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OPEN ACCESS Review Article

Toll-Like Receptors (TLRs) and Their Role in Diabetic Mellitus Disease: A Review

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ABSTRACT

Background: Toll-like receptors (TLRs), which are an integral component of the innate immune system, have been identified as a key player in this inflammatory process. Toll-Like Receptors appeared as important elements in early defending against infectious diseases. These receptors are responsible for the promotion of antigen-presenting cell (APC) activation, e.g. dendritic cells and macrophages, thereby improving adaptive immune responses by T-cell activation promotion as well as improving B cell response.
Objective: This study aimed to explore association between TLRs and diabetes development and progression, and find their role in diabetes development and progression and the possible treatment implications.
Method: This study reviewed previous studies on TLRs and their relationship to DM, as this study reviewed 71 studies.
Results: TLRs play essential roles in both types of DM (Type I and Type II) via contribution to insulin resistance and inflammations. The inflammatory environment which aggravates β-cell dysfunctions and insulin resistance can be promoted by specific TLRs activation, e.g. TLR-2, TLR-4 and TLR-9.
Conclusion: New treatment strategies may be provided to treat DM through targeting such receptors. It is recommended to investigate how TLR activation in pancreatic islets triggers immune cell infiltration (e.g., macrophages, dendritic cells), and to study TLR4 inhibitors (e.g., TAK-242) in T2DM models.

Keywords: TLR-s, innate immunity, humoral immunity, cellular immunity, diabetes mellitus.

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INTRODUCTION

The class of pattern recognition receptors known as Toll-like receptors (TLRs) play central roles in innate immune systems. These receptors have the ability for recognizing various microbial constituents called pathogen associated molecular patterns (PAMPs), in addition to damage associated molecular patterns (DAMPs) in injured or stressed host cells. Discovery of TLRs was first initiated in Drosophila melanogaster (a fruit fly), as these receptors appeared to participate in immune responses against pathogenic microbes. TLRs contribute to a wide range of microbial infection detection in mammals. Human-beings have I0 types of TLR (TLR1-TLRI0), each one of these types recognize various PAMPs. The expression of TLRs can be seen on different immune cells such as B-cells, macrophages, dendritic cells in addition to some non-immune cells such as epithelial cells (1).The type I trans-membrane proteins known as TLRs have (20–27) extra- cellular leucine-rich repeat to recognize PAMP/DAMP, trans-membrane domain, and intra-cellular toll–interleukin-I receptor (TIR) domains, and are needed to activate down-stream the signal transduction pathway as shown in figure 1 (1, 2). The trans-membrane receptors (TLRs) are composed of an extracellular leucine-rich repeats domain, a single trans-membrane segment, as well as an intra-cellular Toll/IL-1 receptor domain. The extra-cellular LRR domains recognize PAMP or DAMP, whereas intra-cellular TIR domains transduce signal for initiating an immune response. Leucine-Rich repeat s(LRR) domains are causing binding to the ligands (PAMP or DAMP). The TIR domains are necessary for intra-cellular signaling, and they usually involve adaptors of MyD88 or TRIF for activation of down-stream pathways like NF-κB, MAPK as well as IRF3 necessary for immune response (3).

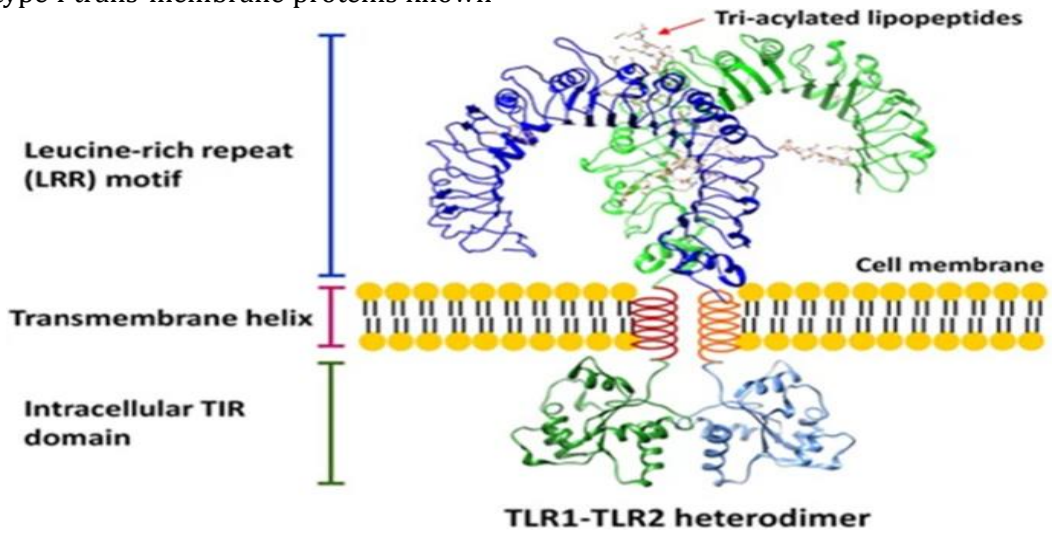

Figure 1: Structure of TLRs (1, 2)

When TLRs bind to ligands, they start a signaling pathways which result in immune activations and inflammatory response. Two main down-stream signaling pathways are present which are: MyD88-dependent pathways. The majority of TLRs involving TLR4, TLR7 & TLR9 utilize MyD88 as adaptor proteins., and this pathway causes NF-κB and MAPK activation resulting in the promotion of pro-inflammatory cytokine production such as TNF-α, IL-1β and IL-6. TRIF-dependent pathways: TLR3 and TLR4 utilize TRIF as adaptor proteins, and such pathway causes IRF3 and IRF7 activation, leading to type-I interferon production (such as IFN-α & IFN-β) (4). The class of pattern recognition receptors known as Toll-like receptors (TLRs) play central roles in innate immune systems. These receptors have the ability for pathogen associated molecular pattern detection (PAMP) as well as damage associated molecular pattern (DAMP), leading to inflammatory response triggering. TLRs were found to be associated with the progression and development of chronic inflammatory diseases, such as diabetes. In diabetic individuals, inflammations play crucial roles

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in pancreatic β-cell dysfunctions and insulin resistances (1). TLRs have central roles in inflammation induction. When they are activated, TLRs initiate chemokine and pro-inflammatory cytokine production, that not only contribute to defense against pathogenic agents, but also help in chronic inflammations development in certain diseases such as diabetes, autoimmune disorders and cardiovascular disorders. TLR4 has a main role in inflammation mediation in certain conditions like obesity & sepsis. TLR4 activation by lipopolysaccharides (LPS) from Gram (-ve) bacteria result in release of cytokines and activation of NF-κB (5). This study aimed to explore association between TLRs and diabetes development and progression, and find their role in diabetes development and progression and the possible treatment implications.

METHOD

This study aimed to search the role of the Toll-Like Receptors (TLRs) and their role in DM. A comprehensive search was made to identify relevant previous studies in this area in PubMed and Google Scholar databases. The following keywords were used during the search: "Toll-Like Receptors", "Innate Immunity" and "Diabetic Mellites Disease". In this review, 71 previous studies were conducted on the types of TLRs and their numbers as shown in results.

RESULTS

TLRs and Immune Response

TLRs appeared as important elements in early defending against infectious diseases. These receptors are responsible for the promotion of antigen-presenting cell (APC) activation, e.g. dendritic cells and macrophages, thereby improving adaptive immune responses by T-cell activation promotion as well as improving B cell response. For instance, peptidoglycan from Gram-(+ve) bacteria is recognized by TLR-2, while LPS from Gram-(-ve) bacteria is recognized by TLR-4, leading to inflammation and adaptive immunity stimulation (6). There are several types of TLRs that differ in location, Ligands Recognized and their role in immunity, as shown in Table 1.

Table (1): Summary of Toll Like receptors (TLRs) and their roles in immunity

Toll-Like Receptor (TLR)	Location	Ligands Recognized	Role in Immunity	References
TLR1	Cell membrane (Plasma membrane)	Lipoproteins (e.g., triacyl lipopeptides)	Initiates inflammatory responses by recognizing bacterial lipoproteins, activating NF-κB signaling.	7
TLR2	Cell membrane (Plasma membrane)	Lipoproteins, peptidoglycan, zymosan, lipoteichoic acid	Recognizes a broad range of microbial components, promoting immune response and cytokine production.	6
TLR3	Endosome	Double-stranded RNA (dsRNA)	Senses viral RNA, triggers antiviral immune responses, activates type I interferons.	8
TLR4	Cell membrane (Plasma membrane)	Lipopolysaccharide (LPS), heat-shock proteins (HSP)	Recognizes bacterial LPS, initiating inflammation, phagocytosis, and adaptive immune responses.	9
TLR5	Cell membrane (Plasma membrane)	Flagellin (protein in bacterial flagella)	Recognizes bacterial flagella, leading to activation of NF-κB and inflammation.	10
TLR6	Cell membrane (Plasma membrane)	Diacyl lipopeptides, lipoteichoic acid	Works with TLR2 to recognize bacterial and	11

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			fungal components, inducing immune responses.	
TLR7	Endosome	Single-stranded RNA (ssRNA), viral RNA	Detects RNA viruses, stimulates antiviral immunity, and induces type I interferons.	12
TLR8	Endosome	Single-stranded RNA (ssRNA), viral RNA	Similar to TLR7, involved in viral detection, promoting immune responses.	13
TLR9	Endosome	Unmethylated CpG DNA (common in bacteria and viruses)	Recognizes microbial DNA, triggers inflammation, and stimulates type I interferon production.	14
TLR10	Endosome (or plasma membrane)	Unknown	Modulates immune responses, but its ligands and role in immunity are less well understood.	15
TLR11	Cell membrane (Plasma membrane)	Profilin, uropathogenic E. coli flagellin	Recognizes bacterial flagellin and profilin, involved in immune surveillance and protection against infections.	16
TLR12	Endosome	Profilin (similar to TLRII)	May participate in innate immune response to pathogens, particularly bacteria.	17
TLR13	Endosome	Ribosomal RNA (rRNA)	Senses bacterial rRNA, contributing to host defense mechanisms.	18

TLRs in Autoimmune Diseases

TLRs are involved in autoimmune disorders like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) as well as type-I Diabetes mellitus (TIDM). In such disorders, abnormal TLRs activation results in inflammations and excessive immune responses, causing damage to tissues and progression of diseases. because of their roles in autoantigen recognition such as DNA and RNA, TLR-7 & TLR-9 are mainly involved in SLE (19). The autoimmune disorder TIDM is known by the destruction of pancreatic insulin producing β-cells. Several studies propose that TLRs, especially TLR-2 & TLR-4 contribute to autoimmunity initiation and propagation in TIDM. The pro-inflammatory cytokine release can be triggered by the activation of TLR-2 & TLR-4, resulting in the destruction of pancreatic β-cells. In TIDM, TLR-9 is also involved in autoreactive T-cell activation (20). TLRs participate in the dysfunction of β-cell via inflammation induction. For example, endoplasmic reticulum (ER) stress can be induced and apoptosis is triggered by the activation of TLR-4 in β-cells.

TLR-2 also contribute to β-cell deaths via promotion of production of inflammatory cytokines. Some studies indicated that protections against diabetes-induced β-cell loss showed TLR antagonisms or TLR knockout mice (21). In T2DM, there is a sign of chronic low-grade inflammation. TLRs, especially TLR-4 can be activated by increased circulating free fatty acid & lipopolysaccharide (LPS) levels from intestinal microbiota resulting in insulin resistances. TLR-2 & TLR-9 were also correlated with adiposities and insulin resistance development in T2DM. The activation of TLR-4 by LPS is implicated in cytokine induction like TNF-α, a cytokine that impairs the signaling of insulin and exacerbates metabolic dysfunctions (22). In T2DM, TLR-4 was widely investigated because it plays a significant role in the resistance of insulin. TLR-4 activation by LPS or free

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fatty acids results in NF-κB & other signaling molecule recruitments, leading to inflammatory cascade promotion which impair the sensitivity of insulin. To improve the sensitivity of insulin in diabetes, TLR-4 antagonists were explored as possible treatment agent (23).

Epidemiology

Toll-like receptor (TLR) plays an essential role in the immune responses and is broadly investigated in diabetes context. TLR is a central mediator of the immune responses and plays a key role in both type-I and type-2 diabetes as seen in Table (2).

Table (2): Summary of former studies on TLR types with their roles in immunity

TLR	Diabetes Type	Findings	Mechanism	Reference
TLR1	T2D	Involvement in Inflammatory Pathways	Plays a role in the activation of inflammatory pathways that contribute to insulin resistance and pancreatic beta-cell dysfunction in type 2 diabetes.	4
	T2D	Involvement in Inflammatory Pathways	TLRI activation contributes to insulin resistance via inflammatory cytokine production (TNF-α, IL-6).	24
	T2D	Genetic Polymorphisms and Diabetes Risk	Polymorphisms in TLRI gene associated with increased risk of T2D.	25
	T2D	Obesity and TLR1 in Adipose Tissue	TLRI activation in adipocytes by free fatty acids links to obesity-induced inflammation and insulin resistance.	26
	T1D	TLR1 in Autoimmune Processes	TLRI activation may contribute to autoimmune beta cell destruction in TID by modulating immune responses.	27
	T2D	Therapeutic Targeting of TLRI	Inhibiting TLRI signaling pathways could reduce inflammation and improve insulin sensitivity in T2D.	28
TLR2	T2D	Involvement in Inflammatory Pathways	Contributed to inflammation induction and resistance of insulin. Increased expression of TLR-2 in macrophages and fatty tissues participates in the inflammatory environments observed in type-2 Diabetes mellitus.	29
	T2D	TLR2 Expression in Adipose Tissue	Upregulation of TLR2 in adipose tissue contributes to inflammation and insulin resistance in type 2 diabetes.	30
	T2D	TLR2 in Diabetic Nephropathy	TLR2 activation exacerbates inflammation and fibrosis in the kidneys, leading to nephropathy.	31
	T2D	TLR2 and Insulin Resistance	TLR2 knockout mice showed improved insulin sensitivity and reduced inflammation.	23
	T1D	LR2 and Inflammation in Diabetic Monocytes	TLR2 activation leads to increased cytokine production in monocytes from diabetic patients.	32
	T1D	Immune activation, β-cell destruction	Activation of TLR-3 is associated with the apoptosis of beta cells in the pancreas and with inflammations. The role of TLR-3 in diabetes is not understood yet, but it is believed that it exacerbates dysfunctions of beta cells when accompanied with chronic hyperglycemias.	33

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TLR3	T1D	Immune activation, β-cell destruction	TLR3 contributes to β-cell apoptosis and autoimmunity in TID.	34
	T2D	Inflammatory signaling, insulin resistance	TLR3 activation induces chronic inflammation, contributing to insulin resistance and obesity.	35
	T1D & T2D	β-cell apoptosis	TLR3 activation induces cytokine release leading to β-cell apoptosis and dysfunction.	36
	T2D	Chronic inflammation, insulin resistance	TLR3 signaling exacerbates inflammation and impairs insulin signaling, contributing to insulin resistance in adipocytes and macrophages.	37
	T2D	Genetic variation, susceptibility	SNPs in TLR3 associated with susceptibility to T2D, modulating immune responses.	38
	T1D & T2D	Potential therapeutic target	Targeting TLR3 with antagonists could reduce inflammation and improve insulin sensitivity.	39
TLR4	T1D & T2D	inflammatory cytokine release	In both type-I & type-2 diabetes, TLR-4 is a serious inflammation mediator. The lipopolysaccharide (LPS) is recognized and release of inflammatory cytokines is triggered by TLR-4 resulting in resistance of insulin. The expression of TLR-4 can be increased by high fat diets in liver and fatty tissues, leading to dysregulation of metabolism.	40
	T1D	TLR4 and Inflammation	TLR4 plays a central role in inflammatory response in diabetes.	41
	T2D	TLR4 in Obesity and Insulin Resistance	Elevated TLR4 expression in adipose tissue links to insulin resistance.	42
	T2D	TLR4 in Beta Cell Dysfunction	TLR4 activation promotes beta-cell apoptosis in diabetes.	43
	T2D	TLR4 in Diabetic Complications	TLR4 contributes to complications such as nephropathy and retinopathy.	44
	T2D	TLR4 Inhibition as Therapy	TLR4 inhibitors may reduce insulin resistance and inflammation.	45
	T2D	TLR4 and Gut Microbiota	Gut microbiota influences TLR4 activation and inflammation.	46
	T2D	Hyperglycemia and TLR4 Activation	Chronic hyperglycemia induces TLR4 activation and worsens insulin resistance.	47
TLR5	T2D	modulate the immune response	The role of TLR-5 in diabetes is still not completely investigated, however, it appeared to modulate the immune responses and affect intestinal microbiota. Insulin resistance and inflammation can be affected by a change in the composition of microbiota.	48
	T2D	TLR5 Overview	TLR5 is involved in immune responses and inflammation.	4
	T2D	Inflammation in Diabetes	TLR5 activation contributes to insulin resistance.	49
	T1D & T2D	Diabetic Complications	TLR5 may contribute to diabetic nephropathy and retinopathy.	50
	T2D	Gut Microbiota	Dysbiosis can activate TLR5, leading to insulin resistance.	51

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	T2D	Polymorphisms	TLR5 gene variants may affect diabetes susceptibility.	52
	T2D	Therapeutic Targeting	Inhibition of TLR5 can alleviate insulin resistance.	53
TLR6	T2D	Investigate the role of TLR6 in inflammation associated with diabetes	TLR6 is upregulated in diabetic models, contributing to chronic inflammation, particularly in type 2 diabetes.	54
	T2D	Study the effect of TLR6 genetic variation in diabetic patients	Certain genetic variations in TLR6 are linked with an increased risk of diabetes and diabetic complications.	55
	T1D & T2D	Explore TLR6 expression in diabetic neuropathy	Elevated TLR6 expression contributes to the progression of diabetic neuropathy.	56
	T1D & T2D	Investigate TLR6 role in diabetic wound healing	TLR6 activation impairs wound healing in diabetic mice by exacerbating inflammation.	57
	T2D	Assess TLR6 in diabetic cardiovascular complications	Increased TLR6 activity exacerbates cardiovascular complications in diabetes by promoting inflammation.	58
TLR7	T1D	inflammatory cytokine release	TLR-7 is implicated in innate immune responses and can participate in the release of inflammatory cytokines. It is correlated with autoimmune Diabetes mellitus, particularly in type-I diabetes context.	59
	T1D	TLR7 activation leads to increased inflammatory cytokines, potentially contributing to autoimmune responses.	TLR7 activates NF-κB and other inflammatory pathways, which may exacerbate autoimmune beta-cell destruction.	60
	T1D	Deficiency of TLR7 protects against autoimmune diabetes in NOD mice, suggesting a pro-inflammatory role of TLR7 in TID.	TLR7 activation in NOD mice worsens the autoimmune response by enhancing ThI/ThI7 responses.	61
	T2D	TLR7 is implicated in the development of insulin resistance and inflammation in adipose tissue.	TLR7 activation leads to increased inflammatory cytokines like TNF-α and IL-6, contributing to insulin resistance in adipose tissue.	62
	T2D	TLR7 influences macrophage	TLR7 affects macrophage polarization, promoting a pro-inflammatory MI phenotype, which	63

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		polarization and increases the production of pro-inflammatory cytokines, linking it to insulin resistance.	contributes to chronic low-grade inflammation in T2D.	
	T1D & T2D	TLR7 signaling is linked to pancreatic islet inflammation and beta-cell dysfunction in both T1D and T2D.	TLR7 promotes inflammatory cytokine production in pancreatic islets, leading to beta-cell dysfunction and insulin resistance.	64
	T2D	TLR7-mediated immune responses are involved in the progression of diabetes complications such as nephropathy.	TLR7 activation exacerbates diabetic nephropathy by promoting renal inflammation and fibrosis.	65
TLR8	T2D	mediating inflammation	TLR8 also plays a role in mediating inflammation and insulin resistance. It is thought to contribute to the development of metabolic disorders through its activation of the NF-kB pathway.	66
	T2D	TLR8 expression is increased in the immune cells of diabetic patients, contributing to chronic inflammation.	TLR8 activation triggers the production of pro-inflammatory cytokines such as TNF-α, IL-Iβ, and IL-6, leading to insulin resistance.	67
	T2D	TLR8 signaling induces the activation of NF-κB and MAPK pathways in macrophages, promoting chronic inflammation in T2D.	TLR8 activation in macrophages promotes the release of inflammatory cytokines, contributing to insulin resistance and inflammation in adipose tissue.	68
	T2D	TLR8 activation accelerates inflammation in adipose tissue, leading to increased risk of insulin resistance and obesity.	TLR8 influences macrophage polarization, promoting MI pro-inflammatory macrophages, which are linked to insulin resistance.	69
	T2D	TLR8 deficiency reduces pancreatic islet inflammation and improves insulin	TLR8 deficiency reduces inflammation in pancreatic islets and improves insulin sensitivity by inhibiting the activation of pro-inflammatory cytokine pathways.	70

		sensitivity in a mouse model of T2D.		
	T1D & T2D	TLR8 activation exacerbates systemic inflammation and beta-cell dysfunction in diabetic mice.	TLR8 activation in immune cells enhances the release of pro-inflammatory cytokines, which contribute to beta-cell dysfunction and impaired insulin secretion.	7I
	T2D	TLR8-induced macrophage activation worsens insulin resistance and endothelial dysfunction in diabetes.	TLR8 activation induces MI macrophage polarization, increasing insulin resistance and endothelial dysfunction, both of which contribute to diabetic complications.	72
	T1D & T2D	TLR8 enhances the expression of inflammatory cytokines, aggravating systemic inflammation and beta-cell dysfunction.	TLR8 activation increases inflammatory cytokine expression in pancreatic islets, contributing to the dysfunction of beta-cells and the progression of both T1D and T2D.	73
TLR9	T1D	inflammatory cytokine response	TLR9 activation in response to DNA and methylated CpG motifs can contribute to beta-cell apoptosis and insulin resistance, especially under chronic inflammatory conditions.	74
	T1D	TLR9 activation in diabetic mice exacerbates pancreatic inflammation and accelerates beta-cell destruction.	TLR9 activation induces a pro-inflammatory cytokine response that contributes to beta-cell apoptosis and autoimmunity.	75
	T2D	TLR9 is involved in the induction of insulin resistance in obese mice through increased macrophage activation.	TLR9 activation promotes macrophage polarization to the MI phenotype, leading to chronic inflammation and insulin resistance in adipose tissue.	76
	T2D	TLR9-induced inflammatory response in the liver contributes to insulin resistance in T2D models.	TLR9 activation in liver cells induces inflammation, leading to insulin resistance and hepatic dysfunction.	77
	T2D	Inhibition of TLR9 signaling improves glucose metabolism and reduces	TLR9 inhibition reduced the production of inflammatory cytokines and improved insulin sensitivity in adipose and liver tissues.	71

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	inflammation in diabetic mice.		
T2D	TLR9 activation exacerbates insulin resistance by inducing adipose tissue inflammation in obesity.	TLR9 activation in adipose tissue increases the release of pro-inflammatory cytokines, contributing to insulin resistance.	78
T2D	TLR9-induced inflammation worsens both pancreatic islet function and systemic insulin resistance in T2D.	TLR9 activation in both immune cells and pancreatic islets increases the release of pro-inflammatory cytokines, worsening insulin resistance and beta-cell dysfunction.	79
T2D	TLR9 activation in immune cells increases systemic inflammation, contributing to vascular complications in diabetes.	TLR9-induced inflammation in immune cells leads to increased vascular inflammation, which contributes to endothelial dysfunction and complications in T2D.	80

DISCUSSION

This study reviewed 71 previous studies on the role of TLRs in the pathogenesis of diabetes mellitus for type 1 and type 2 as shown in Table 1. This table showed that the TLRs are impartment components of innate immune system and it have impartment role in the progression of diabetes mellitus by promoting chronic inflammation and insulin resistance. TLRI activation contributes to insulin resistance via inflammatory cytokine production (TNF-α, IL-6) (24). TLR2 activation leads to increased cytokine production in monocytes from diabetic patients (32). TLR3 contributes to β-cell apoptosis and autoimmunity in T1D (34). In both type-I & type-2 diabetes, TLR-4 is a serious inflammation mediator (40). TLR5 is involved in immune responses and inflammation (4). Increased TLR6 activity exacerbates cardiovascular complications in diabetes by promoting inflammation (58). TLR-7 is implicated in innate immune responses and can participate in the release of inflammatory cytokines (59). TLR8 activation triggers the production of pro-inflammatory cytokines such as TNF-α, IL-Iβ, and IL-6, leading to insulin resistance (67). TLR9 activation induces a pro-inflammatory cytokine response that contributes to beta-cell apoptosis and autoimmunity (75).

CONCLUSION

In conclusion, Toll-like receptors (TLRs) play a pivotal role in the pathogenesis of both type 1 and type 2 diabetes mellitus by mediating chronic inflammation and impairing insulin signaling. Previous research has highlighted the critical involvement of TLR2, TLR4, and TLR9 in modulating disease pathophysiology, establishing these receptors as promising therapeutic targets. Modulation of TLR signaling pathways may attenuate inflammatory responses, enhance insulin sensitivity, and preserve pancreatic β-cell function, thereby presenting novel therapeutic strategies for diabetes management and its associated complications. It is recommended to investigate how TLR activation in pancreatic islets triggers immune cell infiltration (e.g., macrophages, dendritic cells), and to study TLR4 inhibitors (e.g., TAK-242) in T2DM models.

Conflict of Interest

The authors declare that there is no conflict of interest.

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