



## Original Paper

# Immune Memory in Diabetes: Recent Discoveries and Clinical Implications

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## ABSTRACT

Diabetes mellitus (DM) is a complex immunometabolic disorder characterised not only by chronic hyperglycaemia but also by persistent immune dysregulation that contributes to chronic inflammation, impaired host defence, and the development of microvascular and macrovascular complications. Increasing evidence indicates that long-term immune alterations persist despite adequate glycaemic control, highlighting the importance of immune memory in disease progression. Recent advances have shown that immune memory extends beyond adaptive immunity to include trained immunity, whereby innate immune cells undergo durable metabolic and epigenetic reprogramming that results in enhanced inflammatory responses upon subsequent stimulation. This review summarises current knowledge of the mechanisms of innate and adaptive immune memory in diabetes, emphasising the interplay between trained immunity, metabolic memory, epigenetic regulation and immunometabolism. It also discusses how chronic hyperglycaemia reshapes immune-cell function through alterations in glycolysis, mitochondrial metabolism, histone modifications, chromatin remodelling and inflammatory signalling pathways. Recent advances in multi-omics are highlighted, particularly their potential applications in biomarker discovery, disease monitoring and precision medicine. The review further examines the role of the gut microbiota in modulating immune memory and discusses emerging therapeutic approaches, including antigen-specific immunotherapy, cytokine-targeted therapies, metabolic and epigenetic interventions, microbiota-based strategies and nanoparticle-mediated drug delivery systems. Finally, current challenges, knowledge gaps and future research priorities are addressed. A better understanding of immune memory is expected to facilitate the development of personalised immunotherapeutic strategies that restore immune homeostasis, reduce chronic inflammation, prevent diabetic complications and improve long-term clinical outcomes in individuals with diabetes.

**KEYWORDS:** *Diabetes mellitus, Immune memory, Trained immunity, Adaptive immunity, Metabolic memory, Epigenetics, Immunometabolism.*

## 1-INTRODUCTION

Diabetes mellitus (DM) is one of the most prevalent chronic metabolic disorders worldwide and represents a major public health challenge because of its rapidly increasing incidence and its association with severe microvascular and macrovascular complications. Beyond persistent hyperglycaemia, diabetes is now recognised as a disease characterised by profound immune dysregulation that contributes to chronic inflammation, impaired host defence, delayed tissue repair and increased susceptibility to infection [1,2]. Although glycaemic control remains the cornerstone of diabetes management, accumulating evidence indicates that normalisation of blood glucose alone is insufficient to reverse completely the long-term inflammatory and vascular consequences of the disease, suggesting the involvement of persistent immunometabolic alterations known as immune and metabolic memory [3].

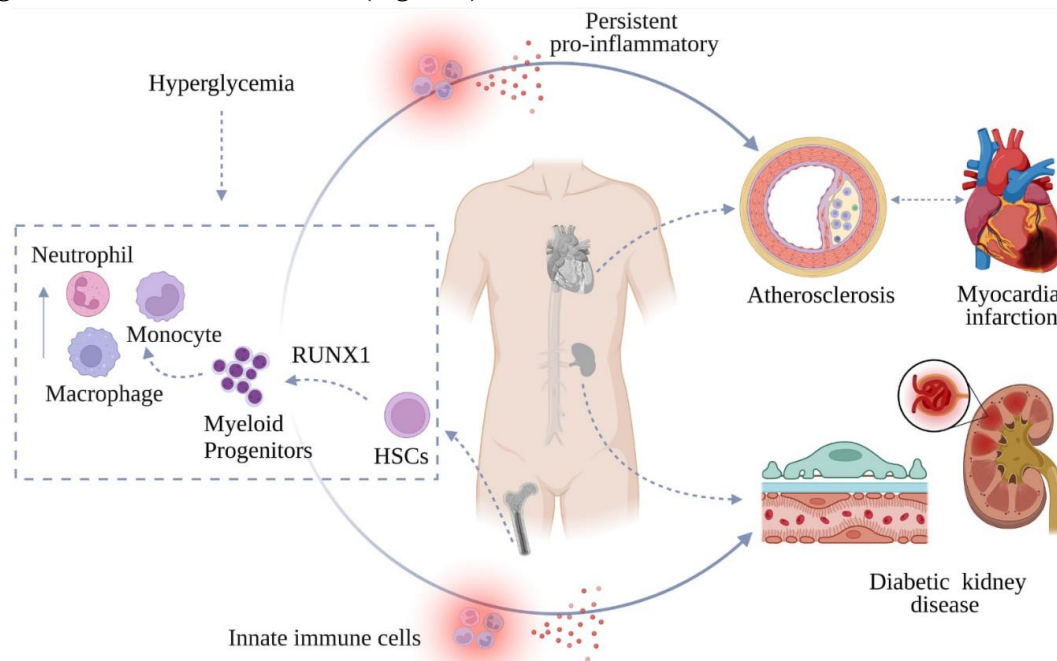
For many years, immunological memory was considered an exclusive characteristic of the adaptive immune system, mediated by antigen-specific memory T and B lymphocytes that provide rapid and effective responses upon secondary antigen exposure. Recent advances in immunology have challenged this classical concept by demonstrating that innate immune cells, including monocytes, macrophages, natural killer (NK) cells and

haematopoietic stem and progenitor cells (HSPCs), can also develop long-lasting functional memory through epigenetic and metabolic reprogramming, a phenomenon termed trained immunity [4,5]. This discovery has fundamentally reshaped the understanding of immune memory and highlighted its role in chronic inflammatory diseases, including DM.

Chronic hyperglycaemia induces persistent metabolic and epigenetic remodelling of immune cells through alterations in glycolysis, oxidative phosphorylation, cholesterol metabolism and histone modifications. These changes promote sustained production of pro-inflammatory cytokines, exaggerated innate immune responses and impaired adaptive immune regulation, thereby contributing to the progression of diabetic complications even after glycaemic improvement [3,6]. Furthermore, diabetes affects both the number and the functional quality of memory T and B lymphocytes, leading to impaired vaccine responses, diminished immune protection, accelerated immune ageing and increased vulnerability to infectious diseases [7,8].

Recent technological advances, particularly single-cell transcriptomics, epigenomics, metabolomics and systems immunology, have considerably expanded the understanding of the complex interaction between innate and adaptive immune memory in diabetes. These approaches have identified novel biomarkers, immune-cell subsets and molecular pathways involved in immune dysregulation, opening new opportunities for precision medicine and targeted immunotherapy [8–10]. In parallel, emerging therapeutic strategies, including antigen-specific immunotherapy, cytokine modulation, metabolic reprogramming, epigenetic interventions and nanoparticle-based drug delivery systems, are being investigated to restore immune homeostasis and prevent long-term diabetic complications [9–11].

This review summarises current knowledge of the mechanisms underlying innate and adaptive immune memory in DM, discusses recent discoveries linking trained immunity with metabolic dysfunction, highlights their clinical significance, and explores emerging therapeutic approaches and future research directions aimed at improving immune regulation and disease outcomes (Figure 1).



**Figure (1): Hyperglycaemia drives vascular complications in diabetes by inducing trained immunity.**

**Elevated glucose levels stimulate the expansion of haematopoietic stem cells (HSCs) and myeloid progenitors, accelerating the release of pro-inflammatory monocytes and neutrophils. This sustained immune memory, regulated in part by transcription factors such as RUNX1, fuels chronic inflammation**

**and thereby exacerbates atherosclerosis, myocardial infarction and diabetic kidney disease. Reproduced from reference (10).**

## **2-METHODOLOGY**

This review summarises the current evidence on immune memory in DM on the basis of an extensive literature search focused on trained immunity, adaptive immune memory, epigenetic regulation, metabolic memory, the gut microbiota and emerging immunotherapeutic approaches. Relevant publications were identified by searching PubMed, Scopus, Web of Science and Google Scholar. The search covered studies published between January 2019 and 2026; landmark studies published before 2020 were included when needed to provide the theoretical and mechanistic background of immune memory.

The search strategy combined keywords with Boolean operators as follows: ("immune memory" OR "trained immunity" OR "adaptive immune memory" OR "metabolic memory") AND ("diabetes mellitus" OR "type 1 diabetes" OR "type 2 diabetes") AND ("epigenetics" OR "gut microbiota" OR "biomarkers" OR "immunotherapy" OR "precision medicine"). Additional relevant studies were identified by manual searching of the reference lists of the selected articles. Studies were included if they [1] examined immune memory or related mechanisms in DM; [2] investigated molecular, cellular, metabolic, epigenetic or microbiome-related mechanisms associated with immune memory; [3] assessed potential biomarkers, clinical relevance or therapeutic approaches; and [4] were peer-reviewed publications in English. Original research articles, systematic reviews, meta-analyses, clinical trials and high-quality relevant review articles were considered.

Studies unrelated to immunological memory or diabetes, duplicate publications, conference papers lacking adequate data, non-peer-reviewed publications and studies with insufficient material to meet the aims of the review were excluded.

Identified records were first screened for relevance on the basis of title and abstract, and the full texts of potentially eligible publications were then evaluated. The selected papers were critically assessed and synthesised to provide a current summary of the molecular processes, clinical significance and therapeutic potential of immunological memory in DM.

## **3-THE INTERACTION BETWEEN INNATE AND ADAPTIVE IMMUNE MEMORY**

For decades, immunological memory was considered an exclusive property of the adaptive immune system, mediated by antigen-specific T and B lymphocytes that provide rapid and long-lasting protection after repeated exposure to pathogens. Recent discoveries have shown that innate immune cells are also capable of developing a memory-like response through trained immunity, fundamentally changing the traditional understanding of immune memory [4,5]. Rather than functioning independently, innate and adaptive immune memory operate as interconnected systems that communicate continuously to coordinate immune homeostasis and host defence [4].

The interaction between the two arms of the immune system begins during the early stages of immune activation. Following pathogen recognition through pattern-recognition receptors (PRRs), innate immune cells, including monocytes, macrophages, dendritic cells and NK cells, undergo metabolic and epigenetic reprogramming that leads to enhanced cytokine production and improved responsiveness to subsequent stimuli [4,5]. At the same time, dendritic cells bridge innate and adaptive immunity by processing and presenting antigens to naïve T lymphocytes, thereby initiating antigen-specific immune responses and promoting the differentiation of memory T and B cells [5].

Adaptive immune cells, in turn, actively regulate innate immune functions through cytokine secretion and direct cell-to-cell interactions. Memory CD4<sup>+</sup> T cells enhance macrophage activation, support B-cell maturation and antibody production, and coordinate inflammatory responses, whereas regulatory T cells suppress excessive innate

immune activation and maintain immune tolerance [5,10]. This bidirectional communication ensures a balanced immune response capable of eliminating pathogens while minimising tissue damage.

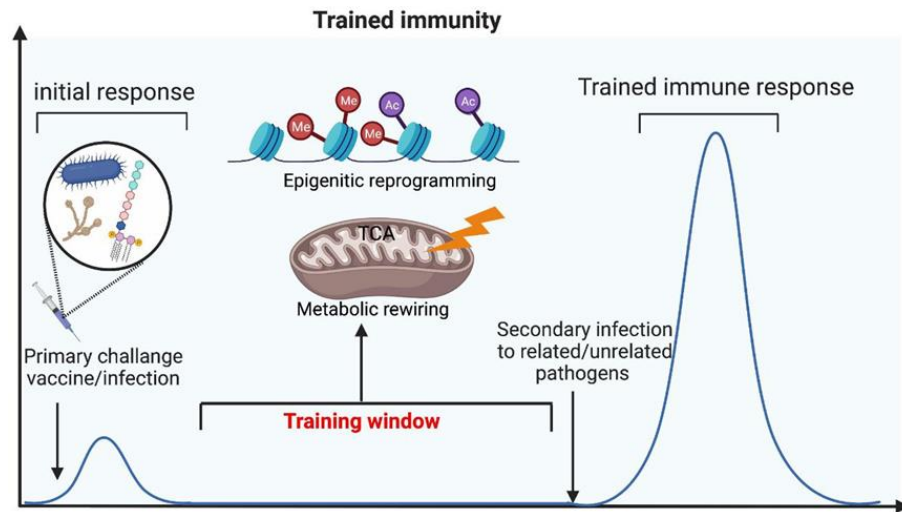
In DM, chronic hyperglycaemia disrupts this finely regulated interaction. Persistent metabolic stress induces prolonged activation of innate immune cells through trained immunity, resulting in sustained production of pro-inflammatory mediators such as interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6) and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ). Simultaneously, adaptive immune memory becomes impaired because of altered T-cell differentiation, reduced numbers of functional memory lymphocytes and accelerated immune ageing, ultimately compromising long-term immune protection [2,3,6–8].

Recent advances in single-cell transcriptomics and systems immunology have further shown that innate and adaptive immune memory share common metabolic pathways, including glycolysis, oxidative phosphorylation and cholesterol metabolism, together with epigenetic mechanisms involving histone modifications and chromatin remodelling [3,4,8]. These shared regulatory networks explain how chronic metabolic disorders such as diabetes can simultaneously influence both branches of the immune system, contributing to persistent inflammation, defective vaccine responses, increased susceptibility to infection and the development of diabetic complications. Understanding the dynamic interaction between innate and adaptive immune memory provides a comprehensive framework for explaining the immunopathogenesis of DM. Moreover, it offers new therapeutic opportunities aimed at restoring immune balance through modulation of trained immunity, enhancement of adaptive immune function and precision immunotherapy, thereby reducing chronic inflammation and improving long-term clinical outcomes [2,6,9].

#### **4-RECENT DISCOVERIES IN IMMUNE MEMORY**

Recent advances in immunology have fundamentally transformed the classical concept of immune memory. Traditionally, immunological memory was believed to be an exclusive feature of the adaptive immune system, mediated by antigen-specific T and B lymphocytes. However, accumulating evidence over the past decade has shown that innate immune cells can also develop long-lasting functional adaptations after exposure to microbial or metabolic stimuli. This phenomenon, known as trained immunity, has emerged as one of the most significant discoveries in modern immunology and has broadened the understanding of host defence and chronic inflammatory diseases [4,5].

One of the most important findings is that trained immunity is mediated by durable metabolic and epigenetic reprogramming rather than by antigen specificity. After an initial stimulus, monocytes, macrophages, NK cells, neutrophils and HSPCs undergo persistent changes in gene expression that enhance their responsiveness to subsequent challenges, even when these are triggered by unrelated pathogens [4,5]. These adaptive-like characteristics distinguish trained immunity from the classical innate immune response and explain its long-lasting biological effects (Figure 2).



**Figure (2): The process of trained immunity. Primary immune activation leads to long-lasting metabolic rewiring and epigenetic changes that enhance the responsiveness of the innate immune system during subsequent exposure to diverse pathogens. Reproduced from reference (12).**

Recent studies have also identified HSPCs as central regulators of trained immunity. Rather than being confined to mature immune cells, inflammatory memory can be established within bone-marrow progenitor cells, enabling sustained production of functionally reprogrammed immune cells over extended periods. This discovery provides a mechanistic explanation for the persistence of chronic inflammatory responses observed in metabolic and autoimmune diseases, including DM [4,6].

Another major breakthrough has been the application of single-cell RNA sequencing, spatial transcriptomics and multi-omics technologies to the investigation of immune-cell heterogeneity. These approaches have revealed previously unrecognised immune-cell subsets, distinct metabolic signatures and alterations in immune-cell differentiation that cannot be detected by conventional immunological methods. In patients with diabetes, these technologies have demonstrated significant changes in memory T-cell populations, reduced CD4<sup>+</sup> T-cell abundance, altered immune-cell metabolism and increased inflammatory activation, highlighting the complex interaction between metabolism and immune regulation [6,8].

Recent evidence has further shown that immune memory extends beyond protection against infectious diseases and contributes to the pathogenesis of chronic non-communicable disorders. Persistent activation of trained immunity has been implicated in diabetes, obesity, atherosclerosis, cardiovascular disease, autoimmune disorders and cancer. These findings suggest that immune memory is not only a protective mechanism but also a potential driver of chronic inflammation when its regulation becomes disturbed [2–4].

The rapid expansion of immunometabolism research has also identified several molecular pathways that regulate immune memory, including glycolysis, oxidative phosphorylation, the mevalonate pathway and mitochondrial metabolism. These metabolic pathways interact closely with epigenetic modifications such as histone acetylation, histone methylation and chromatin remodelling to determine the functional state of immune cells. Understanding these interconnected mechanisms has created new opportunities for developing therapies aimed at selectively reprogramming immune responses rather than broadly suppressing inflammation [3,4,6].

Collectively, these discoveries have reshaped the understanding of immune memory by recognising the dynamic cooperation between innate and adaptive immunity, identifying the molecular mechanisms underlying trained immunity, and revealing their implications for chronic inflammatory diseases such as DM. These advances provide

a strong scientific foundation for the development of precision immunotherapies that target immune memory to improve disease prevention and long-term clinical outcomes [2,4,9].

### **5-EPIGENETIC FOUNDATIONS OF IMMUNE MEMORY**

One of the most significant advances in immunology has been the recognition that epigenetic reprogramming constitutes a fundamental mechanism underlying immune memory. Unlike genetic mutations, epigenetic modifications alter gene expression without changing the DNA sequence, enabling immune cells to retain a long-lasting functional state after an initial stimulus. These reversible molecular changes allow both innate and adaptive immune cells to respond rapidly to secondary challenges while maintaining cellular identity [4,5].

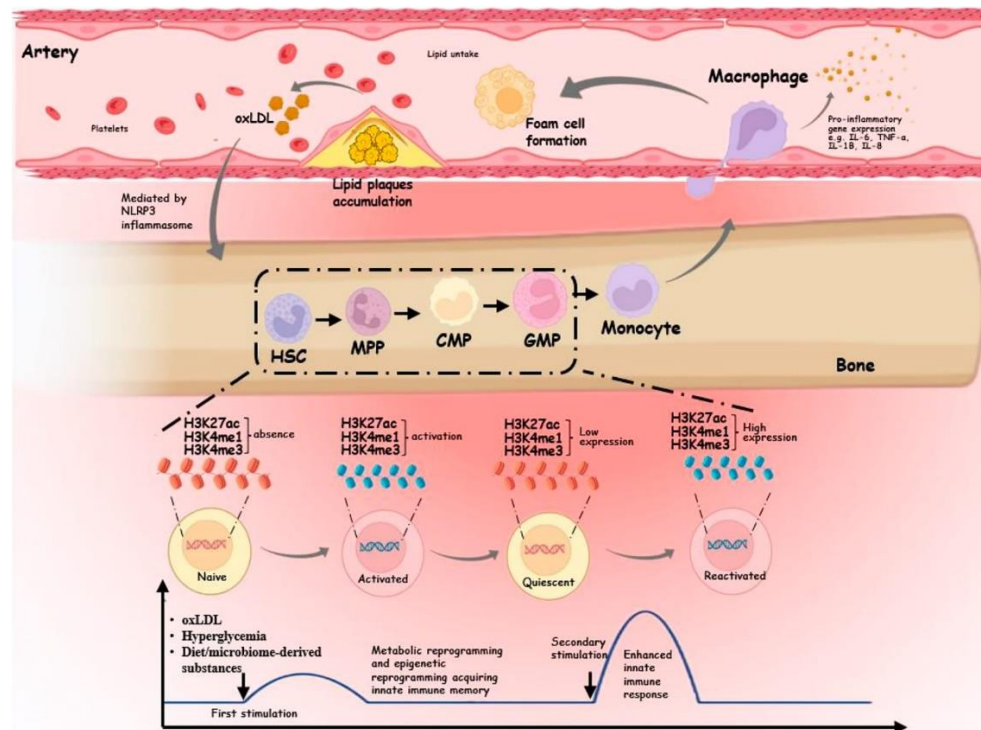
In trained immunity, epigenetic remodelling is initiated by exposure to microbial products, endogenous danger signals or metabolic stress. Activated monocytes, macrophages, NK cells and HSPCs undergo persistent modifications of chromatin architecture that enhance transcription of inflammatory genes during subsequent stimulation. This process is mediated primarily by histone modifications and changes in chromatin accessibility and, to a lesser extent, by DNA methylation, thereby establishing a long-term memory-like phenotype in innate immune cells [4,13].

Histone modifications are among the best-characterised epigenetic mechanisms regulating immune memory. Increased histone acetylation, particularly acetylation of histone H3 lysine 27 (H3K27ac), together with histone methylation marks such as H3K4me3, promotes chromatin relaxation and facilitates transcription of genes encoding pro-inflammatory cytokines, chemokines and antimicrobial molecules. Conversely, repressive histone marks suppress immune-related gene expression and contribute to immune tolerance. The balance between activating and repressive histone modifications ultimately determines the magnitude and duration of immune responses [4,13,14]. Emerging evidence indicates that epigenetic regulation is closely linked to cellular metabolism. Metabolic intermediates generated through glycolysis, the tricarboxylic acid (TCA) cycle, oxidative phosphorylation and the mevalonate pathway serve as substrates or cofactors for epigenetic enzymes, thereby directly influencing chromatin remodelling and transcriptional activity. Consequently, metabolic disturbances such as persistent hyperglycaemia can induce stable epigenetic alterations that sustain inflammatory signalling even after normalisation of blood glucose, providing a mechanistic explanation for the phenomenon of metabolic memory in diabetes [2,3,6].

Adaptive immune cells also rely on epigenetic regulation during the generation and maintenance of immunological memory. After antigen exposure, naïve T and B lymphocytes undergo extensive chromatin remodelling that establishes stable transcriptional programmes required for long-term survival, rapid proliferation and efficient effector function upon re-exposure to the same antigen. Epigenetic modifications therefore play a central role in determining memory-cell differentiation, functional plasticity and immune protection [5,14].

Recent advances in epigenomics and single-cell sequencing have enabled high-resolution mapping of chromatin accessibility and gene-regulatory networks within individual immune cells. These approaches have identified disease-specific epigenetic signatures associated with diabetes, chronic inflammation and autoimmune disorders, providing novel biomarkers for disease monitoring and potential therapeutic targets. Pharmacological modulation of epigenetic enzymes, including histone deacetylases (HDACs), bromodomain proteins and DNA methyltransferases, is currently being investigated as a promising strategy for selectively reprogramming maladaptive immune memory while preserving protective immune responses [6,13,15].

Overall, epigenetic mechanisms provide the molecular foundation of immune memory by integrating environmental, metabolic and inflammatory signals into long-lasting transcriptional programmes. Understanding these regulatory pathways has substantially expanded current knowledge of diabetes pathogenesis and offers new opportunities for developing precision therapies aimed at restoring balanced immune function and preventing chronic inflammatory complications [2,4,6] (Figure 3).



**Figure (3): Trained immunity drives atherosclerotic cardiovascular disease through a multistep epigenetic and metabolic cascade. In the haematopoietic system, endogenous triggers reprogram myeloid cells and induce innate immune memory marked by H3K4me3 at gene promoters, together with accumulation of H3K4me1 or H3K27ac. The trained cells differentiate into hyper-responsive monocytes that infiltrate the arterial intima and transform into macrophages, which secrete elevated levels of pro-inflammatory cytokines (TNF- $\alpha$ , IL-6, IL-8 and IL-18) and give rise to lipid-laden foam cells. Within advanced plaques, sustained endogenous stimulation activates the NLRP3 inflammasome, creating a self-perpetuating cycle of inflammation. Reproduced from reference (16).**

## 6-METABOLIC MEMORY VERSUS TRAINED IMMUNITY

The concepts of metabolic memory and trained immunity have emerged as fundamental mechanisms explaining the persistence of diabetic complications despite successful glycaemic control. Although the terms are sometimes used interchangeably because they share several molecular pathways, they represent distinct but closely interconnected biological processes. Understanding their similarities and differences has become increasingly important for elucidating the pathophysiology of DM and identifying novel therapeutic targets [2,3].

Metabolic memory, also referred to as hyperglycaemic memory, describes the phenomenon whereby prior exposure to prolonged hyperglycaemia induces long-lasting cellular alterations that persist even after blood glucose returns to normal. The concept was first recognised in large clinical trials showing that patients with poor early glycaemic control continued to experience an increased risk of diabetic complications despite subsequent improvement in glucose management. Persistent oxidative stress, mitochondrial dysfunction, accumulation of advanced glycation end products (AGEs), chronic inflammation and epigenetic modifications are considered the principal mechanisms responsible for this long-term pathological memory [3,17].

In contrast, trained immunity refers to the ability of innate immune cells to develop an enhanced functional response after an initial stimulus through metabolic and epigenetic reprogramming rather than antigen-specific recognition. Monocytes, macrophages, NK cells, neutrophils and HSPCs undergo stable transcriptional and metabolic changes that enable them to respond more vigorously to subsequent challenges, even when these are unrelated to the original

stimulus. Unlike adaptive immune memory, trained immunity is independent of antigen-specific receptors and instead relies on chromatin remodelling, histone modifications and metabolic rewiring to establish long-lasting immune responsiveness [4,5].

Although metabolic memory and trained immunity arise in different biological contexts, they share several overlapping molecular mechanisms. Chronic hyperglycaemia is a potent inducer of both processes, promoting glycolytic reprogramming, activation of the mevalonate pathway, mitochondrial reactive oxygen species (ROS) production and persistent epigenetic remodelling. These changes result in sustained activation of inflammatory pathways, increased production of cytokines such as IL-1 $\beta$ , IL-6 and TNF- $\alpha$ , and prolonged immune-cell activation that contributes to vascular injury and tissue dysfunction [2,3,6].

Recent studies suggest that trained immunity may be one of the major cellular mechanisms underlying metabolic memory. Persistent exposure to hyperglycaemia induces stable epigenetic alterations in haematopoietic stem cells and circulating innate immune cells, allowing inflammatory responses to persist long after metabolic control has been achieved. Consequently, immune cells retain a "memory" of previous metabolic stress that promotes chronic low-grade inflammation and accelerates the progression of diabetic nephropathy, retinopathy, cardiovascular disease and other long-term complications [2,6,17].

Despite their close relationship, important differences remain between the two concepts. Metabolic memory describes the long-term pathological consequences of previous metabolic disturbances across multiple tissues, including endothelial cells, pancreatic  $\beta$ -cells, renal tissue and immune cells. Trained immunity, in contrast, refers specifically to the functional reprogramming of innate immune cells and their progenitors. Trained immunity can therefore be considered an important immunological component of metabolic memory rather than a substitute for the broader concept of hyperglycaemic memory [3,5,17].

Recognition of the interaction between metabolic memory and trained immunity has significant clinical implications. Therapeutic strategies aimed solely at lowering blood glucose may not completely eliminate persistent inflammatory responses once immune memory has been established. Combining intensive metabolic control with interventions targeting epigenetic remodelling, immunometabolism and trained immunity may therefore represent a more effective approach to preventing diabetic complications and improving long-term clinical outcomes [2,3,6].

## **7-IMMUNE MEMORY IN DIABETES**

DM is increasingly recognised as an immunometabolic disease in which persistent hyperglycaemia profoundly alters both innate and adaptive immune memory. Beyond its metabolic consequences, chronic hyperglycaemia induces long-lasting functional and molecular changes in immune cells that contribute to sustained inflammation, impaired host defence and progressive tissue damage. These alterations persist even after glycaemic control is achieved, indicating that immune cells retain a "memory" of previous metabolic stress through epigenetic and metabolic reprogramming [2,3,6].

Innate immune memory, or trained immunity, plays a central role in the development of chronic inflammation in diabetes. Continuous exposure to elevated glucose concentrations promotes metabolic rewiring of monocytes, macrophages, neutrophils, NK cells and HSPCs. This reprogramming enhances glycolysis, activates the mevalonate pathway, increases mitochondrial ROS production and induces stable epigenetic modifications, resulting in exaggerated inflammatory responses upon subsequent stimulation [3–6]. Consequently, patients with diabetes exhibit persistent secretion of pro-inflammatory cytokines, including IL-1 $\beta$ , IL-6 and TNF- $\alpha$ , which contribute to endothelial dysfunction, vascular injury and chronic low-grade inflammation.

Adaptive immune memory is also significantly affected by diabetes. Both type 1 and type 2 diabetes are associated with alterations in the differentiation, survival and function of memory T and B lymphocytes. Studies have demonstrated reduced numbers of functional CD4<sup>+</sup> memory T cells, accelerated immune ageing, impaired B-cell maturation and diminished antibody persistence after vaccination. These abnormalities compromise long-term

protective immunity and increase susceptibility to bacterial and viral infections, while contributing to autoimmune responses in type 1 diabetes [7,8].

The interaction between innate and adaptive immune memory further amplifies immune dysregulation in diabetes. Activated innate immune cells continuously produce inflammatory mediators that influence adaptive immune-cell differentiation, whereas dysfunctional adaptive immune responses fail to regulate innate immune activation adequately. This reciprocal interaction establishes a self-perpetuating inflammatory environment that accelerates the development of diabetic nephropathy, retinopathy, neuropathy, cardiovascular disease and impaired wound healing [2,6].

Recent advances in immunometabolism have shown that immune memory is not merely a consequence of diabetes but also an active contributor to disease progression. Persistent metabolic stress reshapes immune-cell metabolism through alterations in glycolysis, oxidative phosphorylation, fatty-acid metabolism and mitochondrial function, thereby sustaining inflammatory signalling independently of blood glucose levels. These findings provide a mechanistic explanation for the persistence of diabetic complications despite improved glycaemic control and highlight immune memory as a promising therapeutic target for disease modification [2,3,6].

### **8-BIOMARKERS OF IMMUNE MEMORY IN DIABETES**

The identification of reliable biomarkers reflecting immune memory has become an important area of research, because such biomarkers may improve disease monitoring, predict diabetic complications, evaluate therapeutic responses and facilitate the development of precision medicine. Since immune memory involves both innate and adaptive immune responses, its biomarkers include inflammatory mediators, immune-cell phenotypes, metabolic regulators and epigenetic signatures that collectively reflect the functional status of the immune system [2,6].

Among inflammatory biomarkers, circulating cytokines remain the most extensively investigated indicators of persistent immune activation. Elevated concentrations of IL-1 $\beta$ , IL-6, TNF- $\alpha$ , C-reactive protein (CRP) and chemokines such as CCL2 are consistently associated with trained immunity, chronic low-grade inflammation and progression of diabetic complications. Increased levels of these inflammatory mediators correlate with endothelial dysfunction, insulin resistance and vascular injury in both type 1 and type 2 diabetes [2,6,18].

Cellular biomarkers have also emerged as valuable indicators of immune memory. Alterations in the proportions of naïve and memory T-cell subsets, reduced CD4<sup>+</sup> memory T cells, increased exhausted T-cell populations expressing programmed cell death protein-1 (PD-1) and changes in B-cell differentiation have all been reported in patients with diabetes. In addition, activation markers expressed by monocytes and macrophages, together with increased production of inflammatory cytokines after secondary stimulation, provide functional evidence of trained immunity [7,8].

Epigenetic biomarkers represent one of the most promising fields in immune-memory research. Persistent changes in histone modifications, chromatin accessibility, DNA methylation patterns and transcription-factor activity have been identified in immune cells exposed to chronic hyperglycaemia. These molecular signatures reflect long-term immune reprogramming and may serve as stable biomarkers capable of predicting disease progression and therapeutic response more accurately than conventional inflammatory markers [3,13].

Recent advances in high-throughput technologies have further expanded biomarker discovery through single-cell transcriptomics, epigenomics, metabolomics and proteomics. These approaches have enabled comprehensive characterisation of immune-cell heterogeneity and revealed disease-specific molecular signatures associated with diabetes. Integration of these multi-omics datasets with artificial intelligence and machine-learning algorithms is expected to improve patient stratification, facilitate early diagnosis of immune dysfunction and support the development of personalised immunotherapeutic strategies [6,15].

Although numerous candidate biomarkers have been identified, their routine clinical application remains limited because of variability among patient populations, differences in analytical methodology and the absence of

standardised validation protocols. Large longitudinal studies are therefore required to establish robust biomarker panels capable of accurately reflecting immune memory and guiding the individualised management of patients with diabetes [2,6,15].

### **9-ADAPTIVE IMMUNE MEMORY IMPAIRMENT IN DIABETES**

Adaptive immune memory is essential for long-term antigen-specific protection through the generation of memory T and B lymphocytes. These cells enable rapid and effective immune responses upon re-exposure to previously encountered pathogens, thereby maintaining durable immune surveillance and protecting the host against recurrent infection. However, accumulating evidence indicates that DM profoundly disrupts the development, maintenance and function of adaptive immune memory, contributing to immune dysfunction and increased susceptibility to infectious and inflammatory diseases [2,7,8].

Chronic hyperglycaemia creates a persistently inflammatory and metabolically stressful environment that adversely affects lymphocyte homeostasis. Elevated glucose levels alter cellular metabolism, increase oxidative stress and promote the production of AGEs, all of which interfere with T-cell activation, differentiation and survival. Consequently, patients with diabetes exhibit significant alterations in the distribution of naïve and memory T-cell subsets, accompanied by accelerated immune ageing and reduced immunological competence [3,7].

Several studies have demonstrated a decline in functional CD4<sup>+</sup> memory T cells in individuals with type 1 or type 2 diabetes. In addition, an increased proportion of exhausted T cells expressing inhibitory receptors such as PD-1 has been reported. These exhausted lymphocytes show reduced proliferative capacity, impaired cytokine secretion and a diminished ability to generate effective secondary immune responses. Similar abnormalities have been observed in CD8<sup>+</sup> memory T cells, leading to compromised antiviral immunity and impaired long-term protection after vaccination [7,8,19].

Diabetes also affects humoral immune memory through abnormalities in B-cell differentiation and antibody production. Chronic metabolic inflammation impairs germinal-centre formation, reduces the generation of long-lived plasma cells and compromises the maintenance of memory B cells. As a result, patients with diabetes frequently develop lower antibody titres and reduced durability of vaccine-induced immunity compared with healthy individuals. These defects have been particularly evident after influenza and SARS-CoV-2 vaccination, after which diminished antibody persistence and impaired memory B-cell responses have been consistently reported [8,20,21].

The interaction between adaptive immune dysfunction and trained innate immunity further amplifies immune dysregulation in diabetes. Persistent activation of innate immune cells results in continuous production of inflammatory cytokines, including IL-1 $\beta$ , IL-6 and TNF- $\alpha$ , which influence T-cell differentiation and promote immune exhaustion. At the same time, defective regulatory T-cell function weakens immune tolerance and enhances chronic inflammatory responses, establishing a vicious cycle that contributes to progressive tissue injury and diabetic complications [2,6,18].

Recent advances in single-cell transcriptomics and immunophenotyping have provided detailed insight into the molecular basis of adaptive immune dysfunction in diabetes. These technologies have revealed disease-specific alterations in transcriptional programmes, metabolic pathways and immune-cell heterogeneity, demonstrating that adaptive immune impairment extends beyond numerical changes in lymphocyte populations to include profound functional and molecular abnormalities. Such findings have strengthened the concept that adaptive immune memory is an active participant in diabetes pathogenesis rather than merely a consequence of chronic hyperglycaemia [6,8].

Improving adaptive immune memory has therefore emerged as an important therapeutic objective. Strategies aimed at reducing chronic inflammation, correcting metabolic abnormalities, restoring T-cell function and enhancing vaccine responsiveness may improve long-term immune protection and reduce the burden of diabetes-associated

complications. Continued research into the mechanisms governing adaptive immune memory is expected to facilitate the development of personalised immunotherapeutic approaches capable of restoring immune homeostasis in patients with diabetes [2,6,9].

### **10-ROLE OF THE GUT MICROBIOTA IN IMMUNE MEMORY**

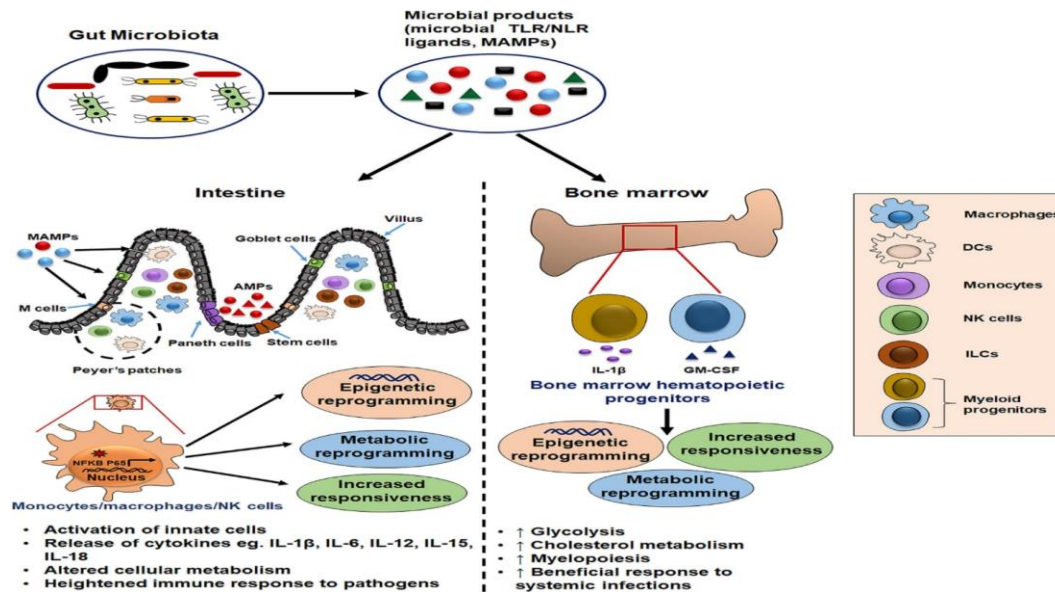
The gut microbiota has emerged as a critical regulator of immune homeostasis and immune memory, influencing both innate and adaptive immune responses through continuous interaction with the host immune system. The human gastrointestinal tract harbours trillions of microorganisms that contribute to nutrient metabolism, maintenance of intestinal barrier integrity and immune maturation. Under physiological conditions, the gut microbiota promotes immune tolerance while preserving the ability to mount effective protective responses against pathogens. Alterations in microbial composition, commonly referred to as gut dysbiosis, have been increasingly implicated in the pathogenesis of DM and immune dysfunction [22,23].

Recent evidence indicates that the gut microbiota plays an essential role in shaping trained immunity. Microbial metabolites, including short-chain fatty acids (SCFAs) such as butyrate, acetate and propionate, regulate the metabolic and epigenetic programming of monocytes, macrophages and haematopoietic stem cells. These metabolites influence histone acetylation, chromatin accessibility and cytokine production, thereby modulating long-term innate immune responses. In contrast, dysbiosis promotes systemic inflammation through increased intestinal permeability, endotoxin translocation and activation of inflammatory signalling pathways, contributing to persistent immune activation in diabetes [4,22].

The gut microbiota also exerts profound effects on adaptive immune memory. Commensal microorganisms regulate the differentiation and maintenance of regulatory T cells (Tregs), T-helper cell subsets and memory B cells through microbial antigens and immunomodulatory metabolites. Loss of microbial diversity has been associated with impaired immune tolerance, defective memory-cell formation and altered antibody responses. These abnormalities may contribute to the increased susceptibility to infection and the reduced vaccine efficacy observed in patients with type 1 or type 2 diabetes [22–24].

Several studies have demonstrated characteristic alterations in the intestinal microbiota of individuals with diabetes, including reduced abundance of beneficial butyrate-producing bacteria and increased proportions of pro-inflammatory microbial species. These microbial changes are associated with chronic low-grade inflammation, insulin resistance, impaired glucose metabolism and immune dysregulation. Emerging evidence further suggests that restoration of microbial balance through dietary intervention, probiotics, prebiotics or faecal microbiota transplantation may improve immune regulation and reduce inflammatory responses, although further clinical studies are required to confirm their long-term therapeutic efficacy [22,23,25].

Collectively, the gut microbiota is an essential environmental factor linking metabolism, immunity and chronic inflammation. Understanding the complex interactions between intestinal microorganisms and immune memory may provide novel opportunities for developing microbiota-based therapeutic strategies aimed at restoring immune homeostasis and preventing the progression of diabetes and its complications (Figure 4).



**Figure (4): The gut microbiota as a systemic inducer of innate immune memory. Microbial products acting as microbe-associated molecular patterns (MAMPs) bind to pattern-recognition receptors (PRRs) on innate immune cells such as monocytes, macrophages and NK cells. This interaction triggers intracellular epigenetic and metabolic reprogramming, leading to heightened cytokine release and enhanced responsiveness upon subsequent challenge. Microbial ligands also enter the bloodstream and reach the bone marrow, where they condition haematopoietic progenitors to promote myelopoiesis and imprint the long-term memory traits required for systemic inflammatory responses. Reproduced from reference (26).**

## 11-RECENT STUDIES LINKING IMMUNE MEMORY AND DIABETES

Over the past few years, substantial progress has been made in understanding the relationship between immune memory and DM. Advances in immunology, single-cell sequencing and systems biology have shown that chronic hyperglycaemia profoundly alters both innate and adaptive immune memory, thereby contributing to persistent inflammation, impaired immune protection and the progression of diabetic complications. These findings have shifted the traditional perception of diabetes from a purely metabolic disorder to a complex immunometabolic disease characterised by long-lasting immune dysregulation [2,3,6].

One of the most significant recent discoveries is the identification of trained immunity as a key mechanism underlying chronic inflammation in diabetes. Studies have shown that prolonged exposure to hyperglycaemia induces stable metabolic and epigenetic reprogramming in monocytes, macrophages and haematopoietic stem cells, resulting in exaggerated inflammatory responses that persist even after normalisation of blood glucose. These findings provide a mechanistic explanation for metabolic memory and its contribution to the vascular complications of diabetes [2,3,6].

Recent single-cell transcriptomic studies have further revealed significant alterations in immune-cell heterogeneity in patients with diabetes. Individuals with type 2 diabetes exhibit reduced CD4<sup>+</sup> T-cell populations, altered naïve-to-memory T-cell ratios and marked metabolic heterogeneity within immune-cell subsets. Similarly, patients with type 1 diabetes show accelerated immune ageing and abnormal distributions of memory T-cell populations, indicating that adaptive immune dysfunction is a common feature across different forms of diabetes [7,8].

Clinical investigations have also highlighted impaired vaccine-induced immune memory in patients with diabetes. Several studies evaluating immune responses after SARS-CoV-2 vaccination reported reduced antibody titres, impaired memory B-cell responses and diminished long-term CD8<sup>+</sup> memory T-cell function compared with healthy

individuals. These observations provide strong clinical evidence that diabetes compromises both humoral and cellular immune memory, increasing susceptibility to infectious disease despite successful vaccination [20,21,27]. More recently, advances in epigenomics and multi-omics technologies have enabled the identification of molecular pathways linking chronic metabolic stress with immune-cell dysfunction. Persistent alterations in chromatin accessibility, histone modifications, DNA methylation and immunometabolic signalling have been recognised as central mechanisms driving immune memory in diabetes. These discoveries have also facilitated the identification of potential biomarkers and therapeutic targets for precision immunotherapy [3,6,13].

Collectively, recent studies strongly support the concept that immune memory plays a central role in the initiation and progression of diabetes-related inflammation and complications. Ongoing research is expected to clarify further the molecular interactions between metabolism and immunity, ultimately contributing to the development of disease-modifying therapies capable of restoring immune homeostasis and improving long-term outcomes in patients with diabetes.

## **12-CLINICAL APPLICATIONS AND EMERGING THERAPEUTIC STRATEGIES**

Increasing evidence indicates that immune memory plays a central role in the pathogenesis and progression of DM, extending far beyond its traditional function in host defence. Persistent activation of trained innate immunity together with impairment of adaptive immune memory contributes to chronic low-grade inflammation, endothelial dysfunction, defective tissue repair and progressive organ damage. Consequently, immune dysregulation has been implicated in the development of diabetic nephropathy, retinopathy, neuropathy, cardiovascular disease and delayed wound healing, while also increasing susceptibility to bacterial and viral infections and reducing the effectiveness of vaccination [2,6,18]. These findings highlight immune memory as both a biomarker of disease progression and a promising therapeutic target for preventing long-term diabetic complications.

Advances in immunology have stimulated the development of novel therapeutic strategies aimed at restoring immune homeostasis rather than simply suppressing inflammation. Antigen-specific and T-cell-directed immunotherapies, particularly the anti-CD3 antibody teplizumab, have been shown to delay the onset of type 1 diabetes by modulating autoreactive T-cell responses while preserving pancreatic  $\beta$ -cell function [9,28]. Similarly, cytokine-targeted therapies directed against inflammatory mediators such as IL-1 $\beta$ , IL-6 and TNF- $\alpha$  have shown encouraging results in reducing chronic inflammation and improving metabolic outcomes by interrupting key inflammatory pathways involved in trained immunity [18,29].

Another promising approach involves targeting the metabolic and epigenetic mechanisms responsible for maintaining immune memory. Pharmacological modulation of glycolysis, the mevalonate pathway, mitochondrial metabolism and histone-modifying enzymes has been shown in preclinical studies to reverse maladaptive immune reprogramming and attenuate persistent inflammatory responses. In parallel, nanoparticle-based drug delivery systems have emerged as innovative platforms capable of delivering immunomodulatory agents selectively to immune cells, thereby improving therapeutic efficacy while minimising systemic adverse effects [3,11].

Recent clinical trials further support the feasibility of immune-targeted interventions in diabetes. In addition to teplizumab, monoclonal antibodies such as ustekinumab, which targets the IL-12/IL-23 signalling pathway, have shown favourable immunological effects in patients with recent-onset type 1 diabetes by preserving  $\beta$ -cell function and modulating pathogenic T-cell responses [30]. Ongoing clinical studies are also investigating epigenetic modulators, metabolic regulators and combination immunotherapies designed to reprogram trained immunity and improve long-term clinical outcomes. Although many of these approaches remain under investigation, their early results provide encouraging evidence that immune memory can be manipulated therapeutically to modify disease progression rather than merely to treat its complications [29,30].

The rapid expansion of precision medicine has further accelerated the translation of immune-memory research into clinical practice. Advances in single-cell transcriptomics, epigenomics, metabolomics, proteomics and systems

immunology have enabled comprehensive characterisation of immune-cell heterogeneity and the identification of disease-specific molecular signatures. These technologies facilitate patient stratification according to individual immunological profiles and support the development of personalised therapeutic strategies tailored to specific immune abnormalities [6,8,15]. Furthermore, integration of artificial intelligence and machine-learning algorithms with multi-omics data is expected to improve biomarker discovery, predict therapeutic responses and optimise individualised treatment decisions. Collectively, these advances suggest that future diabetes management will increasingly rely on precision immunotherapy aimed at restoring balanced immune memory while achieving optimal metabolic control, ultimately reducing the burden of chronic complications and improving long-term patient outcomes [6,15,30].

### **13-CURRENT CHALLENGES AND KNOWLEDGE GAPS**

Despite remarkable advances in the understanding of immune memory in DM, several important challenges and knowledge gaps remain. A major limitation is the incomplete understanding of the molecular mechanisms that govern the initiation, maintenance and reversibility of trained immunity and adaptive immune memory under chronic hyperglycaemic conditions. Although epigenetic remodelling and metabolic reprogramming have been identified as central mechanisms, the precise signalling pathways responsible for sustaining long-term immune dysfunction remain incompletely characterised [3,6,13].

Another major challenge is the marked heterogeneity among patients with diabetes. Disease type, duration of diabetes, age, obesity, genetic background, glycaemic control, lifestyle and antidiabetic medication may all influence immune memory, making it difficult to identify universal biomarkers or therapeutic targets. Moreover, significant differences exist between type 1 and type 2 diabetes with respect to immune-cell composition, inflammatory pathways and mechanisms of immune dysregulation, highlighting the need for disease-specific investigation [2,7,8].

The absence of standardised biomarkers is a further obstacle to clinical translation. Although several inflammatory mediators, immune-cell subsets and epigenetic signatures have been proposed as potential biomarkers, none has yet been sufficiently validated for routine clinical use. Likewise, the long-term safety and efficacy of therapies targeting trained immunity remain largely unknown, because most of the available evidence originates from experimental studies or early-phase clinical trials [6,15,18].

In addition, most current studies are cross-sectional or involve relatively small patient cohorts, limiting the ability to establish causal relationships between immune memory and disease progression. Large multicentre longitudinal studies integrating immunological, metabolic, genomic and clinical data are therefore required to improve the understanding of disease heterogeneity and to facilitate the development of evidence-based therapeutic strategies. Addressing these knowledge gaps will be essential for translating recent scientific discoveries into effective clinical interventions for patients with diabetes.

### **14-FUTURE DIRECTIONS**

Future research should integrate immunology, metabolism, genomics and artificial intelligence to achieve a more comprehensive understanding of immune memory in diabetes. Advances in single-cell sequencing, spatial transcriptomics, epigenomics, proteomics and metabolomics are expected to characterise immune-cell heterogeneity further and to identify novel molecular pathways involved in chronic inflammation and disease progression [6,13,15].

Another promising direction is the discovery of robust biomarkers capable of accurately predicting disease progression, therapeutic response and the risk of diabetic complications. Integration of multi-omics technologies with machine-learning algorithms may facilitate patient stratification and support precision-medicine approaches tailored to individual immunological profiles. Such strategies could improve treatment efficacy while minimising unnecessary immunosuppression [15].

Future therapeutic research should also evaluate combination strategies that simultaneously target metabolic dysregulation and immune dysfunction. Modulation of trained immunity, epigenetic reprogramming, cytokine signalling, the gut microbiota and antigen-specific immune responses may provide synergistic benefits beyond conventional glucose-lowering therapy. Large randomised clinical trials are required to establish the long-term safety, efficacy and clinical applicability of these emerging interventions across diverse diabetic populations [2,6,22].

Ultimately, a deeper understanding of the dynamic interaction between innate and adaptive immune memory is expected to facilitate the development of disease-modifying therapies capable of restoring immune homeostasis, preventing diabetic complications and improving long-term clinical outcomes. Continued interdisciplinary collaboration between immunologists, endocrinologists, molecular biologists and computational scientists will be essential to translate these scientific advances into routine clinical practice.

## CONCLUSION

Immune memory has emerged as a fundamental component of diabetes pathophysiology, extending far beyond its traditional role in host defence. Persistent hyperglycaemia induces long-lasting metabolic and epigenetic reprogramming of both innate and adaptive immune cells, resulting in sustained inflammation, impaired immune regulation, reduced vaccine responsiveness and increased susceptibility to infection and diabetic complications. The interaction between trained immunity, adaptive immune dysfunction and metabolic memory provides a comprehensive framework for understanding disease progression and its long-term consequences.

Recent advances in immunometabolism, epigenetics, single-cell technologies and systems immunology have considerably expanded current knowledge of immune memory and identified several promising biomarkers and therapeutic targets. Emerging immunomodulatory strategies, including antigen-specific therapies, cytokine-targeted interventions, epigenetic modulation, microbiota-based approaches and precision immunotherapy, offer new opportunities to complement conventional glucose-lowering treatment and improve long-term clinical outcomes.

Although important challenges remain, ongoing research continues to redefine diabetes as a complex immunometabolic disorder. Future integration of molecular biomarkers, multi-omics technologies and personalised therapeutic approaches is expected to transform diabetes management from a primary focus on glycaemic control towards restoration of immune homeostasis. A better understanding of immune memory may ultimately facilitate the development of disease-modifying therapies capable of preventing diabetic complications and improving the quality of life of individuals living with diabetes.

## REFERENCES

1. American Diabetes Association Professional Practice Committee. Standards of Care in Diabetes—2026. *Diabetes Care*. 2026;49(Suppl 1):S1-S300.
2. Atkinson MA, Roep BO, Posgai A, et al. The challenge of modulating  $\beta$ -cell autoimmunity in type 1 diabetes. *Lancet Diabetes Endocrinol*. 2021;9(7):475-485.
3. Bai Y, Wu J, Jian W. Trained immunity in diabetes: emerging targets for cardiovascular complications. *Front Endocrinol (Lausanne)*. 2025;16:1533620. doi:10.3389/fendo.2025.1533620
4. Netea MG, Domínguez-Andrés J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. *Nat Rev Immunol*. 2020;20(6):375-388. doi:10.1038/s41577-020-0285-6
5. Schlüter T, van Elsas Y, Priem B, et al. Trained immunity: induction of an inflammatory memory in disease. *Cell Res*. 2026;36:792-802.
6. Gong Q, Huang Y, Liu F, Zhou T, Huang W, Xu Y. Trained immunity: new insights into pathogenesis and therapeutic targets in diabetes and diabetic complications. *Genes Dis*. 2026;13(5):101940. doi:10.1016/j.gendis.2025.101940

7. Shapiro MR, Dong X, Perry DJ, McNichols JM, Thirawatananond P, Posgai AL, et al. Human immune phenotyping reveals accelerated aging in type 1 diabetes. *JCI Insight*. 2023;8(17):e170767. doi:10.1172/jci.insight.170767
8. Li H, Zou L, Long Z, Zhan J. Immunometabolic alterations in type 2 diabetes mellitus revealed by single-cell RNA sequencing: insights into subtypes and therapeutic targets. *Front Immunol*. 2024;15:1537909. doi:10.3389/fimmu.2024.1537909
9. Ray S, Palui R. Immunotherapy in type 1 diabetes: novel pathway to the future ahead. *World J Diabetes*. 2024;15(10):2022-2035. doi:10.4239/wjd.v15.i10.2022
10. Liu Y, Lei Y, Dai Z, Luo C, Gong Q, Li Y, et al. Trained immunity: novel perspectives in diabetes and associated complications. *Front Immunol*. 2025;16:1613602. doi:10.3389/fimmu.2025.1613602
11. Huang M, Chen W, Wang M, Huang Y, Liu H, Ming Y, et al. Advanced delivery strategies for immunotherapy in type I diabetes mellitus. *BioDrugs*. 2023;37(3):331-352. doi:10.1007/s40259-023-00594-6
12. Joseph J. Trained immunity as a prospective tool against emerging respiratory pathogens. *Vaccines (Basel)*. 2022;10(11):1932. doi:10.3390/vaccines10111932
13. Novakovic B, Netea MG. Epigenomics of innate immune memory and inflammatory diseases. *Trends Immunol*. 2022;43(10):800-813.
14. Lau CM, Adams NM, Geary CD, et al. Epigenetic control of T-cell and B-cell memory differentiation. *Nat Immunol*. 2023;24(9):1424-1436.
15. Figueroa-Guillen L, Xie H, Netea MG. Epigenetic regulation of trained immunity. *Nat Rev Immunol*. 2025;25(2):112-126.
16. Wang J, Liu YM, Hu J, Chen C. Trained immunity in monocyte/macrophage: novel mechanism of phytochemicals in the treatment of atherosclerotic cardiovascular disease. *Front Pharmacol*. 2023;14:1109576. doi:10.3389/fphar.2023.1109576
17. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353(25):2643-2653. doi:10.1056/NEJMoa052187
18. Donath MY, Dinarello CA, Mandrup-Poulsen T. Targeting innate immune mediators in type 1 and type 2 diabetes. *Nat Rev Immunol*. 2019;19(12):734-746. doi:10.1038/s41577-019-0213-9
19. Wherry EJ. T cell exhaustion. *Nat Immunol*. 2011;12(6):492-499. doi:10.1038/ni.2035
20. Chen Y, Shen H, Huang R, et al. Immune responses to COVID-19 vaccination in patients with diabetes mellitus: a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2024;40(3):e3690.
21. Painter MM, Mathew D, Goel RR, Apostolidis SA, Pattekar A, Kuthuru O, et al. Rapid induction of antigen-specific CD4<sup>+</sup> T cells is associated with coordinated humoral and cellular immunity to SARS-CoV-2 mRNA vaccination. *Immunity*. 2021;54(9):2133-2142.e3. doi:10.1016/j.immuni.2021.08.001
22. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol*. 2021;19(1):55-71. doi:10.1038/s41579-020-0433-9
23. Gurung M, Li Z, You H, Rodrigues R, Jump DB, Morgun A, et al. Role of gut microbiota in type 2 diabetes pathophysiology. *EBioMedicine*. 2020;51:102590. doi:10.1016/j.ebiom.2019.11.051
24. Honda K, Littman DR. The microbiota in adaptive immune homeostasis and disease. *Nature*. 2016;535(7610):75-84. doi:10.1038/nature18848
25. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. *Cell Res*. 2020;30(6):492-506. doi:10.1038/s41422-020-0332-7
26. Negi S, Das DK, Pahari S, Nadeem S, Agrewala JN. Potential role of gut microbiota in induction and regulation of innate immune memory. *Front Immunol*. 2019;10:2441. doi:10.3389/fimmu.2019.02441

27. Sette A, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. *Cell*. 2021;184(4):861-880. doi:10.1016/j.cell.2021.01.007
28. Herold KC, Bundy BN, Long SA, Bluestone JA, DiMeglio LA, Dufort MJ, et al. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. *N Engl J Med*. 2019;381(7):603-613. doi:10.1056/NEJMoa1902226
29. Donath MY. Targeting inflammation in the treatment of type 2 diabetes: time to start. *Nat Rev Drug Discov*. 2014;13(6):465-476. doi:10.1038/nrd4275
30. Tatovic D, Marwaha A, Taylor P, Hanna SJ, Carter K, Cheung WY, et al. Ustekinumab for type 1 diabetes in adolescents: a multicenter, double-blind, randomized phase 2 trial. *Nat Med*. 2024;30(9):2657-2666. doi:10.1038/s41591-024-03115-2