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Review

TLR4 is a link between diabetes and Alzheimer's disease

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HIGHLIGHTS

- TLR4 is involved in the physiological and pathological progress of DM and AD respectively.
- In DM, chronic TLR4 activation may contribute to the insulin resistance.
- In AD, chronic long-term TLR4 activation may lead to Aβ deposition.
- TLR4 as a potential link between DM and AD is reviewed.
- TLR4 as a link of between DM and AD further explain the theory that AD is regarded as types 3 diabetes.

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ABSTRACT

Recently, more and more studies have shown that there is an essential link between diabetes mellitus (DM) and Alzheimer's disease (AD). In addition, innate immunity plays an important role in the occurrence and development of DM and AD, which increase the risk of developing type 2 diabetes (T2D) and AD. Although the pathogenesis of those diseases is still a matter of debate, the important role of Toll-like receptor 4 (TLR4) in the two diseases has been receiving much attention at present. TLR4 and insulin resistance do have close ties, and chronic TLR4 activation may contribute to the insulin resistance. Aside from this, TLR4-mediated chronic inflammation also causes many DM complications such as diabetic nephropathy, diabetic retinopathy and diabetic neuropathy and has a profound impact on the internal environment of the body and brain's microenvironment. In parallel, TLR4 is widely distributed in the brain and also has an important role in the central nervous system (CNS) via regulation of neuroinflammation. The cerebrum under the circumstances of insulin resistance may lead to mitochondrial dysfunction in neurons. Interestingly, in the initial stage, the activation of TLR4 has a useful scavenging effect on amyloid beta (Aβ), but chronic long-term activation leads to Aβ deposition in the brain. Therefore we speculate that the TLR4 signaling pathway may be a potential link between DM and AD.

Contents

Abbreviations: LPS, lipopolysaccharide; HSPs, heat shock proteins; HMGB1, high mobility group box-1 protein; S100A, S100 calcium-binding protein A; mmLDL, minimally modified low-density lipoprotein; OxLDL, oxidized low-density lipoprotein; FFAs, free fatty acids; AGE-LDL, advanced glycation end products-modified LDL; FetA, fetuin-A.

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1. Introduction

In 1905, Dr. Alzheimer found that neurofibrillary tangles and amyloid deposits were the two pathological features of AD. Although researchers have conducted numerous studies since then to treat the disease, its pathogenesis is not yet fully known. Various theories about the pathogenesis of AD have been constantly proposed in this regards. Around 2005, the type 3 diabetes (T3D) theory was put forward [1]. Recent studies have found that innate immunity plays an important role in the development of AD, whereas TLR4 is responsible for activating the innate immune system. But in recent years, Aβ immunotherapy has not made much progress. Most drugs in vitro experiments achieved good results but failed in clinical trials [2]. The actions of TLR4 in AD and DM were both reported early. Subsequently, more and more physiological and pathological functions of TLR4 in the AD and DM were uncovered, and recently a series of studies have revealed the important role of TLR4 in it. So we have reasons to believe that TLR4 may be a potential link between DM and AD, and that joint action by the inflammation and insulin resistance which are both caused by excessive activation of TLR4, may be the cause of AD. Herein, we review the most compelling evidences about the role of TLR4 both in AD and DM and the link of TLR4 between DM and AD.

2. Role of TLR4 in DM

DM is a group of metabolic diseases characterized by high blood sugar, in which environmental and genetic factors play an important role. With the development and duration of DM, microvascular complications and diabetic neuropathy have frequently occurred. Since 1993, Hotamisligil et al. provided the contact between high fat diets and infections, which is one of the causes of insulin resistance [3]. However, although the mechanisms remain unclear, it has raised a very good idea to be construed as an epidemiological link between obesity and DM, as 70% of people with DM are obese [4]. Since then, despite scientists having taken some interesting detours in it, a number of experiments have demonstrated that innate immunity especially TLR4 plays an important role in it.

2.1. TLR4 and insulin resistance

TLR4 has a close relationship with inflammation, and insulin resistance in the early stage of a chronic inflammatory state affects the development of DM. Recent studies have suggested that TLR4 contributes to insulin resistance. Available evidence shows that this situation has led to two possible sources: one is free fatty acids (FFAs) from adipose tissue, and the other is the change in the gut microbiota (Fig. 1). From the viewpoint of organizational embryology, concerning adipose tissue and the immune system from the same germ layer, with the evolution of the organism the immune function of human adipose tissue gradually diminishes. But in the case of obesity, fat cells can become activated inflammatory cells, and secrete a variety of inflammatory cytokines. It is not only the energy reserves of adipose tissue sites, but also an activated endocrine organ [5,6]. Both animal and human studies reveal the same result. In 2004 it was first found that TLR4/cluster of differentiation 14 (CD14) complex mutant mice aged longer, have normal activity and fertility, have a “Adonis” (vegetation god of the Greek mythology, a very handsome young man) body phenotype, and compared with wild-type (WT) mice cannot be infected with multiple strains, suggesting a potential role in the metabolic regulation of TLR4 [7]. However, during high-fat feeding the loss-of-function mutation in TLR4 mice named C3H/HeJ is protected against the development of diet-induced obesity. They did not lose their good physical shape and enhanced insulin-signaling capacity in liver, muscle, and adipose tissue. In addition, control mice show an increase in c-Jun N-terminal kinases (JNKs) and IkB kinase (IKK) activity at the same tissues [8]. FFAs act as an endogenous ligand of TLR4 stimulating adipose tissue via the TLR4 signaling pathway, resulting in insulin resistance [3,9,10]. However, research has shown that FFAs are not directly bound to TLR4, but are still capable of being regarded as an endogenous ligand for TLR4. It has been suggested that fetuin-A (FetA) could be this endogenous ligand and that it has a key role in modulating lipid induced insulin resistance via TLR4 signaling in mice [11]. In a study in which 210 adult middle-class Mexicans with non-diabetic obesity were divided into two groups according to the average weight, it was shown that there was a close relation between obesity and TLR4 expression. Although these volunteers did not have DM and there is no difference among interleukin-1β (IL-1β), interleukin-10 (IL-10) and interleukin-8 (IL-8) in obese individuals compared with normal weight individuals, tumor necrosis factor alpha (TNF-α), FFAs up regulation and insulin levels were lower than normal weight individuals [12]. TLR4 has already been activated in individuals with obesity but without diabetes early, resulting in insulin resistance, but if this experiment can make a long-term survey of those obese volunteers to show that the risk of DM is higher than that of the normal group, then there will be a good phenomenon to explain the important role of TLR4 in DM. In addition, Mraz et al. showed that TLR4 messenger RNA (mRNA) in the peripheral monocytes of obese subjects was increased, while Scholtes et al. demonstrated that TLR4-induced signaling was enhanced in the monocytes of obese subjects with atherosclerosis, showing that macrophages play an important role in human TLR4-induced insulin resistance. Animal experiments have shown that changes in intestinal flora are associated with obesity [13]. Gut microbiota is related to obesity and many other common related diseases such as T2D, some types of cancer and nonalcoholic fatty liver disease [14]. Particular types of gut bacteria such as Verrucomicrobia and Akkermansia muciniphila may lead to this effect [15,16]. A double-blind placebo-controlled randomised crossover clinical trial revealed that colonic microbiota change affects insulin resistance which increases the risk of DM. Selective stimulation of beneficial bacteria in the human colon might offer protection to fight against DM by reducing inflamma-