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Exploring the Benefits of Computational Biology Approaches in Identifying New Drug Targets for Severe Disorders.

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Abstract

Identification and validation of drug targets remains a challenge in drug discovery. It is one of the primary causes of high failure rates of therapeutics and increasing drug development costs. Computational biology has emerged as an approach to address these challenges by developing in silico models to understand the underlying disease pathophysiology. Herein, we provide a comprehensive review of contemporary computational approaches that include integrative bioinformatics, network pharmacology, systems biology, and machine learning to aid target identification. We analyse and report the successes of these approaches for several complex diseases such as neurological disorders (Alzheimer's disease, Parkinson's disease, Huntington's disease), autoimmune disorders (Rheumatoid arthritis, Type 1 diabetes, Systemic lupus erythematosus), and metabolic disorders (Type 2 Diabetes, COPD, Coronary artery disease). For each disease, we provide representative examples highlighting the use of computational strategies to interrogate high-throughput omics datasets to identify key molecular drivers, regulatory networks, and druggable targets. This review highlights the computational methods accelerating the translation of large-scale multi-omics data into validated drug targets. Ultimately, these methods improve the precision and success of drug development for complex human diseases.

Keywords: Computational Biology, Target Identification, Drug Discovery, Machine Learning, Integrative Bioinformatics, Complex Diseases.

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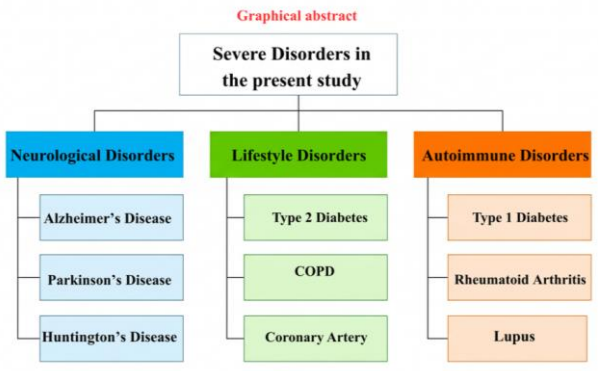

Figure 1: Graphical Abstract

1.Introduction

Selecting and validating drug targets is critical for drug development. Targets are often biomolecules like proteins and nucleic acids involved in the progression of a particular disease. These can be modulated for clinical benefit (Pun et al., 2023). Despite the improvements in biomedical research, only around 10% of drugs that start clinical trials will be given approval (Sun et al., 2022; Wong et al., 2019). This is due to poor selection of targets that do not have any therapeutic efficacy or cause toxicity later on. Better methods for therapeutic target selection are needed to increase success rates, accelerate time to market, and decrease costs.

For decades, scientists have developed drugs through high-throughput screening (HTS) of chemical libraries, in vitro biochemical assays, and rodent models. Though this drug discovery pipeline has produced many life-saving drugs, it is slow, expensive, and often does not translate to clinical trials (Vamathevan et al., 2019). Traditional methods fail to identify appropriate targets for multifactorial diseases. Diseases like neurodegeneration, autoimmunity, and diabetes have complex aetiologies that consist of multiple biological pathways. There is not one specific pathway that is dysregulated. Isolating one drug target using wet-lab techniques will not be sufficient (Barabási et al., 2011). Traditional experiments also cannot keep up with the growing volume of multi-omics data (Schrittwieser et al., 2021).

The advent of bioinformatics, artificial intelligence, and systems biology has allowed scientists to mine large datasets, construct gene-interaction networks, and predict drug-target interactions (Camacho et al., 2018). Genome-wide association studies (GWAS), network pharmacology, molecular docking, and machine learning allow scientists to identify and prioritize promising therapeutic targets (Lavecchia & Di Giovanni, 2013). These approaches have been shown in Figure 2. Additionally, these platforms are highly valuable for drug repurposing efforts. Identifying new clinical applications for approved drugs allows researchers to bypass early-stage safety and pharmacokinetic evaluations, thereby accelerating the development pipeline (Pushpakom et al., 2019).

This review investigates the application of various computational approaches for the discovery of novel therapeutic targets across three major categories of complex diseases:

- Neurological disorders, including Alzheimer's disease, Parkinson's disease, and Huntington's disease.
- Autoimmune conditions, such as Type 1 diabetes, rheumatoid arthritis, and systemic lupus erythematosus.
- Lifestyle-associated diseases, including Type 2 diabetes, chronic obstructive pulmonary disease (COPD), and coronary artery disease (GBD 2019 Diseases and Injuries Collaborators, 2020).

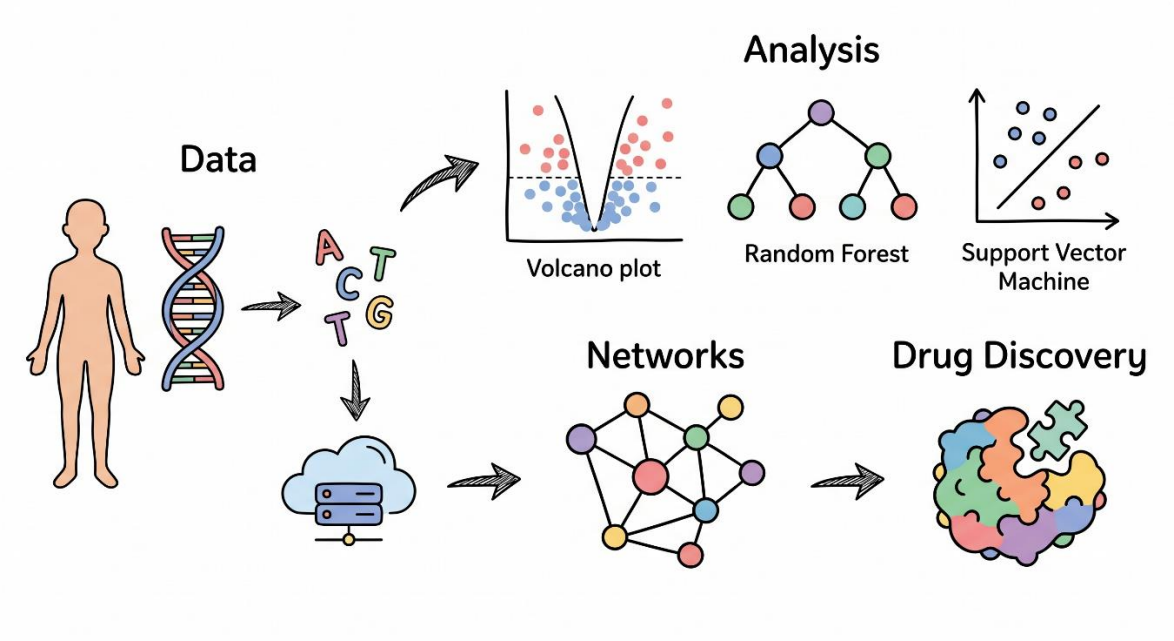

Figure 2: Some of the approaches discussed for drug target discovery.

2. Neurological Disorders

2.1 Alzheimer's Disease

Alzheimer's disease (AD) is the leading cause of dementia. It is marked by a progressive decline in memory and cognitive function (Grujičić & Nikolić, 2021). AD represents a major public health problem due to its intricate pathophysiology and the absence of disease-modifying treatments. Simplified brain pathology can be seen in Figure 3 (Al Madhagi & Nassar, 2025). Both genetic and environmental risk factors contribute to disease progression (Zhang et al., 2021).

There are two major hallmarks of the disease: extracellular amyloid plaque deposition and intracellular tauopathy neurofibrillary tangles (NFTs) (Al Madhagi & Nassar, 2025). Aβ plaques disrupt synaptic function and provoke a chronic inflammatory response by overactivating microglia and astrocytes. As a result, neuronal death occurs (Al Madhagi & Nassar, 2025; Zhang et al., 2021). Concurrently, hyperphosphorylated tau detaches from microtubules and aggregates into tangles within neurons. This destroys the internal transport mechanisms of the cell, leading to synaptic loss and cell death (Al Madhagi & Nassar, 2025; Wang et al., 2026).

Recent research has highlighted the dysregulation of the MAPK and PI3K-Akt pathways, which exacerbates neuroinflammation and tau phosphorylation (Al Madhagi & Nassar, 2025). Researchers have also observed aberrant cell behaviour, where post-mitotic neurons re-enter the cell cycle. This process is driven by dysregulated cell cycle components like CDK6, which pushes affected cells toward senescence and apoptosis (Al Madhagi & Nassar, 2025). More recently, focus has expanded to include non-coding RNAs. Particularly, circular RNAs can alter gene expression in the brain (Vakili et al., 2023).

AD affects approximately 50 million individuals worldwide (Dinesh et al., 2023; Grujičić & Nikolić, 2021). Age and genetics are non-modifiable risk factors in AD (Zhang et al., 2021). Certain lifestyle diseases, such as obesity and hypertension, can also affect the likelihood of developing the disease. By addressing these lifestyle influences, we could see prevention or delay in roughly 40% of dementia diagnoses (Zhang et al., 2021).

Treatment options are currently limited. Most pharmaceutical interventions treat symptoms only (Teipel et al., 2022). Cholinesterase inhibitors are commonly used as a first-line treatment despite limited efficacy and side effects (Lazarević-Pašti, 2023). NMDA receptor antagonists are additionally prescribed (Teipel et al., 2022). The newest class of amyloid-directed monoclonal antibodies have shown only slight benefit as well (Wang et al., 2026). Current drugs are also limited by biological barriers such as the blood-brain barrier

(Teipel et al., 2022). This demonstrates that simply inhibiting one molecular pathway of the disease is not enough. Accordingly, scientists are adopting computational strategies to find novel targets that address various aspects of the disease (Wang et al., 2026).

Emerging candidates such as CDK6 have shown promising results in preclinical models (Lee & Hoe, 2023). Computational investigations of circRNAs may provide crucial insights for developing biomarkers and targeted therapies (Sanadgol et al., 2023; Vakili et al., 2023).

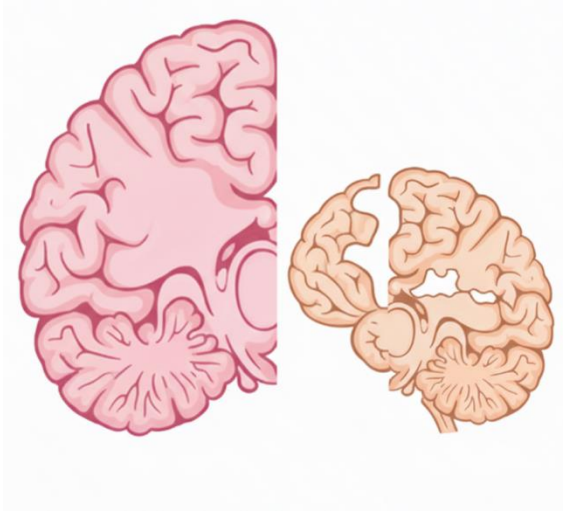

Figure 3: Normal vs Alzheimer's brain

An et al. (2025) merged weighted gene co-expression network analysis (WGCNA) with machine learning to find potential targets for Alzheimer's disease (AD). They began with a transcriptome dataset derived from post-mortem brain tissues. Using WGCNA, they identified an important module and intersected its genes with a list of known iron metabolism genes to reduce the list to 26 genes. Subsequently, four machine learning algorithms, Generalized Linear Model (GLM), Support Vector Machine (SVM), Random Forest (RF), and XGBoost were applied to these candidates. The Generalized Linear Model (GLM) demonstrated the greatest diagnostic accuracy with an AUC of 0.879. Then, single-sample gene set enrichment analysis (ssGSEA) was performed, which revealed CD8 T cells and natural killer cell presence in the samples. A strong correlation between the immune cells and MAP4, GPT, and HIRIP3 genes was also observed. The major outcomes of this study indicated that the genes MAP4, GPT, and HIRIP3 are viable therapeutic targets.

Cao et al. (2024) performed an integrated bioinformatics study to find prospective targets for Alzheimer's disease (AD). They worked with two microarray datasets from the GEO database and identified 197 common differentially expressed genes (DEGs). Next, they developed a protein-protein interaction (PPI) network using the STRING database with these DEGs. They used Cytoscape's MCODE and CytoHubba plugins to examine the network topology. The key finding of this research was six hub genes: RBL1, BUB1, HDAC7, KAT5, SIRT2, and ITGB1, located in three highly connected clusters within the network. The scientists then investigated the diagnostic capability of these genes using principal component analysis (PCA). PCA showed that their expression could distinguish AD samples from healthy controls. Receiver operating characteristic (ROC) curves were generated to confirm these results.

Lamisa et al. (2024) sought to locate potential biomarkers and repurpose existing drugs for Alzheimer's disease. They obtained RNA-Seq datasets from the GEO database and analyzed the data with DESeq2 to identify DEGs between AD patients and control groups. The analysis revealed 12 significant differentially expressed genes, with TTR standing out as the most downregulated. The Enrichr tool was then utilized for functional and pathway enrichment analysis. They found that downregulated genes such as TTR play a role in AD-related pathways including amyloid fiber formation and neutrophil degranulation. Further network analysis using STRING and Cytoscape identified TTR as one of five hub genes within the PPI network. A second screening with the DrugBank database discovered Levothyroxine

as a viable therapeutic drug. To validate this, the authors performed molecular docking, which demonstrated a strong binding affinity between TTR and the drug. Finally, they conducted molecular dynamics simulation using GROMACS, suggesting Levothyroxine as a repurposed drug for AD.

Al Madhagi and Nassar (2025) combined network pharmacology with in silico drug design to find possible therapeutic targets for Alzheimer's disease (AD). They selected two circular RNA (circRNA) datasets from the GEO database to identify 47 differentially expressed circRNAs in AD patients compared to controls. Using the RNAenrich platform, they performed enrichment analysis, which suggested that the circRNAs were involved in biological processes such as apoptosis control, neuronal death, and the PI3K-Akt and MAPK pathways. The scientists then developed a circRNA-miRNA-mRNA regulatory network and analyzed the interactions, which revealed CDK-6 as a druggable target. Following target selection, they performed virtual screening of compounds against the active site of CDK-6. The findings identified five ligands that demonstrated substantial binding affinity. To verify the findings, molecular dynamics (MD) simulations were performed, revealing that the selected ligands made persistent interactions with the target. Finally, they performed binding free energy calculations using the MM/GBSA approach, which revealed the high binding affinity of these compounds, proposing them as candidates for CDK-6 inhibitors.

2.2 Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder caused by both genetic susceptibility and environmental factors (Poewe et al., 2017). Mutations within the SNCA and LRRK2 genes are implicated in some forms of PD. In most instances, Parkinson's disease is understood to be the product of genetic predisposition interacting with environmental factors (Bloem et al., 2021). The pathophysiology of PD involves the loss of dopaminergic neurons in the substantia nigra region, as shown in Figure 4. This leads to a significant dopamine deficit in the basal ganglia, affecting the neural networks responsible for planning and movement.

At the molecular level, the main cause is the misfolding and aggregation of the alpha-synuclein protein. The misfolded proteins aggregate to form Lewy bodies, which are the hallmark of the disease (Kalia & Lang, 2015). Lewy bodies are the fundamental cause of neurodegeneration, which spread from neuron to neuron in a prion-like fashion. Other degenerative processes are also activated. These degenerative processes include severe mitochondrial dysfunction and persistent neuroinflammation (Usha Kiran et al., 2026). This cascade of events culminates in the motor symptoms of PD, including bradykinesia, resting tremor, stiffness, and postural instability (Bloem et al., 2021; Poewe et al., 2017).

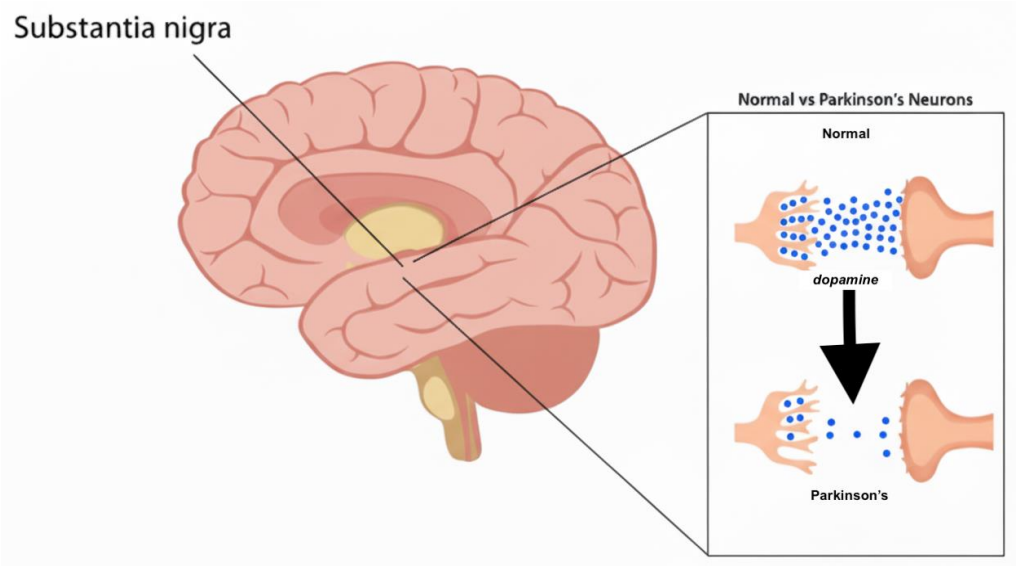

Figure 4: Parkinson's Disease pathophysiology

Wu et al. (2024) used an in-silico method to find novel biomarkers for Parkinson's disease (PD) by reviewing four microarray datasets from the GEO database. They began with differential expression analysis, which discovered 443 differentially expressed genes. They also performed weighted gene co-expression network analysis to identify modules of co-expressed genes linked with PD. By analyzing the intersection of these results, the scientists reduced the list to 42 probable targets. Functional enrichment of these targets indicated their involvement in important pathways, including dopamine synaptic activation and synaptic vesicle cycling. To further refine this list and identify key hub genes, three machine learning algorithms were used: least absolute shrinkage and selection operator, support vector machine recursive feature removal, and random forest. The consensus genes revealed by all three algorithms were SV2C and DENR, which were deemed key biomarkers for PD. The diagnostic utility of these genes was validated using receiver operating characteristic (ROC) curve analysis. Finally, protein-protein interaction (PPI) network construction and immune cell infiltration analysis was used to understand the functional role of these biomarkers.

Sasikumar et al. (2024) merged network pharmacology and structural biology to examine how dietary phytochemicals may help in Parkinson's disease (PD). They started by developing a phytochemical library and a library of FDA-approved PD drugs. Next, the researchers evaluated each compound for drug-likeness using SwissADME. They determined the protein targets of these compounds using the STITCH database. STRING was used to build the gene-interaction network. Hub genes were determined through applying various metrics such as degree, betweenness, and proximity centrality. It showed that EP300, MAPK1, and CREBBP were important genes within the network. Functional enrichment and pathway analysis revealed that these hubs were mainly involved in biological processes crucial to PD progression, such as neurodegeneration, apoptosis, and MAPK signalling. A ligand-target interaction network revealed that the phytochemical baicalein and the drug rasagiline were potential interactors with the hub gene MAPK1. Molecular docking was used to validate this prediction. Molecular dynamics simulations of 500 ns were carried out to evaluate how stable the binding was. Simulations showed that baicalein and rasagiline both formed stable complexes with MAPK1, establishing them as potential therapeutics.

Gao et al. performed a proteome-wide association study aimed at identifying druggable targets associated with Parkinson's disease (PD). The researchers combined GWAS genomic data with proteomic (pQTL) information gathered from both plasma and brain tissue. Analysis of plasma proteins was performed using the OTTERS framework, and FUSION was the tool for brain proteins. Subsequently, to establish causality, the researchers subjected their findings to summary-based Mendelian randomization (SMR), colocalization analysis, and reverse MR. Through this in silico screening, they identified 25 causal protein candidates: 16 plasma proteins associated with PD progression and 9 plasma proteins associated with PD onset. GPNMB was found to be a causal factor for PD development in both plasma and brain tissues, highlighting its potential as a therapeutic target. Further in silico analysis involved a phenome-wide MR to analyze putative side effects, which indicated a good safety profile. Next, they constructed a protein-protein interaction (PPI) network using the STRING database, uncovering a key interaction cluster linking proteins involved in both PD onset and cognitive decline. They also performed cellular distribution clustering using the Allen Brain Atlas to understand the targets' expression patterns. Finally, using the DrugBank database, they demonstrated that 15 of these 25 proteins are already regulated by existing medications, highlighting the benefits of drug repurposing in PD.

Torshizi et al. (2024) performed a proteogenomic analysis to identify novel targets for Parkinson’s disease. They conducted a genome-wide association study (GWAS) meta-analysis using data from the UK Biobank and FinnGen databases. The obtained SNP data was then merged with protein quantitative trait loci (pQTL) data, which discovered 577 proteins upregulated in PD. This list was refined using Mendelian randomization (MR) and colocalization analysis, producing 17 high-confidence protein targets. Next, using a protein-protein interaction (PPI) network, they conducted both hypothesis-free and hypothesis-driven investigations. The hypothesis-free method identified highly connected protein modules related to PD, while the hypothesis-driven approach investigated the direct neighbours of PD-related genes. A considerable enrichment of pQTL-associated proteins was observed. Finally, epigenomic and transcriptome analysis revealed dysregulated gene expression in dopamine neurons, microglia, and astrocytes from PD patients. By integrating all three analyses, nine proteins including LGALS3, CSNK2A1,

SMPD3, STX4, and LDLR were proposed as potential mediators of PD pathogenesis.

Tuersong et al. (2025) implemented a multi-omics strategy based on plasma circulating proteins to uncover new targets for Parkinson's disease dementia. They began with a two-sample Mendelian randomization (MR) investigation to establish a causal link between plasma proteins and PDD, which yielded 76 candidate genes. Next, differential expression analysis identified 1771 altered genes from transcriptome data derived from PDD brain tissue. The intersection of these two datasets indicated three important genes, which were further refined using ROC curves and machine learning models (LASSO and SVM-RFE). A nomogram prediction model exhibited remarkable accuracy for PDD diagnosis with an AUC of 0.925. Further in silico characterization using single-cell RNA-seq data revealed that USP8 and STXBP6 were most highly expressed in astrocytes and neurons. Finally, network analysis indicated co-localization between USP8 and STXBP6, demonstrating their potential as therapeutic targets for PD.

2.3 Huntington's Disease

Huntington's disease (HD) is an ultimately fatal, fully penetrant autosomal dominant neurodegenerative disorder resulting from a single unique mutation (Heinzmann et al., 2026). The mutation responsible for HD is caused by an unstable expansion of a cytosine-adenine-guanine (CAG) trinucleotide repeat in the Huntingtin (HTT) gene. Individuals with less than 36 CAG repeats are considered normal adults, whereas individuals with HD have 36 or more repeats in the HTT gene. The higher the number of repeats, the earlier the onset of disease and the greater severity of disease (Canbek et al., 2026).

This unstable CAG repeat translates into a longer polyglutamine (polyQ) tract when translated into the huntingtin protein (Htt). The mutant Htt misfolds and becomes proteolytically cleaved. The cleaved fragments accumulate into intracellular aggregates, forming neuronal intranuclear inclusion (Zuccato et al., 2010). These aggregates interfere with many vital cellular processes such as transcriptional regulation, proteolytic degradation pathways, and mitochondrial functioning. Medium spiny neurons (MSNs) of the striatum, an integral component of the basal ganglia network, are particularly susceptible to degeneration from the mutant Htt protein (Huang et al., 2026). Dysfunction and death of these neurons interrupt key motor and cognitive circuitry. It leads to the characteristic symptoms of chorea, cognitive decline, and psychiatric issues seen in Huntington's disease (Canbek et al., 2026).

Patel et al. (2023) utilized a computational and machine learning approach to uncover putative biomarkers for Huntington's disease (HD). They worked on a large transcriptome dataset sourced from the brains of young and aged mice. They first conducted bioinformatics preprocessing of miRNA and mRNA sequencing data to eliminate variance. Due to the uniformity across the data, all genotypes with 80 or more CAG repeats were classified as "HD" to enhance statistical power for machine learning methods. They utilized scikit-learn to create classification models using Recursive Feature Elimination (RFE) and k-best methods. This allowed them to train Random Forest, Adaboost, and Gaussian Naïve Bayes models to identify HD from wild-type (WT) data. A "predisposition model" was also constructed, trained on data from older mice and evaluated on data from younger mice. The findings demonstrated the performance of these models, predicting Gm5067 and Gm6089 genes. Their miRNA model identified six feature miRNAs (including hsa-miR-154-5p, hsa-miR-181a-5p, and hsa-miR-382-5p) as being differentially expressed in the blood of HD patients.

Vastrad and Vastrad (2025) utilized a bioinformatics approach to identify significant genes and signalling pathways in Huntington's disease (HD). They worked on a next-generation sequencing dataset, which included 28 HD samples and 20 normal samples. DESeq2 analysis was used to detect differentially expressed genes (DEGs), yielding a total of 958 DEGs, with 479 upregulated and 479 downregulated genes. To investigate the biological relevance of these genes, Gene Ontology (GO) and REACTOME pathway enrichment analyses were conducted using g:Profiler, revealing that the DEGs were primarily associated with processes such as multicellular organismal development, GPCR signaling, and MHC class II antigen presentation.

A protein-protein interaction (PPI) network was then built using the Integrated Interactions Database (IID) and assessed using Cytoscape software to uncover significant molecular players. Their network analysis identified ten hub genes: LRRK2, MTUS2, HOXA1, IL7R, ERBB3, EGFR, TEX101, WDR76, NEDD4L, and COMT, which were screened based on highest node degree, betweenness, stress, and proximity values. miRNA-hub gene and transcription factor (TF)-hub gene networks were constructed to determine possible regulation of

these genes. Target prediction revealed hsa-miR-4521 and SREBF1 as regulators of gene expression. To validate their findings, receiver operating characteristic (ROC) curve analysis was used, which pointed to the diagnostic relevance of these hub genes.

Meem et al. (2023) used computational and systems biology tools to identify biomarkers and therapeutic targets for Huntington's disease (HD). The authors first retrieved two different gene expression datasets, one from post-mortem brain tissue and another from neural cells, from the GEO database. Next, they used GEO2R and GREIN algorithms and established a consensus set of 162 DEGs. Functional enrichment of these common DEGs was conducted using DAVID and Enrichr tools, which led to Gene Ontology (GO) keywords including sequence-specific DNA binding and the KEGG pathway for antigen processing and presentation.

A PPI network was constructed from these DEGs using the STRING database. Analysis of this network identified ten significant hub genes: DUSP1, NKX2-5, GLI1, KLF4, SCNN1B, NPHS1, SGK2, PITX2, S100A4, and MSX1, which were downregulated. To understand gene regulation, the authors constructed interaction networks using Network Analyst. The researchers also pinpointed key transcription factors like FOXC1 and GATA2 using the JASPAR database, along with significant miRNAs, specifically hsa-miR-340 and hsa-miR-34a, identified through the TarBase database. Via Enrichr, they utilized the Drug Signatures Database (DSigDB) and determined that cytarabine and arsenite were possible molecules for modulation of the disease.

Cheng et al. (2020) combined bioinformatics and machine learning to identify drug targets for Huntington's disease. They worked on transcriptome data from prefrontal brain samples with 157 HD patients and 157 controls. Using an initial phase of feature reduction, researchers filtered the initial 10,000 genes down to 271 by selecting genes with an expression fold change > 1.2 or < 0.85. This dataset was then input into four separate machine learning models: decision tree, rule induction, random forest, and generalized linear model (GLM). After comparing the cross-validated accuracies of each model, researchers were able to produce a list of 66 potential genes that contribute to HD. Gene enrichment analysis and interaction network studies were performed using KOBAS 3.0 and the STRING database. KOBAS revealed that these genes were significantly enriched in pathways including transcriptional regulation, inflammatory response, neuron projection, and cytoskeleton organization. Interaction network analysis found genes like HSPB1, ITPKB, and POU4F2 to be closely interacting with the HTT protein.

3. Lifestyle Disorders

3.1 Type 2 Diabetes

Type 2 diabetes (T2D) is recognized as a worldwide public health issue that currently affects approximately 537 million individuals. Low-income and middle-income countries have been experiencing an increase in T2D incidence (Ong et al., 2023). Genetic and environmental factors, along with unhealthy lifestyles, combine to trigger T2D. Conditions that commonly overlap with diabetes include obesity, physical inactivity, and poor nutrition (Cole & Florez, 2020; Defronzo et al., 2015).

Type 2 diabetes is characterized by insulin resistance and dysfunction in pancreatic beta-cells (Siddiquea et al., 2026). The pathophysiology is depicted in Figure 5. Initially, tissues like muscle, liver, and fat develop resistance to insulin, forcing the pancreatic β-cells to respond by increasing insulin secretion to maintain normal blood glucose levels. After a while, these β-cells cannot keep up with the body's demand for insulin, which leads to insulin deficit and chronic hyperglycaemia (Halban et al., 2014).

The disease process is enhanced by chronic, low-grade inflammation. It is strongly correlated with obesity, as excessive levels of free fatty acids disrupt both insulin signalling and β-cell function (Arreguín-Cano et al., 2026). Persistent hyperglycaemia causes long-term microvascular complications (retinopathy, nephropathy, neuropathy) and macrovascular complications (coronary artery disease, stroke), which contribute to morbidity and mortality (Cole & Florez, 2020; Siddiquea et al., 2026).

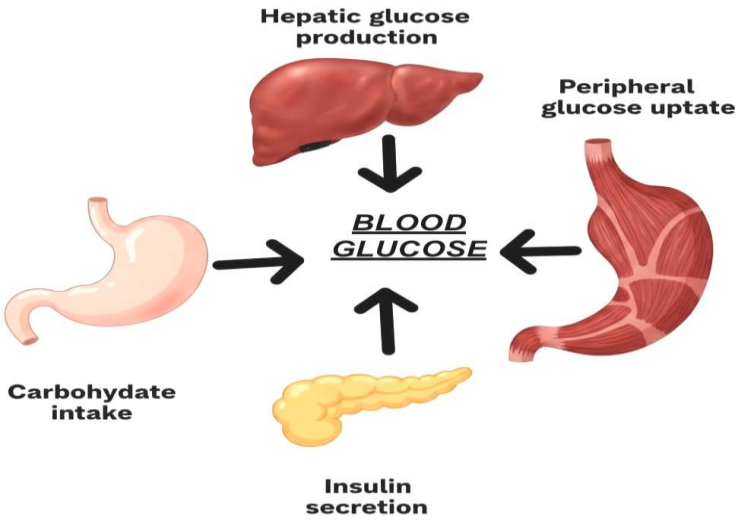

Figure 5: Type 2 Diabetes contributing factors.

Alhumaydhi (2022) worked to identify significant genes and potential therapeutic targets for Type 2 Diabetes Mellitus (T2DM) in their study. They extracted two microarray datasets from the GEO database and analysed them against T2DM-related genes from DisGeNET. A differential gene expression analysis was conducted to pinpoint dysregulated genes, keeping P-value < 0.05. They obtained a curated list of 61 genes for further investigation. Functional enrichment and pathway mapping of these genes were performed using Gene Ontology (GO) and Reactome databases, highlighting their involvement in pathways such as glucagon signaling and cytokine signaling.

Next, a Protein-Protein Interaction (PPI) network was built using the STRING database in Cytoscape, which was further improved by co-expression analysis to decrease the gene list. The network analysis highlighted CD8A and CCL5 as the hub genes. A further search in the Drug Gene Interaction Database (DGIdb) revealed these genes were separate targets not related to existing medications. Finally, to evaluate their druggability, molecular docking of a phytochemical library against the protein structures of CD8A and CCL5 was performed, followed by 100 ns molecular dynamics (MD) simulations on the most promising protein-ligand complexes. The simulation data verified the stability of these interactions, leading the authors to conclude that CD8A and CCL5 are potent biomarkers for the diagnosis and therapy of T2DM.

Di et al. (2021) employed an in-silico network pharmacology approach to investigate the mechanism of berberine against Type 2 Diabetes Mellitus (T2DM). They identified molecular targets for BBR from the STITCH, CHEMBL, and PharmMapper databases, while T2DM-associated targets were obtained from the TTD, DrugBank, and PharmGKB databases. The intersection of these datasets uncovered 31 protein targets associated with both BBR and T2DM. DAVID was used to perform functional enrichment analysis on the targets and revealed their involvement in 21 biological processes (BPs) and 18 KEGG pathways. Oxidation-reduction, steroid metabolism, and glucose homeostasis stood out as crucial biological processes in which these genes were involved. Key pathways included PPAR signaling, insulin resistance, and the AMPK pathway. A "BP-Target-Pathway" network was developed using Cytoscape, which indicated RXRA, KCNQ1, and NR3C1 as critical hub targets regulating BBR's antidiabetic effects.

Alur et al. (2023) conducted a bioinformatic analysis to discover key molecular biomarkers for Type 2 Diabetes Mellitus (T2DM). The authors analysed an NGS dataset from the GEO database. Using the Limma tool in R, they detected 927 differentially expressed genes (DEGs) between T2DM and control samples. A total of 461 upregulated and 466 downregulated genes were identified. Next, Gene Ontology (GO) and REACTOME pathway analyses were conducted using the g: Profiler tool. The DEGs were largely focused on biological processes such as protein metabolic activities, establishment of localization, and overall metabolism.

A Protein-Protein Interaction (PPI) network was developed using the IID interactome database. Through topological analysis of the PPI network based on various

parameters, they identified 10 key hub genes: APP, MYH9, TCTN2, USP7, SYNPO, GRB2, HSP90AB1, UBC, HSPA5, and SQSTM1. To understand the regulatory landscape, a miRNA-hub gene regulatory network using the miRNet database and a TF-hub gene regulatory network using the NetworkAnalyst database were created. The prognostic value of the 10 identified hub genes was examined using Receiver Operating Characteristic (ROC) curve analysis, which demonstrated their efficacy as potential biomarkers. The investigation demonstrated these 10 hub genes as novel targets for T2DM.

Zhong et al. (2023) utilized a network pharmacology framework to investigate empagliflozin for Type 2 Diabetes Mellitus (T2DM). They first identified the drug's potential targets through the TCMSP, Swiss Target Prediction, and SuperPred databases. T2DM-related genes were identified from GeneCards, OMIM, and GEO datasets. With the common targets of the drug and T2D, a protein-protein interaction (PPI) network was created using STRING and Cytoscape. Functional enrichment analysis via Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) indicated that empagliflozin exerted therapeutic effects on several critical pathways, including the AMPK, MAPK, NF-κB, HIF-1, PI3K-Akt, and FoxO signalling pathways.

Molecular docking was conducted for validation, which indicated binding affinities to multiple key proteins. The study concluded that empagliflozin exerts its therapeutic advantages by modulating critical targets such as SLC5A2, SLC5A1, LDHA, KLK1, KLF5, and GSTP1, which are active in T2DM pathogenesis.

Qi et al. (2023) worked to identify novel therapeutic targets for the T2DM drug sitagliptin, beyond its known target, the DPP4 gene. They used a network pharmacology approach where probable drug targets were identified using the PharmMapper and Super-PRED databases, while T2DM-related targets were gathered from DrugBank and TTD. The intersection of these datasets revealed 35 common targets. Next, a PPI network created using the STRING database in Cytoscape demonstrated that ACE2 was strongly related to DPP4.

To corroborate their findings, the scientists performed molecular docking using AutoDock Vina, which predicted a binding affinity of -8.7 kcal/mol between sitagliptin and ACE2. Then, a 50 ns molecular dynamics (MD) simulation was performed using Gromacs, which demonstrated the stability of the complex. Finally, KEGG pathway enrichment analysis suggested that sitagliptin's action via ACE2 might involve the ACE2/Ang-(1-7)/MasR axis, suggesting a possible mechanism.

3.2 Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a complex, progressive disease characterized by irreversible airflow limitation and obstruction. It is usually precipitated by exposure to irritants or pollution (Agustí et al., 2023). Globally, COPD is considered a disease epidemic and affects over 380 million people. COPD can present as bronchitis or emphysema, as shown in Figure 6 (Adeloye et al., 2015; GBD 2019 Diseases and Injuries Collaborators, 2020; Meng et al., 2026).

COPD is caused by an exaggerated inflammatory response to particles or chemicals that are breathed in (Xie et al., 2026). This chronic inflammation (Barnes, 2013a) leads to a critical protease-antiprotease imbalance where elastase and matrix metalloproteinase enzymes lead to tissue damage (Zhang et al., 2026). At the same time, oxidative stress from pollutants also induces cellular damage (Kirkham & Barnes, 2013; MacNee, 2005). The lungs undergo structural changes, along with hypersecretion of mucus and tissue fibrosis (Agustí et al., 2023; Caramori et al., 2014).

Current therapy involves bronchodilators and inhaled corticosteroids (ICS). These treatments offer symptom relief and slow the worsening of the condition (Celli & Wedzicha, 2019; Pavord et al., 2018). Current drugs fail to stop the continuous loss in lung function, cannot restore damaged tissues, and are ineffective against neutrophilic inflammation (Barnes, 2013a, 2013b). This highlights the essential need for novel drugs that address the root causes.

Promising novel strategies include controlling inflammation with CXCR2 antagonists (Hoenderdos & Condliffe, 2013), restoring the protease-antiprotease balance (Zhang et al., 2026), combating oxidative stress by activating pathways like Nrf2 (Kirkham & Barnes, 2013), neutralizing damage-associated molecular patterns (DAMPs) that perpetuate lung injury (Pouwels et al., 2014), and clearing pro-inflammatory senescent cells with senolytics (Barnes et al., 2019). Regenerative therapy is also considered a long-term goal for tissue restoration (Weiss, 2014).

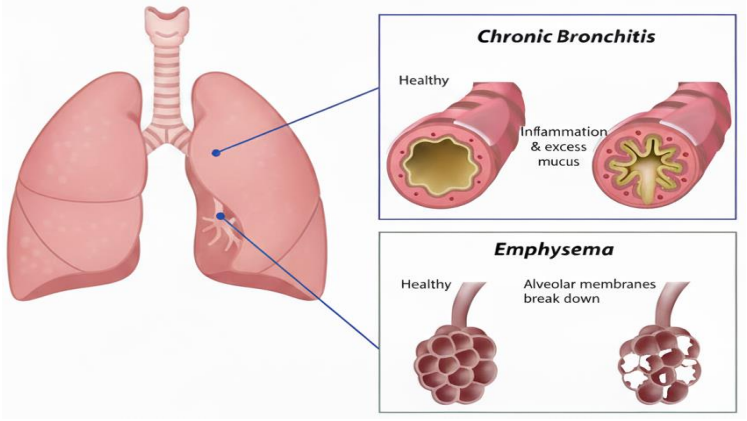

Figure 6: COPD pathophysiology

Delkhah et al. (2025) utilised a bioinformatic and machine learning approach to identify genes involved in smoking-induced COPD. They downloaded five transcriptome datasets from the GEO database and selected smoker samples to evaluate individuals with COPD versus controls. They performed differential expression analysis using the "limma" R package and weighted gene co-expression network analysis (WGCNA) to identify genes linked with COPD. After combining the two datasets, the intersecting genes were input into a machine learning workflow to identify biomarkers. This involved using a Random Forest (RF) method, followed by Least Absolute Shrinkage and Selection Operator (LASSO) regression to further refine the list. Through receiver operating characteristic (ROC) curve analysis, they identified six genes: CCL19, FCRLA, CD79A, SLITRK6, GRM8, and KRT4 as potential biomarkers and therapeutic targets for intervention.

Zhao et al. (2021) performed a bioinformatics analysis to identify genes linked with macrophage polarization in COPD. They selected a suitable peripheral blood gene expression dataset for analysis. A Weighted Gene Co-expression Network Analysis (WGCNA) was performed to identify 4,922 genes linked with macrophage polarization. Using the DESeq2 package, they discovered 203 differentially expressed genes (DEGs) in COPD and normal samples. By intersecting these two sets, they identified 25 genes linked to both COPD and macrophage polarization. Functional annotation of these genes was performed using the DAVID database, which identified three immune-related genes: GEM, S100B, and GZMA.

Protein-Protein Interaction (PPI) networks revealed that GEM may be involved in regulating PI3K/Akt/GSK3β signalling. To analyse the druggability of these candidates, receiver operating characteristic (ROC) curves were used. Their findings revealed that GEM has the ability to discriminate COPD from normal samples as a diagnostic biomarker.

Zhang et al. (2022) applied a machine-learning approach to identify COPD biomarkers linked to immune cell activity. They first combined two Gene Expression Omnibus (GEO) datasets and utilized the "limma" package to discover 80 differentially expressed genes (DEGs) between COPD and control samples. To refine this gene list, they applied Least Absolute Shrinkage and Selection Operator (LASSO) regression and Support Vector Machine Recursive Feature Elimination (SVM-RFE) analysis. The intersection of the results from both algorithms revealed four possible biomarkers, which were tested in an independent validation dataset.

This step confirmed that two genes, SLC27A3 and STAU1, were significantly upregulated in COPD, confirmed by their AUC values of 0.900 and 0.971. The CIBERSORT algorithm was used to estimate the proportions of 22 immune cells. It revealed that the expression of SLC27A3 and STAU1 was significantly correlated with the infiltration of several immune cells, including plasma cells, resting NK cells, activated mast cells, and memory B cells.

Chen et al. (2022) attempted to identify critical hub genes of smoking-linked COPD. They selected two distinct GEO datasets, then using the Limma and AFFy R packages, they identified 132 differentially expressed genes (DEGs) between smokers with severe COPD and healthy smoker controls. To understand the biological relevance of these DEGs, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG)

pathway analyses were performed, indicating enrichment in processes such as extracellular matrix (ECM)-receptor interaction and PI3K-Akt signalling.

They also conducted a Weighted Gene Co-expression Network Analysis (WGCNA) on one dataset, which revealed the "brown module" as the gene cluster substantially linked with COPD. The intersection between the DEGs and the genes from the cluster identified nine hub genes: COL14A1, SULF1, MOXD1, CXCL12, CHRNA1, COMP, POU2AF1, MMP11, and THBS2.

Banaganapalli et al. (2022) conducted a multi-omics study with transcriptome and genomic data to identify common genes involved in COPD and lung cancer. They used two microarray datasets, one from blood and one from lung tissue, to identify 63 common DEGs. Using these common DEGs, they established a Protein-Protein Interaction (PPI) network in Cytoscape. The network was analysed based on centrality metrics to identify important genes. This revealed 12 major hub gene-network clusters, including SREK1, TMEM67, IRAK2, MECOM, and ASB4.

Functional enrichment analysis established the association of these genes with protein degradation, inflammatory cytokine release, and immune cell activity. To verify these results, the hub genes were searched in Genome-Wide Association Study (GWAS) databases, which indicated that variations in IRAK2 and MECOM are strongly linked with eosinophil counts and pulmonary function, respectively. Further analysis with cancer expression databases found that some of these COPD-associated hub genes were also implicated in lung cancer.

3.3 Coronary Artery Disease

Coronary artery disease (CAD) is a chronic progressive degenerative disease characterized by the development of atherosclerotic plaques in the walls of coronary arteries (Figure 7) (Malakar et al., 2019). The coronary arteries develop plaque that slowly narrows the lumen of the artery, decreasing blood flow and oxygen delivery to the heart. CAD can present as stable angina pain or progress to myocardial infarction (Knuuti et al., 2020).

It occurs when lipids, inflammation, and thrombosis arise as a result of endothelial dysfunction. This allows low-density lipoprotein cholesterol (LDL-C) to infiltrate the wall of the artery (Gimbrone & García-Cardeña, 2016; Libby et al., 2002). Oxidized LDL-C then attracts inflammatory components that trigger the migration of monocytes, which become foam cells (Moore et al., 2013; Stocker & Keaney, 2004). Smooth muscle cells migrate to the plaque in response to inflammation and create a fibrous cap over the plaque. Continued inflammation can rupture the cap, causing erosion of the plaque and resulting in a life-threatening thrombus (Faxon et al., 2004; Libby, 2002; Verboova et al., 2026).

Risk factors that drive the disease include dyslipidemia, hypertension, and diabetes (Ference et al., 2017; Roth et al., 2020; World Health Organization, 2020; Yusuf et al., 2020). Treatments for coronary artery disease include statins, antiplatelet medicines, and antihypertensive agents. Additionally, interventions such as stenting or bypass graft surgery may be utilized (Cholesterol Treatment Trialists' Collaboration, 2010; Knuuti et al., 2020; Malakar et al., 2019; Sabatine et al., 2017).

Despite these medications, there remains a high likelihood of adverse events because currently available therapies only arrest disease progression and do not promote plaque regression. Additionally, current therapies do not target inflammation or address risk factors such as Lipoprotein(a) (Campbell et al., 2008; Libby et al., 2002; Tsimikas, 2017).

The high morbidity and mortality associated with coronary artery disease underscores the need for new therapies that extend beyond lowering LDL-C, such as therapies that target inflammation, develop Lp(a)-lowering therapies such as antisense oligonucleotides, treat triglyceride-rich lipoproteins, and promote plaque regression utilizing new pathways such as senolytics (Bhatt et al., 2019; Childs et al., 2016; Duewell et al., 2010; O'Donoghue et al., 2022; Ridker et al., 2017).

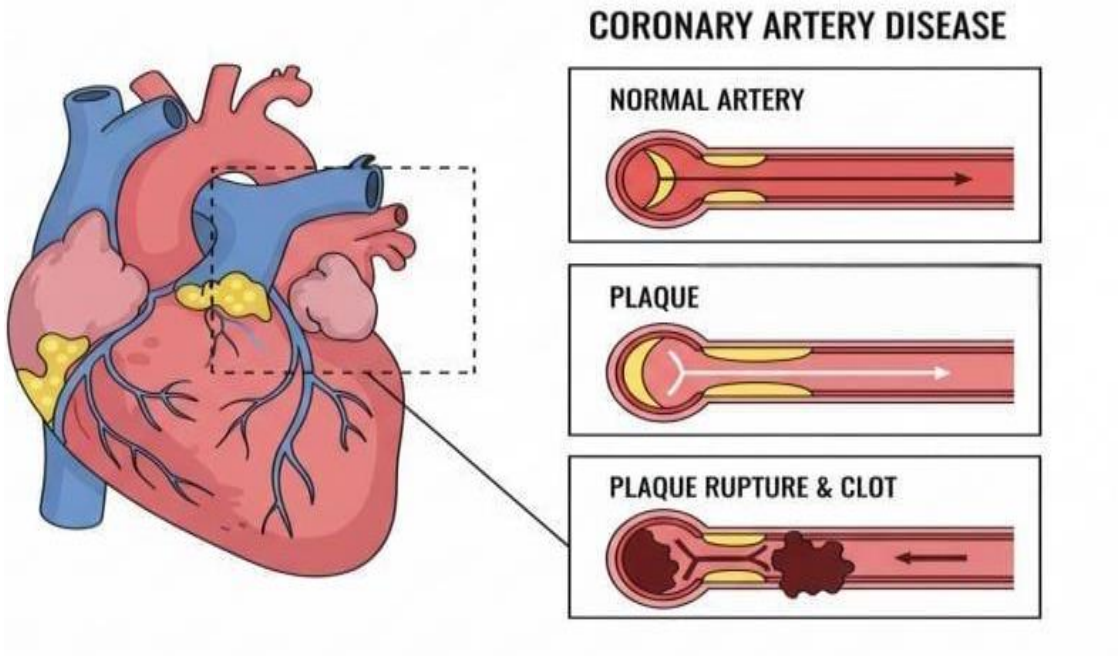

Figure 7: Coronary Artery Disease pathophysiology

Zhang et al. (2022) worked to identify potential biomarkers and drug targets for coronary artery disease (CAD). They obtained microarray expression data from two GEO datasets and used the limma R package to identify differentially expressed miRNAs between CAD patients and healthy controls. Their target analysis pointed toward miR-22-3p as a potential biomarker for CAD. They used the miRWalk database to predict the target genes for this microRNA. Following this, GO and KEGG analyses were conducted on the target genes, uncovering their enrichment in pathways such as HIPPO signalling.

The authors constructed a ceRNA interaction network centered around miR-22-3p. When the authors overlaid miR targets from the TransmiR database on the network, eight transcription factors emerged as novel targets associated with CAD: CTCF, JUN, JUND, NFATC1, NFE2L2, RAD21, RELA, and TAL1.

Huang et al. (2022) integrated bioinformatics and machine learning techniques to discover candidate biomarkers associated with coronary artery disease (CAD). The authors used three GEO datasets and applied the limma package in R to identify differentially expressed genes (DEGs). Three machine learning algorithms were utilized to further narrow down the list of genes. These included least absolute shrinkage and selection operator (LASSO), support vector machine recursive feature elimination (SVM-RFE), and random forest (RF).

The researchers pinpointed four crucial hub genes as potential therapeutic targets and biomarkers by examining the overlap in data from all three algorithms. The identified hub genes were MMP9, PELI1, BTG2, and ITGB2. Functional enrichment analysis revealed that the DEGs were implicated in inflammatory pathways such as IL-17, NF-kappa B, and TNF signalling. Finally, the authors employed the CIBERSORT algorithm, revealing that all four identified hub genes correlated with the infiltration of diverse immune cells such as neutrophils and CD8 T cells. Their work established a clear link between the hub genes and inflammation observed in CAD.

Jia et al. (2025) worked to identify biomarkers for CAD based on phagocytosis regulatory factors (PRFs). The researchers looked for PRFs showing differential expression levels in a microarray dataset using limma for analysis. Following this, WGCNA was applied to pinpoint genes strongly connected to the disease, resulting in 503 genes and 32 CAD-related PRFs. STRING was used to construct a protein-protein interaction (PPI) network to screen for gene interactions and hub genes.

To further refine the list, multiple machine learning approaches were employed. Least absolute shrinkage and selection operator (LASSO) and support vector machine

recursive feature elimination (SVM-RFE) were applied to the candidate genes. The intersection of these results indicated six biomarkers as probable therapeutic targets: IL1B, TLR2, FCGR2A, SYK, FCER1G, and HCK. Furthermore, they built a regulatory network revealing that transcription factors such as RUNX1 and SPI1, and the microRNA hsa-miR-1207-5p, play a role in the expression of these biomarkers. The DGIdb database was used to identify 95 probable therapeutics. The researchers noted that aspirin could alter the expression of IL1B and FCER1G genes.

Chang et al. (2025) merged bioinformatics methods and machine learning to identify biomarkers for coronary artery disease (CAD). The researchers first merged eight independent RNA-seq datasets from the GEO database and performed differential expression analysis to discover genes associated with CAD. To refine this list, scientists used three machine learning algorithms: least absolute shrinkage and selection operator (LASSO), random forest (RF), and support vector machine-recursive feature elimination (SVM-RFE).

The intersection from these three approaches identified eleven important hub biomarkers: ITM2B, GNA15, PLAU, GNG11, HIST1H2BH, SLC11A1, RPS7, DDIT4, CD83, GNLY, and S100A12. Independent dataset validation confirmed ITM2B as the most significant biomarker, suggesting reduced expression in CAD. Functional enrichment and the CIBERSORT algorithm further indicated that these genes are involved in immunological responses, apoptosis, and cardiac muscle contraction. The genes were also linked to the infiltration of CD8+ T cells and NK cells.

4. Autoimmune Disorders

4.1 Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a chronic autoimmune disease marked by persistent synovial inflammation (Dorgó et al., 2026). It leads to progressive joint destruction, as shown in Figure 8. It affects 0.5–1.0% of people worldwide, with females being affected three times more than males (Alamanos et al., 2006; Myasoedova et al., 2010). Beyond the joints, RA can inflict damage on other parts of the body, including the skin, heart, and lungs (Xie et al., 2026).

Its development is influenced by a combination of genetic elements like HLA-DRB1 and environmental exposures (Kumar et al., 2026). Smoking causes modifications to self-proteins that are not recognized by the immune system, provoking an immune response (Klareskog et al., 2006). Self-tolerance is lost in RA, and T cells and B cells react against self-tissues (Liu et al., 2026). Immune complexes are deposited in joints, driving synovitis through pro-inflammatory cytokines (Bartok & Firestein, 2010; Choy & Panayi, 2001). The synovium of the joints becomes inflamed and transforms into pannus, an aggressive tissue that erodes cartilage and bone (Gravallese, 2002; Xie et al., 2026).

Disease management involves controlling inflammation with methotrexate (Singh et al., 2016), the use of TNF inhibitors (Burmester & Pope, 2017), and JAK inhibitors (Yamaoka, 2016). About 40% of patients do not respond well to current therapies, and these treatments only suppress symptoms rather than offering a cure (Kearsley-Fleet et al., 2018; Schett et al., 2016). This highlights the need for novel therapeutic targets that address the root cause of the disease.

Novel approaches aim to target synovial fibroblasts (Croft et al., 2019), upregulate regulatory T-cells (Ferreira et al., 2019), downregulate the BTK pathway (Ringheim et al., 2021), and target the metabolism of immune cells (Weyand & Goronzy, 2021). Treating microbial dysbiosis has also been found to modulate the disease (Scher et al., 2016).

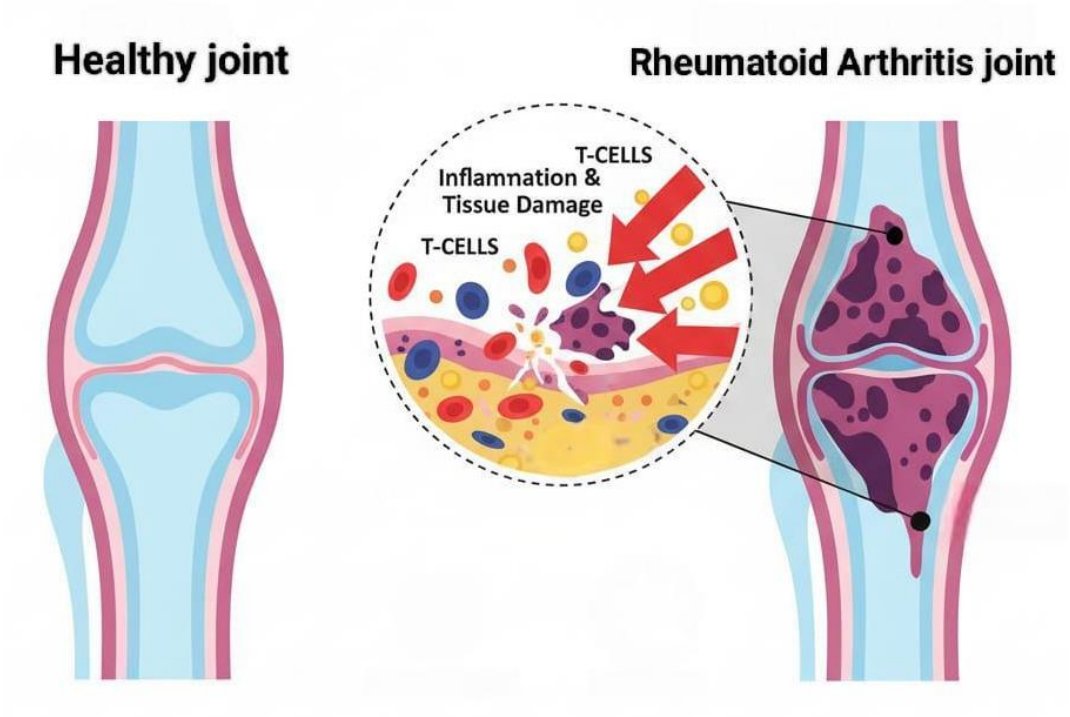

Figure 8: Rheumatoid Arthritis Pathophysiology

Xu et al. (2025) used computational methodologies to identify novel biomarkers and drug targets for rheumatoid arthritis (RA) connected to disulfidptosis. They first obtained microarray datasets from the GEO database. Differential expression analysis along with WGCNA was performed to uncover genes related to RA. By comparing their results with a list of disulfidptosis-related genes from the FerrDb database, the researchers identified two critical genes: OXSM and ACTN4.

Further, multivariate Cox regression and ROC curve analysis revealed OXSM as a major hub gene, exhibiting strong diagnostic potential with high accuracy. CIBERSORT revealed a significant correlation between high OXSM expression and enrichment of gamma delta T cells and M2 macrophage immune infiltrates in RA. The researchers searched the Comparative Toxicogenomics Database and identified twelve drugs predicted to inhibit OXSM. Molecular docking results showed that ICG 001 had the highest binding affinity for OXSM. Binding stability of the complex was confirmed with 100 ns molecular dynamics simulations.

Liu et al. (2025) used an in-silico methodology, combining network pharmacology and molecular docking, to investigate kaempferol's mechanism in rheumatoid arthritis (RA). Potential targets of kaempferol were retrieved from the TCMSP database, while genes related to RA were searched from GeneCards, OMIM, and DrugBank databases. Thirty-five overlapping targets were identified and used to construct a protein-protein interaction (PPI) network using the STRING plugin in Cytoscape.

Eleven target genes were identified from topological analysis of the network. Validation of the results was performed through analysis of three GEO microarray datasets and revealed that MAPK8, PPARG, and NF-kB were upregulated in RA tissues. Using AutoDock Vina, molecular docking was carried out to assess the binding of kaempferol to the selected proteins. Results demonstrated that kaempferol had the highest binding affinity toward MAPK8, forming the most stable complex.

Ao et al. (2023) sought to pinpoint key genes and biomarkers for rheumatoid arthritis (RA). They downloaded four microarray datasets from the GEO database. The authors utilized the Robust Rank Aggregation (RRA) approach to identify 184 DEGs between RA and normal tissues. Then, they constructed a PPI network and utilized the cytoHubba plugin of Cytoscape to identify the top 20 hub genes. Meanwhile, they performed WGCNA on the DEGs and identified a key module of genes related to RA.

The intersection of these two analyses yielded four hub genes: LCK, CXCL13, IGHM, and MS4A1. The authors

confirmed the diagnostic value of these four genes with ROC curve analysis. Moreover, the study demonstrated that expression levels of the hub genes were correlated with infiltration of different immune cells through ESTIMATE and ssGSEA algorithms.

Jin et al. (2024) aimed to identify therapeutic targets for rheumatoid arthritis through genomic and proteomic approaches. The authors performed a proteome-wide Mendelian Randomization (MR) analysis to investigate the effects of 734 circulating proteins on RA. Summary statistics from protein quantitative trait loci (pQTL) and rheumatoid arthritis GWAS were used for the study. The authors validated their results using Bayesian co-localization, Steiger filtering, and reverse MR. Phenotype scanning was conducted to remove bias due to pleiotropic effects.

This identified four proteins associated with RA: SWAP70, SIGLEC6, ISG15, and FCRL3. Finally, the authors constructed a protein-protein interaction (PPI) network. The network identified that these targets interact with current therapeutic targets. FCRL3 was found to be associated with CTLA4 and MS4A1, targets of rheumatoid arthritis medications abatacept and rituximab, respectively. This provided justification for their participation in RA pathogenesis.

To identify immune-related biomarkers for RA, Chen et al. (2022) used network analysis along with machine learning. First, three gene expression datasets from the GEO database were merged. Then, a Weighted Gene Co-expression Network Analysis (WGCNA) was performed on the integrated data. This identified a cluster comprised of 87 genes related to RA.

To refine this list, the authors applied a Least Absolute Shrinkage and Selection Operator (LASSO) regression model and a Support Vector Machine Recursive Feature Elimination (SVM-RFE) algorithm. The intersecting genes provided 13 possible biomarkers, and their diagnostic efficiency was examined using Receiver Operating Characteristic (ROC) curve analysis. This revealed three essential hub genes: FADD, CXCL2, and CXCL8. CIBERSORT revealed correlations between the expression of these genes and the infiltration of various immune cells.

Pati et al. (2025) used an in-silico approach to identify novel drug targets for RA. The authors identified phytocompounds present in rhizome extract of Curcuma caesia, selected after ADMET study. The protein targets for these compounds were identified using SwissTargetPrediction, SEA, SuperPred, and PharmMapper prediction tools. These targets were cross-checked with already established RA-associated genes from DisGeNet and GeneCards databases to derive 41 probable targets for RA.

To uncover hub proteins, a protein-protein interaction (PPI) network was created for these targets using the STRING database. The analysis highlighted NFKB1, PRKCA, and RAC1 as the central targets for RA. The researchers then employed molecular docking via the Schrödinger suite, starting with high-throughput virtual screening before moving to extra-precision (XP) and induced fit docking (IFD). Binding free energies were calculated using the Prime MM/GBSA method.

Following docking analysis, TPA emerged as a promising bioactive ligand. After molecular docking, molecular dynamics simulations of 200 ns were performed using GROMACS on the TPA-RAC1 and TPA-PRKCA complexes, indicating stable interactions.

4.2 Type 1 Diabetes

Type 1 diabetes (T1D) is a chronic autoimmune disorder marked by the loss of insulin-producing beta cells in the pancreas. In this condition, the body cannot regulate blood glucose, leading to hyperglycaemia. If left untreated, it becomes life-threatening (Vohidova et al., 2026). The pathophysiology arises due to the loss of immune self-tolerance. Genetic predisposition and environmental factors together determine the risk. People with HLA genes such as DR3-DQ2 and DR4-DQ8 are more susceptible (Noble & Valdes, 2011; Rewers & Ludvigsson, 2016).

The attack on beta cells is carried out by T cytotoxic cells. Helper T-cells (CD4+) first recognize proteins from beta cells and then activate cytotoxic T-cells (CD8+) to mediate damage (In't Veld, 2011). T1D is most commonly diagnosed in childhood, although it can occur at any age. Scandinavian countries also have a high incidence rate of T1D, suggesting a strong gene-environment interaction (Gregory et al., 2022; Patterson et al., 2009).

Current management involves insulin replacement along with glucose level monitoring (ElSayed et al., 2023). There are certain limitations with current therapies; insulin therapy comes with a risk of hypoglycaemia. High blood glucose in the long term can cause retinopathy, nephropathy, and cardiovascular diseases

(DiMeglio et al., 2018; The DCCT/EDIC Research Group, 2014).

Newer therapeutics like the anti-CD3 monoclonal antibody teplizumab may delay the development of T1D but do not prevent or treat the current illness (Herold et al., 2019). Thus, there is an urgent need for novel therapeutic targets that can address the underlying autoimmune illness. The identification of novel immunomodulatory targets aims to stop autoimmune destruction by inhibiting pro-inflammatory cytokines or enhancing the function of regulatory T-cells (Tregs) (Bluestone et al., 2015; Khongorzul et al., 2026; Obeagu, 2026).

There is also an ongoing search for therapeutic targets that may retain the existing beta-cell mass or stimulate the regeneration of new beta cells (Weir & Bonner-Weir, 2013). The goal is a curative therapy, which would eliminate the need for daily insulin (Berishvili et al., 2024; Shapiro et al., 2017).

Li et al. (2022) worked to identify key biomarkers for Type 1 Diabetes Mellitus (T1DM) from peripheral blood mononuclear cells (PBMCs). The researchers analysed three GEO datasets to identify 85 common differentially expressed genes (DEGs). Using these DEGs, they constructed a protein-protein interaction (PPI) network with the STRING database. The cytoHubba plugin in Cytoscape, with the Maximal Clique Centrality (MCC) parameter, was used to pinpoint hub genes.

This approach identified four hub genes: CHI3L1, CXCL1, and MMP9, which were upregulated, and GZMB, which was downregulated in T1DM. Functional enrichment analysis revealed that these genes are involved in critical immune and inflammatory responses. Finally, the authors constructed a disease-gene-drug interaction network based on CTD and DGIdb databases. This network identified MMP9 as an interactive drug target for captopril, marimastat, minocycline, and celecoxib, while GZMB could be inhibited by hexachlorophene.

Luo et al. (2025) used multi-omics coupled with machine learning techniques to identify potential antioxidant biomarkers for Type 1 Diabetes (T1DM). First, the authors collected transcriptomic data from diabetic mice alongside a human transcriptomic dataset. The authors used Weighted Gene Co-expression Network Analysis (WGCNA) and the limma package for differential expression analysis to identify correlations between oxidative stress and T1DM.

Following this, a proteomic study was carried out on 25 samples with T1DM and 25 healthy controls. They discovered that 33 proteins differentially expressed between the two groups participated in oxidative stress pathways. Researchers wanted to identify the best-performing biomarkers and decided to train four machine learning algorithms: RF, SVM-RFE, LASSO, and ElasticNet to screen for the most promising proteins.

The authors selected the intersection of the proteins chosen by all four algorithms and identified five proteins that could serve as potential drug targets: GPX3, GSTP1, PRDX6, SOD1, and MSRB2. GPX3 was found to have the highest Area Under the Curve (AUC) of 0.936, making it the most promising biomarker for further analysis.

Yang et al. (2022) attempted to screen autophagy-related biomarkers in Type 1 Diabetes Mellitus (T1DM). To start, the researchers obtained a gene expression dataset from the GEO database, which included 302 T1DM and 422 normal samples. Then, the Limma package in R was used to identify 568 differentially expressed genes (DEGs).

Using STRING and Cytoscape, a protein-protein interaction (PPI) network was generated for the identified DEGs. The cytoHubba plugin within Cytoscape was utilized to screen the top 10 hub proteins. The intersection between DEGs, top PPI hub genes, and autophagy genes yielded the disease-related targets.

Finally, three autophagy-related genes, RAB11A, CASP3, and SIRT1, were identified as significantly downregulated in T1DM. Immune cell infiltration was evaluated through a single-sample Gene Set Enrichment Analysis (ssGSEA). The findings indicated a positive association between RAB11A and CASP3 with the majority of immune cells, whereas SIRT1 exhibited a negative correlation. These autophagy-related genes might be able to distinguish diseased samples from healthy ones pending further validation.

Liu et al. (2024) adopted a machine-learning method to discover biomarkers from gut microbes for T1D. The authors obtained 16S rRNA sequencing data from three datasets to perform their analysis. To identify differences in microbial taxa, they employed Linear Discriminant Analysis Effect Size (LEfSe). A Random Forest (RF)

algorithm further selected an optimal panel of microbial genera from the screened candidates.

This analysis identified 21 microbial genera as significant T1D biomarkers, including Bifidobacterium, Agathobacter, and Barnesiella. The model demonstrated strong diagnostic potential with an area under the curve (AUC) of 0.962 in the discovery set and 0.745 in independent validation. To infer the biological role of these biomarkers, the authors used PICRUSt2 to predict metabolic functions, revealing that the identified microbes were correlated with pathways such as D-arginine and D-ornithine metabolism and steroid hormone biosynthesis. The identified biomarkers could be used to discriminate healthy and diseased samples as well as to modulate the disease.

Pang et al. (2022) conducted a bioinformatics investigation to characterize plasma-derived exosomal circRNA in Type 1 Diabetes Mellitus (T1DM). The researchers began with exosomal circRNA sequencing data obtained from 10 T1DM patients and 10 healthy controls and identified 784 differentially expressed circRNAs. Out of these, 528 were upregulated and 256 were downregulated.

The authors performed Gene Ontology (GO) and KEGG pathway analyses on the parental genes of these circRNAs, which revealed significant enrichment in pathways such as ubiquitin-mediated proteolysis. Using tools like RNAhybrid, miRanda, and the MultiMiR package, they constructed a circRNA-miRNA-mRNA network, which was visualized with Cytoscape.

The network analysis identified two signalling pathways involved in T1DM progression: hsa_circ0005630–miR-1247-5p–ATXN1/ARL6IP1 and hsa_circ0007026–miR-324-5p–NCAPD2/PGAM1. The identified pathways could be modulated as a therapeutic strategy.

4.3 Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disorder in which the body loses immune self-tolerance and attacks its own cells. Lupus is characterized by the production of autoantibodies to nuclear antigens and immune complex formation. It also involves systemic inflammation of different organs (Feng et al., 2026).

SLE is believed to arise from interactions between genetic and environmental factors. Risk increases with genes like HLA genes, genes involved in immune signalling, and clearance of cellular remnants (C1q, STAT4, TREX1). External triggers like UV rays, viruses, and some drugs also play a role in initiating the disease (Chow et al., 2026; Deng & Tsao, 2010; Poole et al., 2006).

Normally, old cells are cleared by phagocytes, but in lupus patients this does not occur efficiently. The release of DNA and proteins from accumulating dead cells causes them to be treated as foreign particles (Munoz et al., 2010).

Upon detecting these signals, plasmacytoid dendritic cells release type I interferons, thereby accelerating disease progression. This interferon-mediated environment recruits multiple immune cells to the area. T-cells help B-cells produce auto-antibodies (Choi et al., 2012). These immune complexes travel to the skin, joints, and kidneys where they deposit.

An inflammatory response occurs, causing tissue damage and lupus nephritis (Anders et al., 2020; Feng et al., 2026; Mok, 2019). SLE is a global concern affecting 20–150 people per 100,000 population. Women are affected nine times more than men. Women of reproductive age are more commonly affected, suggesting the involvement of irregular hormone cycles (Bertoli et al., 2006; Moulton et al., 2017; Rees et al., 2017).

Current treatment focuses on symptom management and preventing damage to vital organs. Hydroxychloroquine is the standard treatment that reduces flare-ups, organ damage, and mortality (Fanouriakis et al., 2019). Steroids are used to control inflammation, but they have severe side effects. Immunosuppressants such as mycophenolate mofetil and cyclophosphamide are used only for life-threatening cases with severe organ damage (Fanouriakis et al., 2019).

Modern therapies based on monoclonal antibodies target specific immune pathways. Belimumab is used to target B-cells, anifrolumab targets the interferon pathway, and rituximab is used for B-cells (Kalunian et al., 2023).

Current therapies come with serious limitations, as they suppress the immune system, increasing the risk of infections and even cancer (Fanouriakis et al., 2019). Long-term use of corticosteroids can cause osteoporosis, avascular necrosis, diabetes, and organ damage. This highlights the need for finding novel drug targets and therapeutics for modulating the disease.

Novel strategies aim to target harmful plasma cells, inhibit JAK and BTK signalling pathways, and block neutrophil extracellular trap formation (Alexander et al., 2015; Choi et al., 2012; Mok, 2019; Papayannopoulos, 2018).

Liu et al. (2025) worked to identify potential targets in systemic lupus erythematosus (SLE). They performed differential expression analysis of lncRNAs, mRNAs, and miRNAs from lupus-prone and healthy mice. They identified 1,852 long non-coding RNAs (lncRNAs), mRNAs, and 25 microRNAs that were differentially expressed, with let-7f-5p being significantly downregulated.

To increase confidence in the results, the DEGs were merged with renal and brain lupus-associated samples from GEO. Using this dataset, they conducted functional enrichment analysis to uncover the biological pathways associated with the DEGs. Subsequently, protein-protein interaction (PPI) networks were generated, which identified Gbp2 and Gbp7 as the key hub genes.

The genes Gbp2 and Gbp7 were direct targets of let-7f-5p, showing increased expression in lupus. Finally, a competing endogenous RNA (ceRNA) network was constructed, indicating that let-7f-5p bridges the interaction between the lncRNA 5031425E22Rik and its mRNA targets Gbp2 and Gbp7. Consequently, Gbp2 and Gbp7 emerged as candidate biomarkers and drug targets in SLE.

Zhao et al. (2021) sought to identify biomarkers and therapeutic targets for SLE. Initially, they downloaded four transcriptome datasets from the GEO database. Following this, they used the GEO2R tool to determine the differentially expressed genes between SLE and healthy samples.

The common DEGs among the datasets were analysed for biological processes (BP) and pathways by GO and KEGG enrichment analysis performed using the Metascape tool. The GENEMANIA tool was used to construct a PPI network of these DEGs. To further screen hub genes related to SLE, Weighted Gene Co-expression Network Analysis (WGCNA) was performed.

Gene Set Enrichment Analysis (GSEA) was also applied to investigate the identified hub genes. The abundance of infiltrating immune cells in these samples was evaluated by CIBERSORT. Candidate biomarkers were validated using receiver operating characteristic (ROC) analysis, and six crucial DEGs were identified: IFI27, IFI44, IFI44L, IFI6, EPSTI1, and OAS1.

The WGCNA and ROC analyses singled out IFI27 as a major hub gene and molecular marker for SLE.

Gao et al. (2024) applied a genome-wide Mendelian randomization approach to identify targets for SLE. They first obtained cis-expression quantitative trait loci (cis-eQTLs) for whole blood from the eQTLGen Consortium. This data was used in a two-sample Mendelian randomization (MR) analysis against two SLE genome-wide association study (GWAS) datasets to identify genes associated with SLE.

To confirm causal inference, the researchers performed Bayesian colocalization analysis. For the selected targets, a phenome-wide association study (PheWAS) was conducted using UK Biobank data to screen for possible off-target effects. Drug-gene interaction databases, including the Drug-Gene Interaction Database (DGIdb), DrugBank, and ChEMBL, were used to identify prospective drug candidates.

The study identified five target genes for SLE: BLK, HIST1H3H, HSPA1A, IL12A, and NEU1. The PheWAS analysis revealed that targeting BLK and IL12A would have fewer adverse effects.

Jiang et al. (2022) combined bioinformatics and machine learning to identify biomarkers for SLE. The researchers obtained gene expression data from two GEO databases and applied the "limma" and "RobustRankAggreg" R packages to identify 11 DEGs between SLE patients and controls. Functional enrichment analysis indicated their involvement in immune-related processes and the necroptosis pathway.

Next, a protein-protein interaction (PPI) network was created using the STRING database. The expression patterns of the genes were also cross-validated using another dataset. To examine the diagnostic capability of these genes, ROC curve analysis was conducted, demonstrating that 10 of the genes could serve as efficient biomarkers.

Further, the miRWalk and ChEA3 databases were used to construct a transcription factor (TF)-miRNA-biomarker network. Potential therapeutic compounds were identified using the CTD database, and a drug-biomarker network was also created.

The researchers used five machine learning methods (Logistic Regression, Random Forest, XGBoost, Support

Vector Machine, and Artificial Neural Network) to analyse all potential combinations of the 10 biomarkers to establish the ideal one. This identified IFI44 as the most significant biomarker across all models.

Conclusion

Drug discovery is undergoing a paradigm shift. Rather than depending on chance discovery and high-throughput screening, drug discovery is becoming mechanism-driven. Computational biology techniques have been spearheading the identification of new targets and drug molecules. The combination of high-throughput omics experiments and sophisticated algorithms has allowed scientists to study the molecular details of complex diseases.

Integrating multi-omics datasets through network biology and machine learning helps identify high-confidence candidate targets that are difficult to detect using traditional experimental methodologies. Approaches like WGCNA, machine learning methods, and proteome-wide Mendelian randomization (MR) have been instrumental in converting omics data into biologically testable hypotheses.
These computational approaches expedite target discovery during the preclinical phase and help us better understand disease pathophysiology, ultimately leading to greater success in drug development.

Declaration

The authors hereby declare that the manuscript submitted for consideration is an original work and has not been published or submitted elsewhere for publication. The authors take full responsibility for the integrity, accuracy, and ethical compliance of the work presented in the manuscript, including all revisions made in response to reviewer comments.

AI Usage Statement: Authors declare that AI tools, if used, were solely employed to improve the clarity, grammar, and language of the manuscript (as indicated in the reviewer's comments). No data, results, or scientific content were generated or altered using AI.

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1) Any potential conflicts of interest, whether financial or non-financial, have been fully disclosed. – Not Applicable
2) All sources of funding and financial support received for the conduct of the study have been appropriately acknowledged, including any updates made during revision. – Not Applicable
3) Necessary ethical approvals have been obtained from the relevant institutional or regulatory bodies for studies involving human participants, animals, or sensitive data, wherever applicable, and are clearly stated in the manuscript. – Not Applicable

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