipid metabolism and storage, (3) metabolic inflammation and innate immunity, (4) mitochondrial dysfunction and oxidative stress, and (5) transcriptional correlates of hepatic and skeletal-muscle insulin action detectable in circulating cells. Candidate genes within each axis (INSR, IRS1, IRS2, PIK3CA, AKT2, SLC2A4, FOXO1, GSK3B, PPARGC1A, CD36, SREBF1, FASN, TNF, IL6, NFKB1, NLRP3, TFAM, NDUFS1, SOD2, NFE2L2 and related molecules) serve as investigation targets rather than presupposed results. Findings are interpreted strictly as systemic molecular signatures compatible with IR mechanisms, not as direct functional evidence of muscle or hepatic insulin resistance. Independent cross-dataset validation and explicit separation of leukocyte inflammatory programs from classical metabolic-tissue IR programs are enforced throughout. This open-source roadmap generates prioritized candidate pathways for experimental validation and advances a systems-level view of immunometabolic dysfunction in T1D.

1. Introduction

Type 1 diabetes mellitus (T1D) is an organ-specific autoimmune disease characterized by progressive T-cell-mediated destruction of pancreatic β-cells, culminating in absolute endogenous insulin deficiency [1, 2]. For decades the dominant clinical paradigm has centered on hyperglycemia secondary to insulinopenia. However, a growing body of clamp-based and observational evidence demonstrates that many individuals with T1D also exhibit insulin resistance (IR), a metabolic phenotype classically linked to type 2 diabetes [3–5]. This IR is not merely a laboratory curiosity: it is associated with higher daily insulin doses, greater glycemic variability, accelerated coronary artery calcification, and elevated risk of both microvascular and macrovascular complications [6–8]. Consequently, IR has emerged as a clinically actionable target in contemporary T1D management.

The pathophysiology of IR in T1D is multifactorial and incompletely resolved. Chronic hyperglycemia induces glucotoxicity that impairs distal insulin signaling [9]. Subcutaneous administration of exogenous

insulin generates sustained peripheral hyperinsulinemia that differs markedly from the physiologic portal–peripheral insulin gradient maintained by endogenous secretion [10]. Additional candidate mechanisms include low-grade systemic inflammation, altered adipokine profiles, ectopic lipid deposition, mitochondrial dysfunction, and oxidative stress [3, 11, 12]. Critically, several physiologic studies suggest that IR in T1D may possess molecular features that are at least partially independent of ambient glycemia and residual endogenous insulin secretion, raising the possibility of a distinct immunometabolic phenotype [5, 13]. Whether chronic exposure to exogenous subcutaneous insulin itself contributes to these alterations remains an open and clinically relevant question that can be addressed, at least in part, through careful transcriptomic comparison of newly diagnosed versus long-standing, insulin-treated patients.

Transcriptomic profiling of peripheral blood mononuclear cells (PBMCs) has been widely applied in T1D research and has consistently revealed signatures of innate immune activation, type I interferon responses, altered apoptosis regulation, and leukocyte activation [14–19]. Landmark datasets such as GSE9006 (newly diagnosed pediatric T1D with longitudinal follow-up after insulin initiation), GSE55098, GSE72377, and GSE156035 have been analyzed both individually and in integrative fashion, yielding candidate biomarkers and co-expression modules enriched for immune and inflammatory processes [14, 15, 17, 19]. Concurrently, transcriptomic studies of adipose tissue and skeletal muscle in insulin-resistant states have delineated classical IR programs characterized by reduced expression of insulin-receptor-substrate and PI3K–AKT pathway components, altered lipid-handling genes, and downregulation of mitochondrial oxidative phosphorylation and biogenesis programs [20, 21]. Despite the availability of both data resources, systematic integration of T1D PBMC transcriptomes with tissue-derived IR signatures has remained limited. Such integration is methodologically non-trivial: PBMC profiles predominantly capture circulating immune cells and therefore cannot be interpreted as direct quantitative readouts of muscle glucose uptake or hepatic glucose production. Any observed molecular overlap must be framed rigorously as systemic transcriptional signatures that are compatible with, rather than diagnostic of, tissue-level IR mechanisms.

The present study proposes an exclusively bioinformatic, open-source integrative strategy designed to address this gap. We define five coordinated molecular axes that together capture the hypothesized IR phenotype in T1D: (1) intracellular insulin signaling components, (2) lipid metabolism and storage pathways, (3) metabolic inflammation and innate immunity, (4) mitochondrial function and oxidative stress, and (5) transcriptional signatures related to hepatic and skeletal-muscle insulin action that may be reflected, even if partially, in circulating cells. Within each axis, a focused panel of candidate genes (INSR, IRS1, IRS2, PIK3CA, AKT2, SLC2A4, FOXO1, GSK3B, PPARGC1A, CD36, SREBF1, FASN, DGAT1, PLIN2, TNF, IL6, NFKB1, NLRP3, TFAM, NDUFS1, SOD2, NFE2L2, HMOX1, GPX1 and related molecules) is designated for investigation; differential expression or module membership is not presupposed. Public GEO datasets are re-analyzed with a transparent, multi-layered pipeline that includes differential expression modeling (limma), network construction (WGCNA), pathway activity scoring (GSVA/ssGSEA), interaction mapping (STRING/Cytoscape), functional enrichment, and machine-learning-based feature prioritization. Independent validation across datasets is emphasized, and leukocyte inflammatory

programs are deliberately distinguished from classical metabolic-tissue IR programs. The overarching goal is to generate a prioritized, literature-anchored molecular map of IR-compatible signatures in T1D that can guide subsequent experimental and clinical investigation.

2. Methods

2.1. Data Sources and Overall Study Design

This investigation is conceived as a purely computational secondary analysis of publicly available transcriptomic data. No new human subjects were enrolled and no primary wet-laboratory experiments were performed. All analyses rely exclusively on open-access resources and free software. The core discovery and validation resources are the following Gene Expression Omnibus (GEO) series:

- • GSE9006 – Affymetrix HG-U133A/B microarray profiles of PBMCs from children with newly diagnosed T1D (n = 43), one-month and four-month follow-up samples after insulin initiation, newly diagnosed type 2 diabetes comparators (n = 12), and healthy controls (n = 24) [14]. This dataset uniquely permits examination of transcriptional changes temporally associated with the introduction of exogenous insulin therapy.
- • GSE55098 – Affymetrix HG-U133 Plus 2.0 PBMC expression data comparing T1D patients with healthy controls [15, 22].
- • GSE72377 – Independent Illumina PBMC cohort of T1D patients and controls used for external replication [17].
- • GSE156035 – PBMC profiles focused on recent-onset T1D and inflammatory signatures, providing an additional independent validation resource [19].
- • GSE245948 – Subcutaneous adipose tissue reference dataset that supplies a tissue-level insulin-resistance transcriptional signature against which circulating signatures can be compared by enrichment analysis.

The analytic strategy deliberately avoids simple re-identification of previously reported differentially expressed genes (DEGs) within these T1D PBMC datasets. Prior integrative studies have already catalogued overlapping immune-related DEGs across GSE9006, GSE55098 and GSE72377 [16, 17]. The novel contribution of the present framework lies in the systematic projection of classical IR pathway signatures onto the T1D leukocyte transcriptome, the multi-axis integration described below, and the explicit interpretive separation of immune versus metabolic signatures.

2.2. Predefined Molecular Axes and Candidate Gene Panels

Five a priori molecular axes were defined on the basis of established IR biology [3, 11, 20, 21] and the clinical hypothesis that IR in T1D involves coordinated alterations across signaling, metabolic, inflammatory and organellar domains:

Axis 1 – Intracellular insulin signaling: INSR, IRS1, IRS2, PIK3CA, AKT2 and immediate downstream effectors that transmit the insulin signal to metabolic and transcriptional endpoints.

Axis 2 – Glucose transport and metabolic regulation: SLC2A4 (GLUT4), SLC2A1, FOXO1, GSK3B, PPARGC1A, molecules that govern glucose uptake, gluconeogenic gene expression and mitochondrial biogenesis.

Axis 3 – Lipid metabolism and storage: CD36, SREBF1, FASN, DGAT1, PLIN2, genes that regulate fatty-acid uptake, de novo lipogenesis, triglyceride synthesis and lipid-droplet coating.

Axis 4 – Metabolic inflammation and innate immunity: TNF, IL6, NFKB1, NLRP3 and related inflammasome and NF-κB pathway components that link metabolic stress to chronic low-grade inflammation.

Axis 5 – Mitochondrial function and oxidative stress: PPARGC1A, TFAM, NDUFS1, SOD2, NFE2L2, HMOX1, GPX1, genes that control mitochondrial biogenesis, electron-transport-chain function, antioxidant defense and redox-sensitive transcription.

These genes constitute candidate investigation targets. Their differential expression, co-expression module membership or enrichment is not assumed a priori; rather, each is subjected to the multi-layered analytic pipeline described below.

2.3. Bioinformatic Pipeline and Statistical Framework

Expression matrices were retrieved from GEO. Quality control included inspection of array intensity distributions, detection of outlier arrays by principal-component analysis and hierarchical clustering, and assessment of potential batch effects. Normalization was performed with platform-appropriate methods (RMA for Affymetrix, quantile normalization for Illumina). When multiple datasets were combined, ComBat or similar empirical-Bayes batch correction was applied after confirmation that biological signal was not removed.

Differential expression was modeled with the limma package, employing moderated t-statistics and Benjamini–Hochberg false-discovery-rate control [23]. Genes with adjusted $P < 0.05$ and absolute log2 fold-change above a pre-specified threshold (typically 0.5) were retained for downstream annotation. Weighted gene co-expression network analysis (WGCNA) was used to construct signed co-expression networks, identify modules of highly correlated genes, and relate module eigengenes to T1D case–control status and, where available, to insulin-treatment duration [24]. Soft-thresholding power was selected to approximate scale-free topology. Module–trait relationships were evaluated by Pearson correlation of eigengenes with clinical covariates.

Gene-set variation analysis (GSVA) and single-sample gene-set enrichment analysis (ssGSEA) quantified the relative activity of curated IR-related gene sets within each individual sample [25]. Custom gene sets corresponding to the five predefined axes were constructed from the candidate panels and from publicly

available pathway collections (MSigDB, KEGG, Reactome). Enrichment scores were compared between T1D and control groups by linear modeling. Protein–protein interaction networks centered on axis-specific candidate genes were retrieved from STRING (confidence score ≥ 0.7) and visualized and analyzed in Cytoscape, with topological metrics (degree, betweenness, closeness) used to identify hub nodes [26]. Functional enrichment of DEG lists and of WGCNA modules was performed with clusterProfiler and Enrichr interfaces against Gene Ontology Biological Process, KEGG, and Reactome databases [27].

Supervised feature prioritization combined least absolute shrinkage and selection operator (LASSO) logistic regression with random-forest importance ranking. The feature space comprised individual gene expression values, GSVA axis scores, and selected module eigengenes. Nested cross-validation was used to estimate generalization performance and to stabilize feature rankings. External validation consisted of testing directional concordance of prioritized features and enrichment patterns across independent T1D PBMC datasets and of comparing circulating enrichment profiles with the adipose IR reference signature derived from GSE245948.

All analyses were designed to be fully executable with freely available R/Bioconductor packages (limma, WGCNA, GSVA, clusterProfiler, glmnet, randomForest) and publicly accessible databases (GEO, STRING, MSigDB), thereby ensuring complete reproducibility by independent investigators.

3. Results

3.1. Established Transcriptomic Landscape of T1D PBMCs

Re-examination of published analyses of GSE9006, GSE55098 and GSE72377 confirms the presence of robust and reproducible immune and inflammatory signatures in T1D PBMCs. Across these series, differentially expressed genes are consistently enriched for cytokine signaling, innate immune activation, antigen presentation, type I interferon responses, and apoptosis-related processes [14–17, 19]. In the foundational GSE9006 study, 282 genes differed between newly diagnosed T1D and healthy controls at a false-discovery rate of 0.05; IL1B, EGR3 and PTGS2 were among transcripts whose dysregulation partially resolved within four months of insulin therapy and were also observed in type 2 diabetes, suggesting a hyperglycemia-linked component [14]. Network analysis placed IL1B and MYC as highly connected nodes. Subsequent integrative analyses that combined GSE9006, GSE55098 and GSE72377 recovered overlapping DEG sets and identified hub genes involved in leukocyte activation and immune response [16, 17]. These established immune signatures constitute the baseline against which IR-axis enrichment is evaluated; the present framework does not seek to rediscover them but rather to test their coordination with classical metabolic IR pathways.

3.2. Axis-Specific Projection of Insulin-Resistance Signatures

Application of GSVA and ssGSEA using curated gene sets corresponding to the five predefined axes is expected to reveal heterogeneous enrichment patterns that reflect both the dominant immune activation of T1D and more subtle metabolic signals. Inflammatory and innate-immune gene sets (Axis 4) typically show elevated activity in T1D PBMCs relative to controls, consistent with the extensive prior literature. Mitochondrial and oxidative-stress gene sets (Axis 5) may display more variable or context-dependent enrichment, reflecting the competing influences of hyperglycemia, immune activation, and exogenous insulin exposure. Insulin-signaling and lipid-metabolism gene sets (Axes 1–3) are not anticipated to exhibit large-magnitude, uniform differential expression in circulating leukocytes; rather, subtle coordinated shifts detectable at the module level by WGCNA, or modest but consistent directional changes in enrichment scores, may emerge. Any observed statistical overlap with the adipose-tissue IR signature derived from GSE245948 is interpreted strictly as a systemic transcriptional echo rather than evidence of identical tissue pathology.

Within Axis 1 (intracellular insulin signaling), literature-supported candidates such as IRS1 and AKT2 have been examined in metabolic tissues of insulin-resistant individuals and show reduced expression or impaired phosphorylation [11, 20]. Their representation within T1D PBMC co-expression modules, if detected, would suggest a circulating correlate of signaling impairment rather than direct proof of muscle or hepatic IR. Axis 2 candidates (SLC2A4, FOXO1, PPARGC1A) likewise function primarily in insulin-target tissues; circulating transcript abundance may reflect systemic metabolic stress or immune-cell metabolic reprogramming. Axis 3 lipid-handling genes (CD36, SREBF1, FASN) participate both in adipocyte lipid storage and in macrophage foam-cell biology, providing a plausible biological bridge between metabolic and immune compartments. Axis 4 inflammatory mediators (TNF, IL6, NLRP3) are already well documented in T1D PBMCs and are expected to show robust enrichment; their inclusion serves to quantify the degree of coordination with the other four axes. Axis 5 mitochondrial and antioxidant genes (TFAM, NDUFS1, SOD2, NFE2L2) are of particular interest because mitochondrial dysfunction has been implicated in both T1D immune pathogenesis and classical IR [3, 12].

3.3. Network Topology, Module–Trait Relationships and Feature Prioritization

WGCNA modules that correlate significantly with T1D status and simultaneously enrich for one or more of the five IR axes constitute high-priority candidates for further scrutiny. Prior WGCNA applications to GSE9006 and related T1D datasets have already recovered modules enriched for immune response and cytokine signaling [16, 28]. The present framework extends these analyses by testing whether any T1D-associated modules also show statistically significant over-representation of insulin-signaling, lipid-metabolism or mitochondrial gene sets. STRING-derived interaction networks centered on the candidate gene panels allow visualization of connectivity between classical insulin-signaling nodes (INSR–IRS–PI3K–AKT) and inflammatory or mitochondrial hubs (TNF, NLRP3, PPARGC1A, TFAM). Topological metrics identify genes that occupy central positions and may therefore represent points of pathway cross-talk.

LASSO and random-forest procedures applied to the combined feature space (individual gene expression values, GSVA axis scores, and selected module eigengenes) generate a ranked list of molecular features that discriminate T1D from control samples while capturing information from multiple IR axes. Nested cross-validation stabilizes feature rankings and provides an estimate of generalization performance. External directional validation across independent PBMC datasets (GSE55098, GSE72377, GSE156035) is used to filter features that lack consistency of direction or statistical support. Features that survive this multi-stage prioritization become the primary candidates recommended for experimental follow-up.

3.4. Methodological Safeguards Against Signature Confounding

A central design decision of this study is the explicit separation of leukocyte inflammatory signatures from metabolic-tissue IR signatures. Enrichment of TNF, IL6 or NLRP3 pathways in PBMCs is recognized as an expected and well-documented T1D immune feature [14–19] and is not automatically equated with adipose or skeletal-muscle insulin resistance. Conversely, coordinated downregulation of IRS1/PI3K/AKT-related transcripts or of mitochondrial biogenesis genes, if observed, is interpreted only as a circulating molecular correlate that warrants tissue-level experimental confirmation. This distinction is maintained throughout enrichment reporting, network annotation, feature prioritization and discussion of biological implications. The adipose reference signature from GSE245948 is used solely for comparative enrichment analysis, never as a direct surrogate for PBMC biology.

4. Discussion

The central hypothesis guiding this work is that patients with T1D can develop an insulin-resistance phenotype characterized by coordinated molecular alterations spanning insulin signaling, lipid handling, immunometabolic inflammation, mitochondrial function and energy metabolism, and that elements of this phenotype may be partially independent of ambient hyperglycemia and absolute endogenous insulin deficiency [3–5, 13]. Chronic subcutaneous insulin exposure is regarded as a potential associated factor rather than a proven unidirectional cause. The integrative transcriptomic strategy outlined here is intended to generate testable molecular hypotheses rather than definitive mechanistic proof.

Prior PBMC transcriptomic studies in T1D have robustly documented innate immune activation, type I interferon signatures, altered apoptosis regulation and leukocyte activation [14–19]. These immune features overlap conceptually with the low-grade inflammation that accompanies IR in other contexts, yet they are not identical to the transcriptional programs observed in insulin-resistant adipose tissue or skeletal muscle [20, 21]. By deliberately projecting classical IR gene sets onto T1D leukocyte data and by employing network and machine-learning methods capable of detecting coordinated multi-axis patterns, the present framework seeks to identify points of molecular convergence while rigorously respecting tissue-context differences.

Several biological considerations motivate the five-axis structure. First, defects in proximal insulin signaling (INSR–IRS–PI3K–AKT) are foundational to IR in metabolic tissues [11]. Although circulating leukocytes are not primary insulin-target tissues, alterations in these pathways within immune cells can influence cytokine production, migratory behavior and metabolic reprogramming, thereby contributing to systemic inflammation. Second, lipid-metabolism genes regulate both energy storage and inflammatory lipid signaling; their dysregulation may link ectopic fat accumulation with innate immune activation. Third, the NLRP3 inflammasome and NF-κB pathways constitute a well-established molecular bridge between metabolic stress and chronic inflammation [12]. Fourth, mitochondrial dysfunction and oxidative stress are common downstream consequences of both hyperglycemia and sustained hyperinsulinemia and can further impair insulin action [3]. Fifth, transcriptional echoes of hepatic and muscle IR programs, if detectable even partially in blood, could serve as accessible surrogate markers for future clinical studies and therapeutic monitoring.

The inclusion of the longitudinal component of GSE9006 is particularly informative. Because this dataset contains newly diagnosed samples as well as one-month and four-month post-insulin-initiation samples, it permits examination of transcriptional trajectories temporally associated with the introduction of exogenous insulin therapy. Genes or enrichment scores that change systematically after insulin initiation, after adjustment for residual hyperglycemia, become candidates for association with peripheral insulin exposure. Such associations remain correlative; causal inference requires experimental designs that are beyond the scope of a purely bioinformatic study.

Methodological strengths of the proposed pipeline include exclusive reliance on public data and open-source tools, multi-dataset validation, a priori definition of biological axes, explicit safeguards against over-interpretation of leukocyte signatures, and full reproducibility. Limitations are equally important and must be acknowledged. PBMC transcriptomes cannot directly quantify insulin-stimulated glucose disposal in skeletal muscle or insulin-mediated suppression of hepatic glucose production. Cross-sectional public datasets generally lack concurrent gold-standard measures of insulin sensitivity (e.g., euglycemic–hyperinsulinemic clamp M-values) and precise quantification of cumulative exogenous insulin exposure. Batch effects across microarray platforms require careful statistical handling and may reduce power. Finally, any candidate genes or pathways prioritized by the computational workflow require orthogonal experimental validation in independent cohorts and, ideally, in relevant metabolic tissues (adipose, skeletal muscle, liver) obtained from individuals with T1D who have been carefully phenotyped for insulin sensitivity.

From a translational perspective, a validated circulating signature of IR-compatible pathways in T1D could support several clinical applications: risk stratification for cardiovascular complications beyond glycemia, monitoring of interventions aimed at improving insulin sensitivity (intensive lifestyle modification, metformin, SGLT2 inhibitors, or dual GIP/GLP-1 receptor agonists), and mechanistic exploration of the “double diabetes” phenotype. The framework is also compatible with future integration of single-cell RNA-seq, spatial transcriptomics, proteomics and detailed clinical phenotyping as such multi-omic resources become available for T1D cohorts.

In summary, this work supplies a transparent, reproducible bioinformatic roadmap for dissecting the molecular footprint of insulin resistance within the T1D transcriptome. By integrating immune-cell data with classical IR pathway knowledge under carefully defined interpretive constraints, it aims to advance understanding of an under-recognized yet clinically important facet of type 1 diabetes pathophysiology and to generate prioritized targets for experimental and therapeutic investigation.

5. Conclusion

An integrative transcriptomic strategy that leverages public T1D PBMC datasets and established insulin-resistance pathway knowledge can identify systemic molecular signatures compatible with insulin-resistance mechanisms. The five-axis framework, multi-layered analytic pipeline, and strict interpretive safeguards provide a rigorous foundation for prioritized experimental follow-up and for a refined systems-level understanding of immunometabolic dysfunction in type 1 diabetes.

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