Immune Discovery

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Review

Transforming Growth Factor-β1 Signaling in Macrophages: From MAD/SMAD Homology to Diabetic Complications

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ABSTRACT: Transforming growth factor-β1 (TGF-β1) is a pleiotropic cytokine that plays pivotal but often opposing roles in immune regulation and tissue homeostasis. In macrophages, TGF-β1 signaling integrates inflammatory, metabolic, and fibrotic responses in a highly context-dependent manner. This review comprehensively investigates TGF-β1 signaling mechanisms, metabolic crosstalk, and clinical significance in macrophages, with a focus on diabetic complications. The canonical SMAD2/3-dependent pathway, together with alternative SMAD1/5-dependent signaling and non-SMAD routes (including mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling), enables signaling divergence that allows TGF-β1 to exert both anti-inflammatory and profibrotic effects. Pioneering work established the core mechanistic framework, while other studies elucidated its role in alternative macrophage activation and tissue remodeling. Recent investigations associate high-glucose culture conditions with increased lactate and altered TGF-β1/SMAD1/5 signaling in human macrophages, suggesting a link between metabolic reprogramming and pro-atherogenic programs. In diabetes, chronic hyperglycemia can reprogram macrophages and alter their responses to TGF-β1, potentially sustaining inflammation and fibrosis. These macrophage responses are discussed in relation to diabetic kidney disease, retinopathy, neuropathy, cardiomyopathy, and impaired wound healing. The glucose–lactate–TGF-β1/SMAD1/5 sequence remains a candidate mechanism: lactate mediation, osmotic effects, and consequent organ injury have not been resolved. Therapeutic targeting of TGF-β1 remains challenging because of its dualistic nature, which requires context-specific modulation and direct assessment of repair and safety. This review discusses emerging strategies, including macrophage-targeted approaches and combined immunometabolic interventions. A deeper understanding of context-dependent TGF-β1 signaling in macrophages is essential for developing precision therapies that mitigate diabetic complications while preserving physiological immune and reparative functions.

Keywords: TGF-β1; Innate immunity; Macrophages; SMAD signaling; Immunometabolism; Diabetic complications

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1. Introduction

Transforming growth factor-β1 (TGF-β1) is a pleiotropic cytokine belonging to the TGF-β superfamily that regulates cellular proliferation, differentiation, apoptosis, extracellular matrix remodeling, and immune responses [1–3]. In the immune system, TGF-β1 regulates both anti-inflammatory responses and fibrotic processes, with outcomes shaped by cellular context, microenvironmental cues, and disease state [1,2].

This narrative review focuses on macrophage TGF-β1 signaling and its immunometabolic regulation in diabetic complications. Particular attention is given to how receptor availability, transcriptional cofactors, and metabolic state shape the functional outputs of the conserved MAD/SMAD signaling machinery. Findings from other innate immune populations provide complementary insights, with their relevance distinguished from direct evidence in diabetic macrophages.

In innate immune cells—particularly macrophages, dendritic cells (DCs), neutrophils, and natural killer (NK) cells—TGF-β1 critically modulates inflammatory signaling, immune tolerance, phagocytosis, and tissue repair [2,3]. The molecular mechanisms of TGF-β1 signaling were elucidated through establishing the core framework of ligand-induced receptor activation, canonical SMAD-dependent transcriptional control, and noncanonical pathways [1,4]. These studies revealed how cellular context, lineage-specific transcription factors, and extracellular signals dictate the remarkable functional diversity of TGF-β1 responses [1]. Building on this foundation, subsequent investigations highlighted TGF-β1's role in driving alternative (M2-like) macrophage activation programs, including induction of immunoregulatory receptors and tissue-remodeling gene signatures [5,6].

TGF-β1 modulates macrophage cytokine secretion, phagocytosis, and tissue-remodeling programs [5,6]. In primary human macrophages, elevated culture glucose was associated with increased lactate and enhanced TGF-β1-induced SMAD1/5 phosphorylation [7]. These findings provide a valuable experimental basis for investigating lactate-mediated signaling, the contribution of osmotic effects, and the relevance of this macrophage response to diabetic organ injury *in vivo*.

Cellular metabolism has emerged as a central regulator of innate immune function, influencing bioenergetics, redox balance, epigenetic landscapes, and inflammatory signaling. Glucose metabolism, in particular, exerts profound effects on immune cell fate [7–9]. TGF-β1 signaling is tightly intertwined with these metabolic pathways, forming a bidirectional regulatory axis. TGF-β1 modulates glucose uptake and glycolytic flux, while metabolic intermediates and nutrient-sensing pathways reciprocally control TGF-β1 production, activation, and downstream signaling. This integration is especially critical in macrophages, where metabolic reprogramming dictates the balance between pro-inflammatory and immunoregulatory phenotypes [7]. In chronic disease settings, sustained crosstalk between hyperglycemia-driven metabolic stress and TGF-β1 signaling drives maladaptive responses, including excessive fibrosis, impaired resolution of inflammation, and immune suppression [7–9].

Diabetes mellitus, particularly type 2 diabetes, involves chronic inflammation associated with nutrient excess, insulin resistance, advanced glycation end-products (AGEs), and oxidative stress [10–12]. In this environment, macrophage metabolic adaptation and TGF-β1 responses may contribute to inflammatory and fibrotic processes [3,5,7,13]. Their contribution must be distinguished from TGF-β1 signaling in other cells; retinal microglial receptor-deletion experiments, for example, concern retinal homeostasis rather than diabetes-induced systemic inflammation [14].

While numerous reviews have addressed the role of TGF-β1 in diabetic complications, most have focused primarily on its direct profibrotic effects in tissue-resident cells such as fibroblasts, mesangial cells, or podocytes. This review focuses on macrophages, investigating the interplay between TGF-β1 signaling and immunometabolic reprogramming and considering trained immunity as a possible contributor to disease persistence. This review discusses how hyperglycemia-associated metabolic reprogramming may alter TGF-β1 responses from homeostatic to maladaptive [7]. By emphasizing signaling divergence and the

context-dependent functions of TGF-β1 in macrophages, this review offers a novel immunometabolic perspective that bridges molecular mechanisms with clinical diabetic complications and identifies promising precision therapeutic opportunities.

We synthesize macrophage TGF-β1 signaling mechanisms and responses to metabolic stress. The contribution of this review is to connect conserved MAD/SMAD architecture with signaling divergence and immunometabolic regulation while distinguishing direct diabetic evidence from indirect observations, mechanistic associations from causal mediation, and proposed therapeutic strategies from demonstrated clinical efficacy.

Targeted searches of PubMed, Clarivate, and Scopus-indexed records and linked publisher full texts were conducted through 20 October 2026 using combinations of TGF-β/TGF-β1, macrophage, innate immunity, diabetes, hyperglycemia, SMAD1/5, SMAD2/3, lactate, glycolysis, trained immunity, metabolic memory, and clinical trial. Original studies were prioritized for mechanistic and clinical claims, with reviews used for context. Sources were selected for relevance to the cell type, model, intervention, and outcome; non-diabetic evidence was identified as indirect. This was a targeted narrative review, not a systematic review or formal risk-of-bias assessment.

2. Molecular Mechanisms of TGF-β1 Signaling in Innate Immune Cells

Active TGF-β1 binds the type II receptor TGFBR2, which recruits and phosphorylates the type I receptor TGFBR1/ activin receptor-like kinase 5 (ALK5) [1]. The conserved receptor framework provides a mechanistic foundation for understanding macrophage TGF-β1 responses, complemented by insights into context-dependent signaling from neural stem-cell and tumor studies [4]. ALK5 phosphorylates SMAD2/3, which associate with SMAD4 and regulate transcription through nuclear partners and chromatin regulators. This canonical pathway can mediate immune restraint, differentiation, or extracellular matrix production depending on the responding cell [1].

TGF-β1 signaling extends beyond the canonical SMAD2/3 pathway to include MAPK, PI3K/AKT, and Rho-GTPase cascades [15,16]. In primary human macrophages, TGF-β1 also activates an alternative SMAD1/5-dependent branch [7,15], expanding its signaling repertoire through both SMAD-dependent and SMAD-independent mechanisms [1,16].

TGF-β1 bioavailability is tightly controlled. The cytokine is secreted in a latent form complexed with latency-associated peptide (LAP) and latent TGF-β1-binding proteins (LTBPs). Activation requires proteolytic cleavage, integrin-mediated release (particularly via αvβ6 and αvβ8 integrins), or mechanical forces within the extracellular matrix, ensuring precise spatial and temporal control during inflammation and repair [1,17].

2.1. TGF-β1-Mediated Regulation of Macrophage Polarization

TGF-β1 shapes macrophage activation through context-dependent immunoregulatory and tissue-remodeling programs [3,5]. These responses reflect a continuum of functional states, with M1-like and M2-like designations serving as experimental descriptors within the broader diversity of macrophage phenotypes *in vivo* [18,19].

Gratchev and colleagues demonstrated that glucocorticoids enhance surface expression of TGFBR2 on human monocyte-derived macrophages, thereby sensitizing them to TGF-β1 and initiating a coordinated multistep gene expression program characteristic of alternative activation [5]. Subsequent work identified key TGF-β1-responsive genes in alternatively activated macrophages. One prominent example is chitinase-3-like protein 2 (YKL-39), which is potently induced by the combination of IL-4 and TGF-β1 and serves as a marker of macrophages involved in extracellular matrix (ECM) remodeling, angiogenesis, and chronic inflammatory conditions [18].

Tumor-associated macrophages illustrate the coexistence of immunosuppression and tissue remodeling under TGF-β-rich conditions [3]. Stabilin-1 provides a related example of a multifunctional homeostatic scavenger receptor [6]. Neither tumor-associated nor M2-like features alone establish beneficial repair in diabetes.

Elevated-glucose culture conditions increase lactate and enhance TGF-β1-induced SMAD1/5 phosphorylation in human macrophages [7]. The proposed progression from these responses to chronic vascular remodeling requires causal testing in diabetic tissues [16].

Macrophage plasticity thus depends on the dynamic balance between canonical SMAD2/3 and alternative SMAD1/5-dependent and non-SMAD TGF-β1 signaling, modulated by the surrounding cytokine environment, metabolic status, and tissue-specific cues [7,18] (Figure 1).

Macrophage activation is heterogeneous, with mixed and transitional states influenced by metabolic, inflammatory, and spatial cues [19]. Consequently, TGF-β1 responses in diabetic tissues cannot be predicted from M1/M2 labels alone [3,7]. Functional measurements alongside transcriptional and metabolic profiling are needed to assess repair, inflammation, and fibrosis.

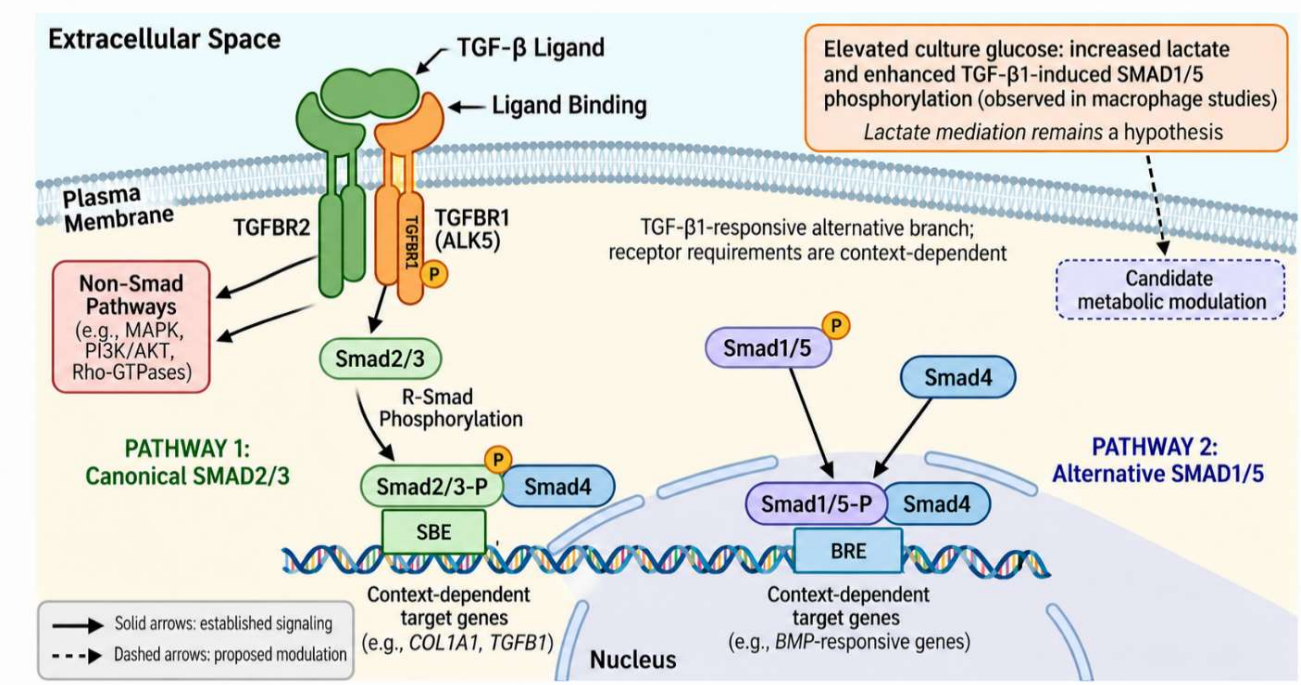


Figure 1. TGF-β1 signaling branches and candidate metabolic crosstalk in macrophages. TGF-β1 receptor signaling engages canonical SMAD2/3, alternative SMAD1/5, and non-SMAD pathways in a cell-dependent manner [1,5,15,16]. Elevated glucose in cultured human macrophages was associated with increased lactate and enhanced TGF-β1-induced SMAD1/5 phosphorylation [7]. Lactate mediation and direct ALK-receptor activation by lactate are not established. This schematic does not demonstrate diabetic organ injury, exclude osmotic effects, or created to assign uniformly protective or pathogenic functions to individual SMAD branches.

2.2. TGF-β1 Signaling in Dendritic Cells and Natural Killer Cells

In dendritic cells, TGF-β1 can inhibit maturation and antigen presentation, providing an immune-regulatory comparison with macrophages [2].

In NK cells, TGF-β1 can suppress cytotoxicity and IFN-γ production, particularly in tumors [2], however, these effects do not establish corresponding mechanisms in diabetic macrophages.

Interferon–TGF-β1 interactions provide broader immune context [20]. High-glucose experiments in virus-infected A549 epithelial cells [21] are distinct from direct TGF-β1 signaling experiments in diabetic dendritic or NK cells.

2.3. TGF-β1 Signaling in Neutrophils and Retinal Microglia

Neutrophil responses to TGF-β1 vary with the inflammatory and tumor environment [16]. Although neural and tumor studies provide additional tissue context [4], but they do not establish a diabetes-specific neutrophil mechanism.

Disruption of TGF-β1 receptor signaling in retinal microglia compromises retinal homeostasis and exacerbates retinal degeneration and choroidal neovascularization [14]. These findings establish a homeostatic role for microglial TGF-β1 signaling in non-diabetic retinal models, providing a foundation for investigating its relationship to macrophage lactate–SMAD1/5 signaling in diabetes.

Table 1 separates biological context from therapeutic evidence, as such established effects in one cell type or disease model should not be generalized across diabetic organs.

Table 1. Innate immune cell context and evidence level of proposed therapeutic strategies.

Cell Context	Biological Interpretation	Therapeutic Strategy and Evidence Level	References
Macrophages	TGF-β1 responses vary by receptor availability and metabolic state. Culture signaling does not prove organ injury.	Hypothesis: selective SMAD1/5 modulation or macrophage-directed delivery. Not yet established clinical efficacy in diabetic complications.	[3,5–7,13,15,22–24]
Dendritic and NK cells	Tolerogenic dendritic and suppressed NK-cell functions provide contextual comparisons; pregnancy and B-cell studies concern other populations.	Hypothesis: cell-specific TGF-β1 modulation in diabetes; tumor/immune findings cannot establish diabetic benefit.	[2,25–27]
Neutrophils	Inflammation and NET-associated injury are distinct from direct macrophage SMAD signaling; plaque and cancer data concern other settings.	Preclinical/indirect: NET-related interventions; combined timed TGF-β1 modulation in diabetes remains hypothetical.	[16,28–30]
Retinal microglia	TGF-β1 receptor deletion in a non-diabetic retinal model impairs homeostasis.	Hypothesis: intraocular pathway modulation with anti-VEGF; the cited evidence does not establish this combination or its safety.	[14,31]
Clinical metabolic treatments	Clinical outcome evidence must be distinguished from a macrophage mechanism.	Clinical evidence: GLP-1 receptor agonists/SGLT2 inhibitors in specified populations. Their proposed macrophage TGF-β1 mediation, and combination with selective SMAD1/5 inhibition, remain as future research direction.	[32,33]
Direct pathway interventions	Clinical trials concern different diseases and different targets.	Clinical, negative in diabetic nephropathy: LY2382770. Clinical studies in other diseases: fresolimumab, galunisertib, bexotegrast. No inference of selective SMAD1/5 efficacy.	[34–37]

Abbreviations: NET, neutrophil extracellular trap formation; GLP-1, glucagon-like peptide-1; SGLT2, sodium–glucose cotransporter 2. Evidence labels apply to the specified intervention and population, not to a proven macrophage-specific mechanism in diabetes.

2.4. TGF-β1 in Chronic Inflammation

Macrophages can both produce TGF-β1 and respond to it during chronic inflammation [6,9,22]. Ligand secretion acting on neighboring matrix-producing cells differs from receptor–SMAD signaling within macrophages, and these processes require separate experimental attribution.

3. SMAD Homology Proteins in TGF-β1 Signaling: Structural Basis, Regulatory Networks, and Functional Implications in Innate Immunity

SMAD proteins are the principal intracellular effectors of transforming growth factor-β1 (TGF-β1) signaling [1,4]. They constitute a highly conserved family of transcriptional regulators that mediate cellular responses to TGF-β superfamily ligands. These proteins are essential for immune homeostasis, cellular differentiation, extracellular matrix remodeling, and inflammatory adaptation [1–3]. The term "SMAD" originates from the evolutionary homology between the *Caenorhabditis elegans* protein SMA and the *Drosophila melanogaster* protein Mothers Against Decapentaplegic (MAD). Mammalian SMADs retain significant structural and functional conservation with these ancestral molecules and function as the primary downstream transducers of TGF-β1 receptor activation [1,4].

The seminal genetic studies in Drosophila provided an important conceptual foundation for understanding TGF-β superfamily signaling as a context-dependent regulatory network rather than a simple linear ligand–receptor cascade. Identification of Schnurri (Shn) as a downstream effector of Decapentaplegic (Dpp) demonstrated that Dpp-dependent developmental responses require transcriptional regulators acting downstream of receptor activation, with Shn activity contributing to tissue patterning, Dpp autoregulation, and midgut morphogenesis [38]. In parallel, studies of the Drosophila viscera demonstrated that Dpp and Wingless (Wg) function as intercellular positional cues that establish and maintain homeotic gene expression through feedback and autoregulatory circuits, emphasizing the importance of communication between neighboring cell populations in determining cellular identity [39]. These observations preceded the molecular delineation of the conserved SMAD pathway, in which TGF-β family ligands activate receptor-regulated SMADs that cooperate with tissue-specific transcriptional regulators to determine target-gene expression [40]. Subsequent work has established that cellular responses to TGF-β1 are shaped by receptor availability, SMAD phosphorylation and complex composition, non-SMAD signaling, transcription-factor partnerships, and chromatin and epigenetic states, providing a mechanistic basis for the remarkable context dependence of TGF-β1 responses [41,42]. This principle is particularly relevant to macrophages, where TGF-β1 can simultaneously reshape transcriptional and metabolic programs. Recent evidence demonstrates that TGF-β1 exposure promotes glycolytic reprogramming through the mechanistic target of rapamycin (mTOR)–MYC proto-oncogene protein (c-MYC)–liver-type phosphofructokinase-1 (PFKL) axis axis while suppressing inflammatory transcriptional programs through SMAD3-associated epigenetic remodeling [43,44]. Moreover, emerging evidence indicates that the metabolic microenvironment itself can alter TGF-β1 signal interpretation: under high-glucose conditions, TGF-β1 activates the SMAD1/5 pathway in primary human macrophages, in addition to canonical SMAD2 signaling, suggesting that metabolic stress can redirect TGF-β1 signaling toward distinct downstream outputs [7,8]. Conservation of the core machinery permits different outputs through receptor regulation and transcriptional partnerships [40,41]. Developmental Dpp studies establish signaling principles; macrophage receptor regulation [5], SMAD1/5 activation [7,15], and glycolysis–inflammation uncoupling [44] provide the context for Sections 4 and 5.

SMAD transcriptional regulation and its control through linker phosphorylation, phosphatases, and phosphoserine-dependent turnover establish how receptor signals acquire context-specific outputs [1,2,23,24]. Macrophage, placental, vascular, and cancer literature illustrates different biological settings and should not be treated as interchangeable evidence of diabetic macrophage injury [3,7,25,28,29].

3.1. Structural Organization of SMAD Proteins

Receptor-regulated SMADs and SMAD4 share a conserved modular structure consisting of two globular domains—the N-terminal MAD homology 1 (MH1) domain and the C-terminal MAD homology 2 (MH2) domain—connected by a variable proline-rich linker region that serves as a key regulatory

platform [1–4]. The MH1 domain primarily mediates sequence-specific DNA binding to SMAD-binding elements (SBEs) in promoter and enhancer regions. SMAD complexes cooperate with transcriptional and chromatin regulators to generate context-specific outputs [1]. The major full-length SMAD2 isoform has an MH1 insertion that limits direct DNA binding; SMAD2 and SMAD3 therefore should not be treated as functionally identical. Inhibitory SMAD7 lack the same MH1 architecture [16,42]. The MH2 domain functions as the main effector region. It mediates receptor interaction, SMAD oligomerization, and recruitment of transcriptional co-regulators. Upon TGF-β1 receptor activation, receptor-regulated SMADs (R-SMADs: SMAD2 and SMAD3 and/or SMAD1 and SMAD5) are phosphorylated at C-terminal serine residues within the MH2 domain. This phosphorylation induces conformational changes that enable formation of active SMAD complexes, nuclear translocation, and transcriptional regulation [1,4,7].

The linker region integrates MAPK, CDK, GSK-3β, and other inputs; phosphorylation and ubiquitination control SMAD activity, localization, and turnover [23,24,27]. Regulatory B-cell biology provides a separate immune-regulatory context [26], rather than direct evidence for these macrophage linker mechanisms.

3.2. SMAD Signaling Networks in Innate Immune Cells

In macrophages, SMAD signaling links receptor availability and metabolic context to cytokine production and tissue-remodeling programs [3,5,7].

Alternative activation and scavenger-receptor expression illustrate macrophage specialization [3,5,6]. In high-glucose cultures, altered SMAD signaling provides evidence of metabolic responsiveness [7], but inflammatory restraint, repair, and fibrosis remain distinct functional outcomes to be elucidated.

IL-6 reversal of tumor-derived TGF-β1-mediated dendritic-cell inhibition provides a non-macrophage example of signaling integration [45]. NK-cell regulation and immune responses to eye injury provide further contextual comparisons [2,31].

3.3. Noncanonical SMAD Signaling and Pathophysiological Consequences

Here, “noncanonical SMAD” denotes alternative SMAD-dependent signaling, not SMAD-independent signaling. SMAD2 and SMAD3 also have distinct functions and should not be treated as interchangeable. SMAD3 can support inflammatory restraint in macrophages while promoting extracellular matrix production in other cells. In obese diabetic mice, systemic Smad3 perturbation reduced myocardial fibrosis but compromised cardiac or aortic geometry, illustrating that antifibrotic effects can coexist with loss of structural integrity [46]. Such whole-animal effects cannot be attributed exclusively to macrophages. Therapeutic selection therefore requires cell- and disease-stage-specific functional evidence [22,42,47,48].

TGF-β1 activates SMAD1/5 in primary human macrophages and induces pro-atherogenic gene expression [15]. Elevated culture glucose enhances this response [7]; neither experiment alone establishes plaque progression or organ injury in diabetes.

SMAD complex composition and metabolic state influence TGF-β1 responses [7,8,16]. SMAD1/5 should not be designated uniformly pathogenic, nor SMAD2/3 uniformly protective; functional consequences require cell- and model-specific evidence.

4. Divergence and Convergence of TGF-β1 Signaling in Innate Immune Cells and Inflammatory Responses

TGF-β1 produces different outcomes through receptor composition, intracellular signaling partners, and the metabolic and inflammatory environment [1,4,49]. The following discussion focuses on how these variables affect macrophage immunometabolism.

Divergence denotes activation of distinct pathways by one receptor system, while convergence denotes integration of different inputs at shared signaling or transcriptional nodes [49,50]. In macrophages, this network organization connects extracellular cues to inflammatory and metabolic responses [1,50].

4.1. Divergence of TGF-β1 Signaling Pathways

4.1.1. Canonical and Noncanonical Signaling Divergence

Canonical SMAD2/3, alternative SMAD1/5, and non-SMAD branches provide distinct routes for signal divergence [1,51]. Their relative activity depends on cell type and microenvironment; general neural or tumor observations are contextual [4].

Canonical SMAD signaling exerts cell-dependent effects, suppressing inflammatory cytokine production in macrophages while promoting extracellular matrix synthesis in other responsive cell populations. Its implications for tissue repair therefore require functional assessment beyond pathway activation or changes in cytokine expression alone [22,42,50].

4.1.2. Cell Type-Specific Divergence

Macrophage-specific outputs include alternative activation and SNAIL-associated suppression of inflammatory cytokines [3,5,52]. These programs can accompany remodeling without demonstrating successful repair.

Dendritic-cell and NK-cell immune regulation provides a comparison for cell-dependent divergence [2,49], however, these mechanisms are not assumed to explain diabetic macrophage phenotypes.

4.1.3. Microenvironment Dependent Divergence

Glucocorticoid-dependent TGFBR2 expression sensitizes human macrophages to TGF-β1 [5]. Tumor-associated and SNAIL-related responses illustrate other contextual effects [49,52]; glucose-associated signaling is considered separately in Section 5.

4.2. Convergence of TGF-β1 Signaling Pathways

4.2.1. Convergence on Shared Transcriptional Programs

SMAD complexes cooperate with transcription factors and chromatin regulators to integrate extracellular signals [1,51]. Autophagy and lipid-droplet biology supplies additional metabolic context in liver disease [53], rather than direct evidence for each macrophage transcriptional interaction.

Convergent pathways can coordinate cytokine regulation and remodeling programs in macrophages [5,52]. Their net effect must be measured rather than inferred from an activation label.

4.2.2. Convergence with Pattern Recognition Receptor Signaling

Interferon–TGF-β1 interactions illustrate immune counter-regulation [20]. TGF-β2/TLR4 crosstalk in trabecular meshwork cells [54], TGF-β1/NF-κB observations in disc degeneration [55], and neuroblastoma drug-resistance experiments [56] demonstrate context-dependent interactions outside diabetic macrophages. Autophagy and lipid-droplet pathways add related metabolic context [53].

4.3. Functional Implications of Signaling Divergence and Convergence

Divergence and convergence support adaptation to infection and injury but can also contribute to fibrosis or immune suppression [4,7,50,51]. Their relevance to diabetes requires evidence from the appropriate responding cells.

Selective therapeutic modulation of specific divergent branches (e.g., SMAD1/5 inhibition) or convergent nodes may hold promise for suppressing pathological signaling in specific cell populations, but preservation of repair and immune function requires direct testing.

5. Interplay Between Glucose Metabolism and TGF-β1 Signaling in Innate Immune Cells

5.1. Metabolic Reprogramming in Innate Immune Cells

Macrophage activation involves changes in glucose uptake, glycolysis, mitochondrial metabolism, and biosynthetic pathways [57]. A glycolytic phenotype can support inflammatory activity, but it is not a sufficient marker of inflammation.

In contrast, alternatively activated or immunoregulatory macrophages rely more on oxidative phosphorylation and fatty acid oxidation, which sustain long-term tissue repair and anti-inflammatory activities [58,59]. TGF-β1 effects cannot be inferred from a glycolytic-versus-oxidative polarization dichotomy: increased glycolysis can coexist with suppression of inflammatory cytokines [44].

5.2. Regulation of Glucose Metabolism by TGF-β1 Signaling

Studies on TGF-β1 pretreatment followed by inflammatory stimulation in macrophages and experimental sepsis have shown increased glycolysis coexisting with reduced inflammatory cytokines, but treated mice showed increased coagulation and reduced survival [44]. These findings do not demonstrate improved tissue repair or overall benefit and still differ from sustained high-glucose differentiation experiments [7].

TGF-β1 signaling interacts with glucose transport, glycolytic enzymes, and nutrient-sensing pathways across cell types [60]. In macrophages, mTOR–c-MYC–PFKL-dependent glycolysis can be separated from SMAD3-associated cytokine suppression [44]. Thus, suppression of inflammatory markers must be assessed alongside coagulation, tissue function, and survival rather than interpreted as restoration of homeostasis [5,7].

5.3. Glucose Availability as a Regulator of TGF-β1 Signaling

Basal and elevated culture glucose of approximately 17.5 and 42.5 mmol/L, respectively [7], have been used as experimental media concentrations in macrophages *in vitro*, showing increased lactate and altered TGF-β1-induced SMAD1/5 signaling. Taken in account that physiological human glycemia and typical diabetic whole tissue conditions are different, continuous glucose exposure, osmotic control, selective lactate manipulation with blockade/rescue, donor variability, and macrophage differentiation conditions along with persistent immune memory after glucose withdrawal or diabetic organ injury *in vivo*, remain as a future investigation challenges.

The interaction between glucose metabolism and TGF-β1 signaling is bidirectional. High glucose availability and metabolic intermediates strongly modulate TGF-β1 production, receptor sensitivity, SMAD activation, and downstream responses [61]. Hyperglycemia promotes oxidative stress and inflammatory signaling, which enhance TGF-β1 expression and activation of latent complexes. Lactate-mediated acidification can activate latent TGF-β1 in non-diabetic pulmonary fibrosis experiments [62]. All may suggest the need to investigate lactate as the mediator of SMAD1/5 activation in human macrophages.

Nutrient-sensing pathways such as mTOR and adenosine monophosphate–activated protein kinase (AMPK) serve as critical nodes in this crosstalk. AMPK activation generally restrains profibrotic TGF-β1 responses, whereas mTOR signaling can potentiate anabolic and fibrotic programs driven by TGF-β1 [22]. Thus, the metabolic state of macrophages directly shapes the intensity and functional outcome of TGF-β1 signaling [63–65].

5.4. Interaction Between TGF-β1 Signaling and Glucose Metabolism

TGF-β-dependent fibrosis involves matrix-producing cells and metabolically active immune populations [22,57]. Lactate-associated activation of latent TGF-β1 has supporting evidence in pulmonary fibroblast models [62]; extrapolation to a macrophage-intrinsic diabetic feedback loop remains hypothetical.

A glucose–lactate–TGF-β1 feedback loop is therefore a candidate mechanism linking metabolic stress to fibrosis [7,22]. Its mediation of injury across kidney, heart, retina, nerves, and wounds has not been demonstrated by the human macrophage culture study.

5.5. Noncanonical Metabolic Signaling and TGF-β1 Responses

Alternative SMAD1/5-dependent signaling and non-SMAD routes involving PI3K/AKT and MAPK further link TGF-β1 receptor activation to glucose metabolism, mitochondrial function, and anabolic pathways [7,16,51].

The integration of canonical and noncanonical TGF-β1 signaling thus enables macrophages to coordinate immune regulation with metabolic adaptation across diverse physiological and pathological contexts.

6. Trained Immunity and Metabolic Memory in TGF-β1 Signaling

Emerging evidence indicates that hyperglycemia induces long-term functional reprogramming of innate immune cells through a process known as trained immunity (or innate immune memory) [66,67]. This epigenetic and metabolic reprogramming enables macrophages and their progenitors to generate adapted inflammatory responses upon subsequent stimulation, even after normalization of glycemic levels, a mechanism that may contribute to the broader phenomenon of "metabolic memory" in diabetes, although the terms are not synonymous [66–68].

Hyperglycemia can produce metabolic and epigenetic reprogramming associated with trained immunity in macrophages and their precursors [66]. Histone methylation, including H3K4me3, and histone lactylation are distinct modifications; the latter should not be inferred from methylation findings. Increased lactate and SMAD1/5 phosphorylation during continuous glucose exposure [7] do not establish persistent trained immunity. Whether histone lactylation sustains TGF-β1/SMAD1/5-dependent profibrotic memory remains a hypothesis requiring direct perturbation and persistence experiments [66–69].

Trained immunity may contribute to persistent diabetic vascular inflammation [66], but durable training requires functional changes after stimulus withdrawal and an appropriate resting interval, often assessed upon subsequent challenge. Ongoing stimulation, acute TGF-β1 pretreatment/LPS responses [44], and broader metabolic memory [68] should be distinguished from such persistence. TGF-β1 acting as both an inducer and downstream effector of diabetic trained immunity is a proposed mechanism rather than a demonstrated causal sequence [66,67,69–71].

Targeting trained immunity represents a promising therapeutic frontier. Interventions aimed at reversing epigenetic marks (e.g., histone methyltransferase inhibitors) or modulating immunometabolism (e.g., mTOR or PKM2 inhibitors) could potentially "de-train" macrophages and restore physiological TGF-β1 responsiveness [69,71].

7. Clinical Perspectives on TGF-β1 Signaling in Innate Immune Cells During Diabetes

7.1. TGF-β1 Signaling and Innate Immune Dysfunction in Diabetes

Chronic hyperglycemia disrupts macrophage function through mitochondrial dysfunction, oxidative stress, AGEs, and persistent inflammation, resulting in maladaptive immune responses and tissue remodeling. In this context, TGF-β1 plays a dual role: it initially limits inflammation and promotes repair but, when persistently activated, drives fibrosis, vascular remodeling, and organ-specific dysfunction [1,7]

(Figure 2). Macrophages are central to diabetic inflammation, producing pro-inflammatory mediators that exacerbate insulin resistance and tissue damage, while chronic TGF-β1 exposure promotes profibrotic phenotypes [3,5,7]. Emerging evidence further highlights a bidirectional interplay between immunometabolic reprogramming and TGF-β1 signaling in diabetic macrophages [7,57].

7.2. Clinical Implications in Diabetic Complications

Macrophage-derived TGF-β1 acting on neighboring cells must be distinguished from signaling within macrophages. Table 2 identifies ligand source, responding cells, interventions, outcomes, and limitations of representative experiments; unspecified sources should not be attributed to macrophages.

Table 2. Experimental evidence separating ligand source from responding cells.

Model and Evidence	Ligand Source	Responding Cells	Intervention	Principal Outcome	Limitations	References
Human macrophages in culture	Added recombinant TGF-β1	Monocyte-derived macrophages	Glucocorticoid-dependent receptor regulation with TGF-β1 exposure	TGFBR2 availability permits a multistep gene-expression response	*In vitro*; not diabetic organ injury or macrophage-derived ligand attribution	[5]
Human macrophages in culture	Added TGF-β1; BMP comparator	Primary macrophages	Ligand stimulation and pathway analysis	TGF-β1 activates SMAD1/5 and pro-atherogenic gene programs	Does not demonstrate plaque formation or universal branch pathogenicity	[15]
Elevated-glucose human macrophage culture	Added TGF-β1; macrophage TGF-β1 expression assessed	Primary macrophages	Approx. 17.5 *vs.* 42.5 mmol/L glucose during differentiation	Increased lactate and enhanced TGF-β1-induced SMAD1/5 phosphorylation	Lactate mediation, osmolality, persistence and *in vivo* injury unresolved	[7]
Macrophage stimulation and mouse sepsis	Experimentally supplied TGF-β1	Macrophages; systemic outcomes also assessed	TGF-β1 pretreatment and inflammatory challenge; pathway perturbation	Glycolysis increased despite lower cytokines; increased coagulation and reduced mouse survival	Not diabetic tissue repair; reduced cytokines do not imply benefit	[44]
Renal cortical fibroblast culture	Autocrine fibroblast-derived TGF-β1	Renal fibroblasts	High-glucose exposure and autocrine TGF-β1 assessment	Proliferation and collagen synthesis linked to autocrine signaling	Non-macrophage ligand source and responder	[61]
Liver fibrosis evidence synthesis	Kupffer/recruited macrophages among multiple sources	Hepatic stellate cells and other neighboring cells	Multiple models summarized in reviews	Paracrine TGF-β1 contributes to matrix-producing cell activation	Review-level synthesis; not proof of macrophage-intrinsic SMAD1/5 mediation	[72,73]
Obese diabetic mouse cardiac/aortic model	Multiple sources; not macrophage-isolated	Multiple cardiac and vascular populations	Systemic Smad3 perturbation	Fibrosis decreased with impaired preservation of geometry	Whole-animal result cannot assign source or response to macrophages	[46]

Human diabetic nephropathy randomized trial	Endogenous ligand; cellular origin not isolated	Renal/systemic populations not resolved	Anti-TGF-β1 antibody LY2382770	No renal efficacy; trial stopped early for futility	Does not test selective SMAD1/5 inhibition or macrophage-targeted delivery	[37]

Diabetic nephropathy is a prototypical example of pathological TGF-β1 overactivation. TGF-β1/SMAD signaling contributes to diabetic renal fibrosis in multiple renal cell populations [22,47]. Renal fibroblast experiments demonstrate high-glucose-associated autocrine TGF-β1-dependent proliferation and collagen synthesis [61]. A separate experimental study examined C1q/TNF-related protein 1 and macrophage activation in renal inflammation and fibrosis [74]; it does not establish macrophage-specific TGF-β1 blockade. Attribution of a renal effect to macrophage-produced ligand or macrophage-intrinsic signaling requires cell-specific perturbation.

In vascular disease, human macrophage experiments identify TGF-β1-induced SMAD1/5 phosphorylation and pro-atherogenic gene expression, with enhancement under elevated culture glucose [7,15]. These readouts do not establish plaque progression, vascular stiffness, or a time-dependent conversion from protection to injury, which require further investigation. General TGF-β1 vascular biology includes inflammatory regulation, matrix production, and maintenance of tissue integrity [1,2,16,22,48]. Endothelial wound responses [75], macrophage glycolysis in atherosclerosis [76], and neutrophil-associated cardiorenal injury [30] provide related but distinct evidence. Their synthesis motivates direct testing of macrophage-specific pathways to implement single mechanisms generalized for all cardiovascular complications.

Diabetic neuropathy involves interacting metabolic, vascular, inflammatory, and neural mechanisms [77,78]. These clinical and mechanistic reviews do not establish a macrophage-specific lactate–TGF-β1/SMAD1/5 pathway in peripheral nerves so such direct nerve-specific perturbation studies are needed.

Diabetic retinopathy involves neurovascular inflammation and interactions among resident microglia, recruited macrophages, and retinal vascular cells [79]. TGF-β1 pathways have been implicated in retinal fibrosis and remodeling [80], but these observations do not establish a macrophage lactate–SMAD1/5 mechanism. Non-diabetic microglial loss-of-function experiments [14] must be interpreted separately from diabetic retinal injury.

Diabetic wounds are characterized by persistent inflammation and failure of macrophages to transition into a reparative phenotype [81]. Dysregulated TGF-β1 signaling—either insufficient in early phases or excessive later—impairs granulation tissue formation, angiogenesis, and timely resolution [82]. These studies concern angiogenesis and phase-dependent wound repair. Endothelial responses to photobiomodulation in diabetic wounds emphasize that improved repair can involve responding cells other than macrophages [75].

Diabetic cardiac fibrosis has experimental support involving SMAD3, including a trade-off between reduced fibrosis and altered cardiac or aortic geometry [46]. This is not a macrophage-specific result. High-glucose endothelial transdifferentiation experiments provide separate vascular evidence [83], whereas glucagon-like peptide-1 (GLP-1) receptor agonist and sodium–glucose cotransporter 2 (SGLT2) inhibitor outcome evidence concerns clinical drug effects [32]; neither establishes cardiac macrophage signaling as the mediator.

Macrophage-derived TGF-β1 can act on hepatic stellate cells and other neighboring matrix-producing cells in liver and adipose fibrosis [72,73]. This paracrine mechanism differs from SMAD activation inside macrophages. Macrophage remodeling programs provide related context [3,5,6], thus, Figure 2 provides an organizing hypothesis rather than a demonstrated mechanism shared across organs.

Liver and adipose fibrosis are related metabolic conditions that overlap with diabetes and influence systemic inflammation [72,73]. Kupffer-cell and recruited-macrophage secretion of TGF-β1 acting on

hepatic stellate cells represents a paracrine interaction, distinct from SMAD activation within macrophages. Aging, oxidative stress, and cellular senescence may modify this inflammatory environment. Tarantino et al. studied 80 obese patients with non-alcoholic fatty liver disease (NAFLD) and found independent associations of age and circulating IL-15 with carotid intima-media thickness (cIMT) [84]. This supports consideration of liver-related metabolic inflammation alongside vascular aging and extends the clinical context of macrophage-associated inflammatory networks. Longitudinal and mechanistic studies are required to test whether, TGF-β1 or SMAD signaling can show cIMT structural vascular correlate, proposing hepatic TGF-β1 mechanism.

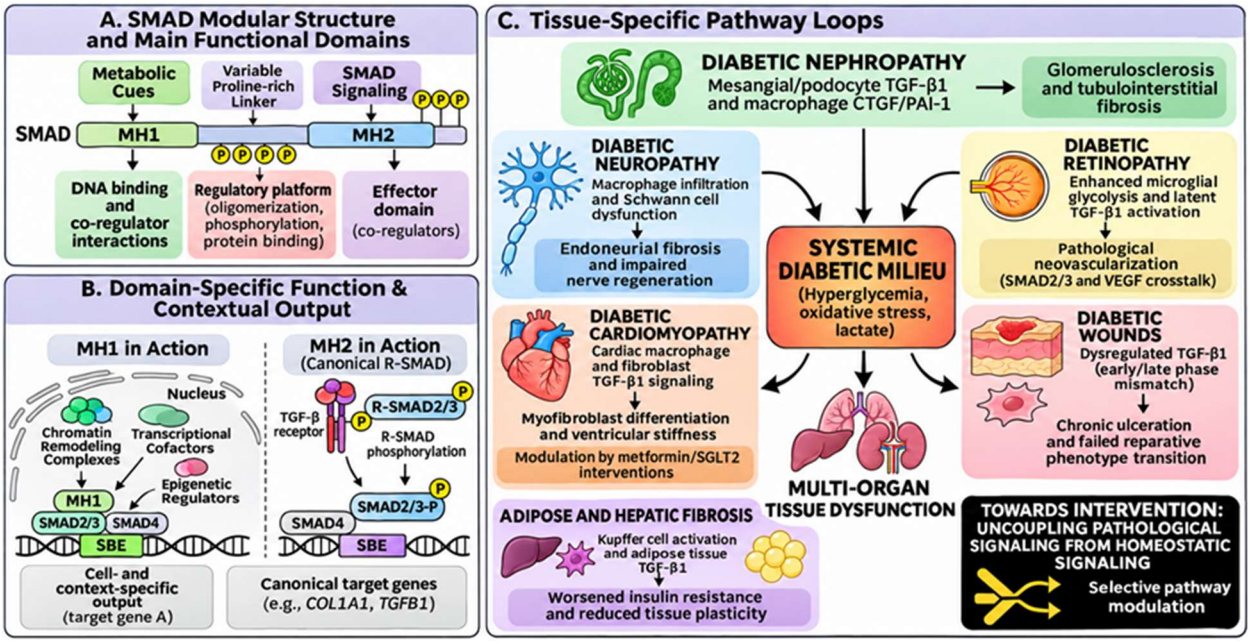


Figure 2. Conserved SMAD architecture and proposed links to diabetic tissue responses. (**A**) Conserved modular structure of receptor-regulated SMADs and SMAD4, showing the MH1 and MH2 domains joined by a regulatory linker. (**B**) Domain-specific functions and context-dependent transcriptional outputs, including DNA binding, co-regulator interactions, and receptor-mediated SMAD activation. Full-length SMAD2 differs in its direct DNA-binding ability [1,42]. (**C**) Proposed relationships between the systemic diabetic milieu and tissue responses in the kidney, peripheral nerves, retina, heart, wounds, adipose tissue, and liver. These relationships integrate evidence from different models and responding cell types [22,47,72,74]; they do not establish a common macrophage glucose–lactate–TGF-β1/SMAD1/5 mechanism causing injury across organs. Macrophage-derived ligand acting on neighboring cells must be distinguished from signaling inside macrophages. Targeted interventions remain hypotheses requiring functional and safety testing [16,85].

8. Current Challenges, Research Gap and Future Directions

8.1. Current Limitations and Challenges

Despite promising advances, several important limitations continue to hinder the clinical translation of TGF-β1-targeted therapies for diabetes [16,85]. Most mechanistic insights into TGF-β1 signaling in macrophages have been derived from preclinical studies, with relatively limited validation in human diabetic tissues [7,22]. In particular, the therapeutic potential of selective SMAD1/5 pathway inhibition, while conceptually attractive, remains largely untested in clinical settings. Furthermore, safely modulating TGF-β1 remains challenging because of its context-dependent, pleiotropic functions, exerting protective anti-inflammatory and tissue-reparative effects in some settings while promoting fibrosis and immune suppression in others [1,2,16,85]. This functional complexity increases the risk of unintended consequences, including impaired wound healing and compromised immune surveillance, thereby complicating the development of safe and effective therapeutic interventions.

Selective SMAD1/5 modulation, macrophage-directed delivery, and targeting downstream profibrotic effectors are candidate approaches [16,85]. Greater efficacy or safety than global inhibition has not been established in diabetic complications.

Metabolic drugs should be evaluated separately from proposed macrophage signaling mechanisms. The sequence in which metformin lowers macrophage lactate and thereby inhibits TGF-β1/SMAD1/5 has not been directly established by the cited studies and is not asserted here [7,57,63]. GLP-1 receptor agonist/SGLT2 inhibitor outcome evidence [32] and SGLT2 inhibitor heart-failure literature [33] cannot establish metformin efficacy or macrophage-specific mediation. Combined metabolic and pathway-targeted treatment remains a research hypothesis [22].

8.2. Research Gap and Proposed Hypotheses

Important gaps concern how hyperglycemia-associated immune training and metabolic memory interact with TGF-β1 signaling [66–69]. TGF-β1, TGF-β2, and TGF-β3 are ligand isoforms; SMAD1/5 and SMAD2/3 are signaling branches, not TGF-β1 isoforms. Receptor regulation, histone lactylation, and non-coding RNAs warrant direct mechanistic testing [7,66,69]. Infection, microbiome-related cues, and communication between tissues provide additional candidate influences [8,9,22,72]. Three testable hypotheses follow.

1. The proposed lactate–TGF-β1/SMAD1/5 immunometabolic checkpoint.
   We hypothesize that lactate contributes to the enhancement of TGF-β1/SMAD1/5 signaling under elevated culture glucose [7]. Causal mediation requires lactate manipulation with inhibition and rescue, pH and osmotic controls, and pathway-specific perturbation. Persistence, pro-atherogenic function, and organ injury must be measured independently [7,66,68]. Selective inhibition may be investigated, but preserved SMAD2/3 activity alone would not establish repair or safety [16,22].
2. Trained immunity reprogramming via TGF-β1 modulation.
   TGF-β1 may interact with metabolic and epigenetic processes underlying trained immunity [66,70]. Whether histone lactylation sustains TGF-β1 responsiveness requires direct testing after stimulus withdrawal, rest, and restimulation [7,66,69]. Epigenetic or lactate-transporter interventions combined with macrophage-directed signaling modulation remain hypotheses without demonstrated prevention of diabetic organ injury.
3. Macrophage specific TGF-β1 context modulation.
   Macrophage TGF-β1 responses depend on the metabolic and cellular environment [7,57,60]. Targeted delivery of branch-specific modulators is a candidate experimental approach. Effects on host defense, repair, fibrosis, and structural integrity must be measured directly before claims of benefit across diabetic complications can be made.

Overall and from a translational perspective, priority should be given to developing selective TGF-β1 modulators, reliable biomarkers of pathway activity, and patient stratification approaches based on trained immunity signatures. Ultimately, shifting from a binary “inhibit-or-activate” paradigm to precision immunometabolic strategies will be essential to safely harness TGF-β1 biology in treating diabetic complications while safeguarding its homeostatic roles.

8.3. Future Directions and Prioritizations

Combining metabolic interventions with cell-specific TGF-β1 pathway modulation warrants preclinical testing [33,57,63]. Effective inflammation control, preserved repair, and clinical benefit are goals rather than established outcomes.

TGF-β1 ligand isoforms, receptor dynamics, and SMAD-dependent or non-SMAD signaling may interact with epigenetic reprogramming and broader metabolic memory [67,68]. Their integration in human diabetic macrophages, including possible microbiome influences, remains incompletely defined.

Macrophage-targeted nanoparticles, SMAD1/5 modulators, and integrin-directed strategies require comparison with broader pathway inhibition. Synergy with SGLT2 inhibitors or metformin should be tested rather than assumed.

Clinical evidence for GLP-1 receptor agonists and SGLT2 inhibitors [32,33] is distinct from proposed effects on macrophage TGF-β1 signaling [57,63]. The same work does not establish cardiovascular or renal benefits of metformin. Hyperglycemia-induced trained immunity has experimental support, whereas its causal mediation by TGF-β1 remains unresolved [66–69]. Macrophage-targeted delivery and selective SMAD1/5 inhibition remain investigational concepts without demonstrated efficacy or safety across diabetic organs [16].

Several TGF-β1 pathway interventions have been studied clinically, but the actual trial populations must be distinguished. Fresolimumab was evaluated in steroid-resistant primary focal segmental glomerulosclerosis [34] (NCT01665391), galunisertib with gemcitabine in pancreatic cancer [35] (NCT01373164), and bexotegrast/PLN-74809 in INTEGRIS-IPF [36] (NCT04396756). These still do not support efficacy claims in diabetic kidney disease or diabetic cardiomyopathy.

The diabetic nephropathy trial of the anti-TGF-β1 antibody LY2382770 enrolled 416 participants and stopped early for futility, with no evidence of renal efficacy [37] (NCT01113801). This negative trial does not establish the efficacy of selective SMAD1/5 inhibition or macrophage targeting. Bexotegrast studies in pulmonary fibrosis cannot establish efficacy in diabetic kidney disease or cardiomyopathy.

Failure or limited efficacy of broad TGF-β1 inhibition cannot be attributed solely to blockade of a presumed protective SMAD2/3 branch. SMAD2 and SMAD3 have distinct, cell-dependent functions, and reduced fibrosis can coexist with compromised tissue integrity. The proposed goal is suppression of pathological signaling in defined cell populations while measuring repair, immune function, and structural safety directly. Macrophage targeting and alternative SMAD1/5 modulation remain candidate strategies requiring validation [16,22,42,47,48].

Prioritizing future research among the mentioned gaps, the integration of hyperglycemia-driven epigenetic reprogramming with TGF-β1 signaling, particularly through histone lactylation and its reinforcement of trained immunity and metabolic memory, represents the most critical priority [7,66,69]. Future studies should prioritize advanced biotechnologies and proteomic techniques in human diabetic tissue macrophages and longitudinal cohorts, and edit and modulate SMAD1/5 and lactate pathway components in humanized animal models. Addressing this nexus will provide the foundational insights needed to rationally design precision immunometabolic therapies.

9. Conclusions

TGF-β1 integrates immune, metabolic, and tissue-remodeling signals in a cell- and context-dependent manner. Elevated culture glucose in primary human macrophages was associated with increased lactate and enhanced TGF-β1-induced SMAD1/5 phosphorylation [7]. Lactate mediation, exclusion of osmotic effects, persistent immune memory, and consequent organ injury remain for future investigations. Evidence from renal, neural, wound, vascular, and general macrophage studies informs clinical context but does not establish one macrophage pathway causing all diabetic complications; rather, it suggests complex disease pathways that figure out the systemic injury accompanied uncontrolled diabetes [32,47,57,74,77,81]; Figure 3A.

Therapeutic strategies must distinguish clinical drug outcomes from proposed macrophage mechanisms. Selective SMAD1/5 modulation, macrophage-targeted delivery, and combined metabolic

interventions require experimental validation; branch selectivity alone cannot infer improved efficacy, safety, or preservation of repair (Figure 3B).

Further studies should identify ligand-producing and responding cells and directly measure inflammation, fibrosis, host defense, tissue integrity, and function. This framework supports testing context-specific treatments without treating candidate signaling links as established diabetic mechanisms [7,18,85].

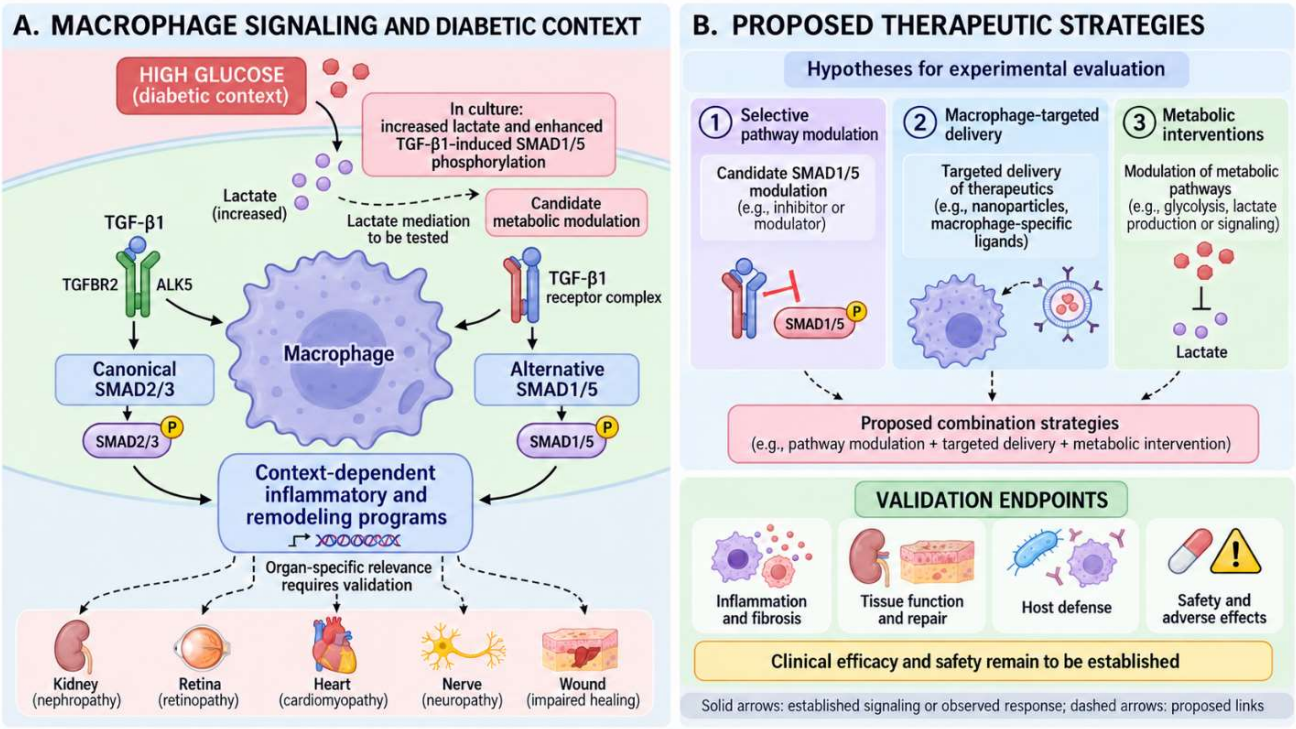


Figure 3. Observed macrophage signaling responses and proposed translational strategies. (**A**) Elevated culture glucose, increased lactate, and enhanced TGF-β1-induced SMAD1/5 phosphorylation have been observed in primary human macrophages [7,15]. Their causal sequence, persistence after withdrawal, and contribution to diabetic organ injury remain to be investigated. Findings across tissue models should not be interpreted as proof of one shared mechanism [5,22,57]. (**B**) Macrophage targeting, selective pathway modulation, and combined metabolic interventions are proposed strategies [16,57,85]. Neither branch selectivity nor preservation of SMAD2/3 activity establishes superior efficacy, safety, or physiological repair. The metformin–lactate–SMAD1/5 sequence can be an interesting future study direction.

Statement of the Use of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, the authors used Grok and ChatGPT/search and chat services as a literature search engine and for language editing to refine some paragraphs and organize the references. The authors used Gemini/drawing services in order to help with drawing the figures. The AI services used were not involved in the conceptualization, organization, developing ideas, or original writing of the review manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Informed Consent Statement

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Declaration of Competing Interest

The author declares no conflicts of interest.

References

1. Massagué J, Sheppard D. TGF-β signaling in health and disease. *Cell* **2023**, *186*, 4007–4037. DOI:10.1016/j.cell.2023.07.036
2. Batlle E, Massagué J. Transforming Growth Factor-β Signaling in Immunity and Cancer. *Immunity* **2019**, *50*, 924–940. DOI:10.1016/j.immuni.2019.03.024
3. Gratchev A. TGF-β signalling in tumour associated macrophages. *Immunobiology* **2017**, *222*, 75–81. DOI:10.1016/j.imbio.2015.11.016
4. Aigner L, Bogdahn U. TGF-beta in neural stem cells and in tumors of the central nervous system. *Cell Tissue Res.* **2008**, *331*, 225–241. DOI:10.1007/s00441-007-0466-7
5. Gratchev A, Kzhyshkowska J, Kannookadan S, Ochsenreiter M, Popova A, Yu X, et al. Activation of a TGF-β-Specific Multistep Gene Expression Program in Mature Macrophages Requires Glucocorticoid-Mediated Surface Expression of TGF-β Receptor II. *J. Immunol.* **2008**, *180*, 6553–6565. DOI:10.4049/jimmunol.180.10.6553
6. Kzhyshkowska J, Gratchev A, Goerdt S. Stabilin-1, a homeostatic scavenger receptor with multiple functions. *J. Cell. Mol. Med.* **2006**, *10*, 635–649. DOI:10.1111/j.1582-4934.2006.tb00425.x
7. Awad K, Kakkola L, Julkunen I. High Glucose Increases Lactate and Induces the Transforming Growth Factor Beta-Smad 1/5 Atherogenic Pathway in Primary Human Macrophages. *Biomedicines* **2024**, *12*, 1575. DOI:10.3390/biomedicines12071575
8. Awad K, Shahin NN, Motawi TK, Abdelhadi M, Barghash RF, Awad AM, et al. Glucose Metabolism and Innate Immune Responses in Influenza Virus Infection: Mechanistic Insights and Clinical Perspectives. *Cells* **2025**, *15*, 47. DOI:10.3390/cells15010047
9. Awad K, Maghraby AS, Abd-Elshafy DN, Bahgat MM. Carbohydrates Metabolic Signatures in Immune Cells: Response to Infection. *Front. Immunol.* **2022**, *13*, 912899. DOI:10.3389/fimmu.2022.912899
10. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat. Rev. Immunol.* **2011**, *11*, 98–107. DOI:10.1038/nri2925
11. Khalid M, Petroianu G, Adem A. Advanced Glycation End Products and Diabetes Mellitus: Mechanisms and Perspectives. *Biomolecules* **2022**, *12*, 542. DOI:10.3390/biom12040542
12. Hotamisligil GS. Inflammation and metabolic disorders. *Nature* **2006**, *444*, 860–867. DOI:10.1038/nature05485
13. Fabre T, Barron AMS, Christensen SM, Asano S, Bound K, Lech MP, et al. Identification of a broadly fibrogenic macrophage subset induced by type 3 inflammation. *Sci. Immunol.* **2023**, *8*, eadd8945. DOI:10.1126/sciimmunol.add8945
14. Ma W, Silverman SM, Zhao L, Villasmil R, Campos MM, Amaral J, et al. Absence of TGFβ signaling in retinal microglia induces retinal degeneration and exacerbates choroidal neovascularization. *eLife* **2019**, *8*, e42049. DOI:10.7554/eLife.42049
15. Nurgazieva D, Mickley A, Moganti K, Ming W, Ovsyi I, Popova A, et al. TGF-β1, but Not Bone Morphogenetic Proteins, Activates Smad1/5 Pathway in Primary Human Macrophages and Induces Expression of Proatherogenic Genes. *J. Immunol.* **2015**, *194*, 709–718. DOI:10.4049/jimmunol.1300272
16. Deng Z, Fan T, Xiao C, Tian H, Zheng Y, Li C, et al. TGF-β signaling in health, disease and therapeutics. *Signal Transduct. Target. Ther.* **2024**, *9*, 61. DOI:10.1038/s41392-024-01764-w
17. Munger JS, Sheppard D. Cross Talk among TGF-β Signaling Pathways, Integrins, and the Extracellular Matrix. *Cold Spring Harb. Perspect. Biol.* **2011**, *3*, a005017. DOI:10.1101/cshperspect.a005017
18. Gratchev A, Schmuttermaier C, Mamidi S, Gooi L, Goerdt S, Kzhyshkowska J. Expression of Osteoarthritis Marker YKL-39 is Stimulated by Transforming Growth Factor Beta (TGF-beta) and IL-4 in Differentiating Macrophages. *Biomark. Insights* **2008**, *3*, 117727190800300. DOI:10.1177/117727190800300003

19. Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, et al. Macrophage Activation and Polarization: Nomenclature and Experimental Guidelines. *Immunity* **2014**, *41*, 14–20. DOI:10.1016/j.immuni.2014.06.008
20. Gauthier T, Chen W. IFN-γ and TGF-β, Crucial Players in Immune Responses: A Tribute to Howard Young. *J. Interferon Cytokine Res.* **2022**, *42*, 643–654. DOI:10.1089/jir.2022.0132
21. Awad K, Abdelhadi M, Awad AM. High Glucose Reduces Influenza and Parainfluenza Virus Productivity by Altering Glycolytic Pattern in A549 Cells. *Int. J. Mol. Sci.* **2025**, *26*, 2975. DOI:10.3390/ijms26072975
22. Meng XM, Nikolic-Paterson DJ, Lan HY. TGF-β: The master regulator of fibrosis. *Nat. Rev. Nephrol.* **2016**, *12*, 325–338. DOI:10.1038/nrneph.2016.48
23. Sapkota G, Knockaert M, Alarcón C, Montalvo E, Brivanlou AH, Massagué J. Dephosphorylation of the Linker Regions of Smad1 and Smad2/3 by Small C-terminal Domain Phosphatases Has Distinct Outcomes for Bone Morphogenetic Protein and Transforming Growth Factor-β Pathways. *J. Biol. Chem.* **2006**, *281*, 40412–40419. DOI:10.1074/jbc.M610172200
24. Aragón E, Goerner N, Zaromytidou AI, Xi Q, Escobedo A, Massagué J, et al. A Smad action turnover switch operated by WW domain readers of a phosphoserine code. *Genes Dev.* **2011**, *25*, 1275–1288. DOI:10.1101/gad.2060811
25. Horvat Mercnik M, Schliefsteiner C, Sanchez-Duffhues G, Wadsack C. TGFβ signalling: A nexus between inflammation, placental health and preeclampsia throughout pregnancy. *Hum. Reprod. Update* **2024**, *30*, 442–471. DOI:10.1093/humupd/dmae007
26. Rosser EC, Mauri C. Regulatory B Cells: Origin, Phenotype, and Function. *Immunity* **2015**, *42*, 607–612. DOI:10.1016/j.immuni.2015.04.005
27. Luo K. Signaling Cross Talk between TGF-β/Smad and Other Signaling Pathways. *Cold Spring Harb. Perspect. Biol.* **2017**, *9*, a022137. DOI:10.1101/cshperspect.a022137
28. Sakkers TR, Mili E, Winter H, Kapteijn D, Perry RN, Barbera N, et al. Atherosclerotic Fibrous Plaques in Women Present ECM Remodeling Linked to TGF-β. *Circ. Res.* **2026**, *138*, e327624. DOI:10.1161/CIRCRESAHA.125.327624
29. Zhao H, Yang F, Yang J, Yang S. SMAD signaling in cancer: Integrative roles in tumor progression, immune evasion, and therapeutic resistance. *Cytokine* **2026**, *198*, 157090. DOI:10.1016/j.cyto.2025.157090
30. Schommer N, Gendron N, Krauel K, Van Bruggen S, Jarrot PA, Maier A, et al. Neutrophil extracellular traps and peptidylarginine deiminase 4–mediated inflammasome activation link diabetes to cardiorenal injury and heart failure. *Eur. Heart J.* **2025**, ehaf963. DOI:10.1093/eurheartj/ehaf963
31. Stepp MA, Menko AS. Immune responses to injury and their links to eye disease. *Transl. Res.* **2021**, *236*, 52–71. DOI:10.1016/j.trsl.2021.05.005
32. Neuen BL, Fletcher RA, Heath L, Perkovic A, Vaduganathan M, Badve SV, et al. Cardiovascular, Kidney, and Safety Outcomes With GLP-1 Receptor Agonists Alone and in Combination With SGLT2 Inhibitors in Type 2 Diabetes: A Systematic Review and Meta-Analysis. *Circulation* **2024**, *150*, 1781–1790. DOI:10.1161/CIRCULATIONAHA.124.071689
33. Verbrugge FH. Role of SGLT2 Inhibitors in Patients with Diabetes Mellitus and Heart Failure. *Curr. Heart Fail. Rep.* **2017**, *14*, 275–283. DOI:10.1007/s11897-017-0340-1
34. Vincenti F, Fervenza FC, Campbell KN, Diaz M, Gesualdo L, Nelson P, et al. A Phase 2, Double-Blind, Placebo-Controlled, Randomized Study of Fresolimumab in Patients With Steroid-Resistant Primary Focal Segmental Glomerulosclerosis. *Kidney Int. Rep.* **2017**, *2*, 800–810. DOI:10.1016/j.ekir.2017.03.011
35. Melisi D, Garcia-Carbonero R, Macarulla T, Pezet D, Deplanque G, Fuchs M, et al. Galunisertib plus gemcitabine vs. gemcitabine for first-line treatment of patients with unresectable pancreatic cancer. *Br. J. Cancer* **2018**, *119*, 1208–1214. DOI:10.1038/s41416-018-0246-z
36. Lancaster L, Cottin V, Ramaswamy M, Wuyts WA, Jenkins RG, Scholand MB, et al. Bexotegrast in Patients with Idiopathic Pulmonary Fibrosis: The INTEGRIS-IPF Clinical Trial. *Am. J. Respir. Crit. Care Med.* **2024**, *210*, 424–434. DOI:10.1164/rccm.202403-0636OC
37. Voelker J, Berg PH, Sheetz M, Duffin K, Shen T, Moser B, et al. Anti–TGF-β1 Antibody Therapy in Patients with Diabetic Nephropathy. *J. Am. Soc. Nephrol.* **2017**, *28*, 953–962. DOI:10.1681/ASN.2015111230
38. Arora K, Dai H, Kazuko SG, Jamal J, O'Connor MB, Letsou A, et al. The Drosophila schnurri gene acts in the Dpp/TGFβ signaling pathway and encodes a transcription factor homologous to the human MBP family. *Cell* **1995**, *81*, 781–790. DOI:10.1016/0092-8674(95)90539-1
39. Bienz M. Homeotic genes and positional signalling in the Drosophila viscera. *Trends Genet.* **1994**, *10*, 22–26. DOI:10.1016/0168-9525(94)90015-9
40. Raftery LA, Sutherland DJ. TGF-β Family Signal Transduction in Drosophila Development: From Mad to Smads. *Dev. Biol.* **1999**, *210*, 251–268. DOI:10.1006/dbio.1999.9282

41. Derynck R, Budi EH. Specificity, versatility, and control of TGF-β family signaling. *Sci. Signal.* **2019**, *12*, eaav5183. DOI:10.1126/scisignal.aav5183
42. Miyazawa K, Itoh Y, Fu H, Miyazono K. Receptor-activated transcription factors and beyond: multiple modes of Smad2/3-dependent transmission of TGF-β signaling. *J. Biol. Chem.* **2024**, *300*, 107256. DOI:10.1016/j.jbc.2024.107256
43. Oliver MA, Davis XD, Bohannon JK. TGFβ macrophage reprogramming: A new dimension of macrophage plasticity. *J. Leukoc. Biol.* **2024**, *115*, 411–414. DOI:10.1093/jleuko/qiae001
44. Gauthier T, Yao C, Dowdy T, Jin W, Lim YJ, Patiño LC, et al. TGF-β uncouples glycolysis and inflammation in macrophages and controls survival during sepsis. *Sci. Signal.* **2023**, *16*, eade0385. DOI:10.1126/scisignal.ade0385
45. Lin CS, Chen MF, Wang YS, Chuang TF, Chiang YL, Chu RM. IL-6 restores dendritic cell maturation inhibited by tumor-derived TGF-β through interfering Smad 2/3 nuclear translocation. *Cytokine* **2013**, *62*, 352–359. DOI:10.1016/j.cyto.2013.03.005
46. Biernacka A, Cavalera M, Wang J, Russo I, Shinde A, Kong P, et al. Smad3 Signaling Promotes Fibrosis While Preserving Cardiac and Aortic Geometry in Obese Diabetic Mice. *Circ. Heart Fail.* **2015**, *8*, 788–798. DOI:10.1161/CIRCHEARTFAILURE.114.001963
47. Lan HY. Transforming growth factor-β/Smad signalling in diabetic nephropathy. *Clin. Exp. Pharmacol. Physiol.* **2012**, *39*, 731–738. DOI:10.1111/j.1440-1681.2011.05663.x
48. Goumans MJ, Ten Dijke P. TGF-β Signaling in Control of Cardiovascular Function. *Cold Spring Harb. Perspect. Biol.* **2018**, *10*, a022210. DOI:10.1101/cshperspect.a022210
49. Chen B, Mu C, Zhang Z, He X, Liu X. The Love-Hate Relationship Between TGF-β Signaling and the Immune System During Development and Tumorigenesis. *Front. Immunol.* **2022**, *13*, 891268. DOI:10.3389/fimmu.2022.891268
50. Chen PY, Qin L, Simons M. TGF-β signaling pathways in human health and disease. *Front. Mol. Biosci.* **2023**, *10*, 1113061. DOI:10.3389/fmolb.2023.1113061
51. Morikawa M, Derynck R, Miyazono K. TGF-β and the TGF-β Family: Context-Dependent Roles in Cell and Tissue Physiology. *Cold Spring Harb. Perspect. Biol.* **2016**, *8*, a021873. DOI:10.1101/cshperspect.a021873
52. Zhang F, Wang H, Wang X, Jiang G, Liu H, Zhang G, et al. TGF-β induces M2-like macrophage polarization via SNAIL-mediated suppression of a pro-inflammatory phenotype. *Oncotarget* **2016**, *7*, 52294–52306. DOI:10.18632/oncotarget.10561
53. Filali-Mouncef Y, Hunter C, Roccio F, Zagkou S, Dupont N, Primard C, et al. The ménage à trois of autophagy, lipid droplets and liver disease. *Autophagy* **2022**, *18*, 50–72. DOI:10.1080/15548627.2021.1895658
54. Hernandez H, Medina-Ortiz WE, Luan T, Clark AF, McDowell CM. Crosstalk Between Transforming Growth Factor Beta-2 and Toll-Like Receptor 4 in the Trabecular Meshwork. *Invest. Ophthalmol. Vis. Sci.* **2017**, *58*, 1811. DOI:10.1167/iovs.16-21331
55. Sun R, Zhu J, Sun K, Gao L, Zheng B, Shi J. Strontium Ranelate Ameliorates Intervertebral Disc Degeneration via Regulating TGF-β1/NF-κB Axis. *Int. J. Med. Sci.* **2023**, *20*, 1679–1697. DOI:10.7150/ijms.86665
56. Louault K, Blavier L, Lee MH, Kennedy RJ, Fernandez GE, Pawel BR, et al. Nuclear factor-κB activation by transforming growth factor-β1 drives tumour microenvironment-mediated drug resistance in neuroblastoma. *Br. J. Cancer* **2024**, *131*, 90–100. DOI:10.1038/s41416-024-02686-8
57. Li M, Wang M, Wen Y, Zhang H, Zhao G, Gao Q. Signaling pathways in macrophages: Molecular mechanisms and therapeutic targets. *MedComm* **2023**, *4*, e349. DOI:10.1002/mco2.349
58. Dussold C, Zilinger K, Turunen J, Heimberger AB, Miska J. Modulation of macrophage metabolism as an emerging immunotherapy strategy for cancer. *J. Clin. Investig.* **2024**, *134*, e175445. DOI:10.1172/JCI175445
59. Wu H, Wu Q, Liang C, Hua J, Meng L, Nakielski P, et al. Immunoregulatory electrospinning fiber mediates Macrophage energy metabolism reprogramming to promote burn wound healing. *Mater. Today Bio* **2025**, *35*, 102430. DOI:10.1016/j.mtbio.2025.102430
60. Liu H, Chen YG. The Interplay Between TGF-β Signaling and Cell Metabolism. *Front. Cell Dev. Biol.* **2022**, *10*, 846723. DOI:10.3389/fcell.2022.846723
61. Han DC, Isono M, Hoffman BB, Ziyadeh FN. High Glucose Stimulates Proliferation and Collagen Type I Synthesis in Renal Cortical Fibroblasts. *J. Am. Soc. Nephrol.* **1999**, *10*, 1891–1899. DOI:10.1681/ASN.V1091891
62. Kottmann RM, Kulkarni AA, Smolnycki KA, Lyda E, Dahanayake T, Salibi R, et al. Lactic Acid Is Elevated in Idiopathic Pulmonary Fibrosis and Induces Myofibroblast Differentiation via pH-Dependent Activation of Transforming Growth Factor-β. *Am. J. Respir. Crit. Care Med.* **2012**, *186*, 740–751. DOI:10.1164/rccm.201201-0084OC
63. Feng L, Chen X, Huang Y, Zhang X, Zheng S, Xie N. Immunometabolism changes in fibrosis: From mechanisms to therapeutic strategies. *Front. Pharmacol.* **2023**, *14*, 1243675. DOI:10.3389/fphar.2023.1243675

64. O'Neill LAJ, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. *Nat. Rev. Immunol.* **2016**, *16*, 553–565. DOI:10.1038/nri.2016.70
65. Van den Bossche J, O'Neill LA, Menon D. Macrophage Immunometabolism: Where Are We (Going)? *Trends Immunol.* **2017**, *38*, 395–406. DOI:10.1016/j.it.2017.03.001
66. Edgar L, Akbar N, Braithwaite AT, Krausgruber T, Gallart-Ayala H, Bailey J, et al. Hyperglycemia Induces Trained Immunity in Macrophages and Their Precursors and Promotes Atherosclerosis. *Circulation* **2021**, *144*, 961–982. DOI:10.1161/CIRCULATIONAHA.120.046464
67. Netea MG, Domínguez-Andrés J, Barreiro LB, Chavakis T, Divangahi M, Fuchs E, et al. Defining trained immunity and its role in health and disease. *Nat. Rev. Immunol.* **2020**, *20*, 375–388. DOI:10.1038/s41577-020-0285-6
68. Dong H, Sun Y, Nie L, Cui A, Zhao P, Leung WK, et al. Metabolic memory: Mechanisms and diseases. *Signal Transduct. Target. Ther.* **2024**, *9*, 38. DOI:10.1038/s41392-024-01755-x
69. Riksen NP, Netea MG. Immunometabolic control of trained immunity. *Mol. Aspects Med.* **2021**, *77*, 100897. DOI:10.1016/j.mam.2020.100897
70. van der Heijden CDCC, Noz MP, Joosten LAB, Netea MG, Riksen NP, Keating ST. Epigenetics and Trained Immunity. *Antioxid. Redox Signal.* **2018**, *29*, 1023–1040. DOI:10.1089/ars.2017.7310
71. Bekkering S, Domínguez-Andrés J, Joosten LAB, Riksen NP, Netea MG. Trained Immunity: Reprogramming Innate Immunity in Health and Disease. *Annu. Rev. Immunol.* **2021**, *39*, 667–693. DOI:10.1146/annurev-immunol-102119-073855
72. Wynn TA, Vannella KM. Macrophages in Tissue Repair, Regeneration, and Fibrosis. *Immunity* **2016**, *44*, 450–462. DOI:10.1016/j.immuni.2016.02.015
73. Kazankov K, Jørgensen SMD, Thomsen KL, Møller HJ, Vilstrup H, George J, et al. The role of macrophages in nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Nat. Rev. Gastroenterol. Hepatol.* **2019**, *16*, 145–159. DOI:10.1038/s41575-018-0082-x
74. Wang F, Gong Z, Yang N, Zhou G, Jia M, Liu W, et al. Local C1q/TNF-related protein 1 attenuates kidney inflammation and fibrosis by regulating macrophage activation. *Am. J. Physiol. Renal Physiol.* **2025**, *329*, F71–F86. DOI:10.1152/ajprenal.00346.2024
75. da Silva Oliveira VR, Varsani R, Zehra M, Dale CS, Arany P. Endothelial Cell Responses to Photobiomodulation Treatments in Diabetic Wounds Are Mediated via Concerted PDGF, VEGF and TGF-β Signalling. *Wound Repair Regen.* **2025**, *33*, e70068. DOI:10.1111/wrr.70068
76. Kotlyarov S. Role of Glycolysis and Nitric Oxide Pathway Crosstalk in Macrophages in Atherosclerosis. *Curr. Med. Chem.* **2026**, *33*, 1690–1710. DOI:10.2174/0109298673339364241224102645
77. Vincent AM, Callaghan BC, Smith AL, Feldman EL. Diabetic neuropathy: Cellular mechanisms as therapeutic targets. *Nat. Rev. Neurol.* **2011**, *7*, 573–583. DOI:10.1038/nrneurol.2011.137
78. Dillon BR, Ang L, Pop-Busui R. Spectrum of Diabetic Neuropathy: New Insights in Diagnosis and Treatment. *Annu. Rev. Med.* **2024**, *75*, 293–306. DOI:10.1146/annurev-med-043021-033114
79. Antonetti DA, Silva PS, Stitt AW. Current understanding of the molecular and cellular pathology of diabetic retinopathy. *Nat. Rev. Endocrinol.* **2021**, *17*, 195–206. DOI:10.1038/s41574-020-00451-4
80. Callan A, Jha S, Valdez L, Baldado L, Tsin A. TGF-β Signaling Pathways in the Development of Diabetic Retinopathy. *Int. J. Mol. Sci.* **2024**, *25*, 3052. DOI:10.3390/ijms25053052
81. DiPietro LA. Angiogenesis and wound repair: When enough is enough. *J. Leukoc. Biol.* **2016**, *100*, 979–984. DOI:10.1189/jlb.4MR0316-102R
82. Pakyari M, Farrokhi A, Maharlooei MK, Ghahary A. Critical Role of Transforming Growth Factor Beta in Different Phases of Wound Healing. *Adv. Wound Care* **2013**, *2*, 215–224. DOI:10.1089/wound.2012.0406
83. Tang R, Gao M, Wu M, Liu H, Zhang X, Liu B. High glucose mediates endothelial-to-chondrocyte transition in human aortic endothelial cells. *Cardiovasc. Diabetol.* **2012**, *11*, 113. DOI:10.1186/1475-2840-11-113
84. Tarantino G, Citro V, Balsano C, Capone D. Age and Interleukin-15 Levels Are Independently Associated With Intima-Media Thickness in Obesity-Related NAFLD Patients. *Front. Med.* **2021**, *8*, 634962. DOI:10.3389/fmed.2021.634962
85. Hill CS. Transcriptional Control by the SMADs. *Cold Spring Harb. Perspect. Biol.* **2016**, *8*, a022079. DOI:10.1101/cshperspect.a022079