



Toll-like Receptor 4: Target of Lipotoxicity and Exercise-Induced Anti-inflammatory Effect?

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Abstract

Toll-Like Receptors (TLRs) are a main target during inflammation and metabolic syndromes as receptors for inflammatory signaling molecules, and are named numerically from 1 to 13 in humans. It is believed that TLR4 plays a key role in exercise training-induced anti-inflammatory effects, whereas new evidence shows that TLR4 is the main receptor in fatty acid-induced inflammation. In this review, we summarized classical theories, and the new discovery in the field of fatty acid-induced inflammation through TLR4. Further, we highlight the anti-inflammation ability of exercise through regulating TLR4 as we try to acquire new clues for the treatment of metabolic diseases, and understand the regulatory effect of exercise.

Toll-Like Receptor, Adipose and Muscle Inflammation and Insulin Resistance

Toll-like receptors (TLRs) belong to a pattern-recognition receptor family, linking innate and adaptive immune responses to environmental stresses; in the context of exercise, Lipopolysaccharides (LPS) are liberated to blood during exhaustive exercise and binds with the soluble LPS binding protein (LBP) that facilitates its interaction with TLR4 to cause inflammation [1]. Whilst TLRs are mainly expressed in immune cells, they are also discovered in various kinds of cells including adipocytes, muscle cells, hepatocytes and islet β cells; all of which are important regulatory cells during metabolism, and within metabolic diseases [2-4].

Among the 10+ kinds of TLRs identified, TLR4 may be the most linked with metabolic diseases. TLR4 is an essential receptor for the recognition of exogenous pathogens such as LPS, and endogenous agonists such as free fatty acids. In macrophages, downstream responses of TLR4 activation include the myeloid differentiation primary response (MyD) 88-dependent signaling pathway, and the TIR-domain-containing adapter-inducing interferon- β (TRIF)-dependent pathway. Activating MyD88 is the main regulation pathway during which nuclear factor-kappa B (NF- κ B) is activated; thus elevated inflammatory cytokines, chemokines and cell adhesion molecules contribute to the cycle of inflammation [4,5]. Elevated levels of adipocyte TLR4 and cellular infiltration by macrophages are observed in various kinds of subjects [6,7]. It is also reported that TLR4 expression is elevated in muscle during insulin resistance [8]. On the other hand, it is reported that a loss-of-function mutation in TLR4 contributes to prevent diet-induced obesity and insulin resistance [9]. It could be concluded that enhanced TLR4 expression in adipose tissue recruits immune cell infiltration and aggravates the inflammation. Subsequently, this may lead to elevated whole-body inflammatory responses, thus inducing muscle TLR4 up-regulation, therefore contributing towards insulin resistance, and diabetes.

Lipotoxicity of Adipokines, Insulin Resistance and TLR4

Insulin resistance is closely involved with a chronically inflamed state. The concept of insulin resistance is a complex process, involving free fatty acids, various adipose-origin molecules, and hormones. Free fatty acids are a main component of lipotoxicity, although their exploration is beyond the scope of this review. Lipotoxicity is a metabolic syndrome that results from the accumulation of lipid intermediates in non-adipose tissue, leading to cellular dysfunction and possibly death. For example, lipotoxicity in skeletal muscle tissue is closely linked to decrease glucose uptake, thus contributing to insulin resistance [10]. Furthermore, palmitate, a classical kind of free fatty acid, is shown to interfere with the key transcription factor FoxO1 in hepatocytes, negating the function of insulin, thus failing to suppress hepatic gluconeogenesis and lipid synthesis in the liver [11].

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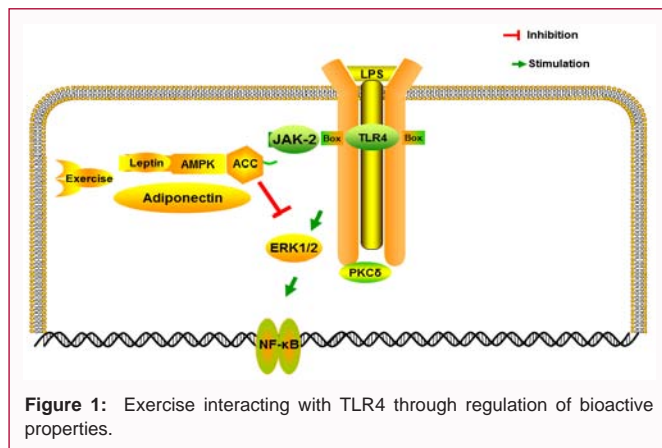


Figure 1: Exercise interacting with TLR4 through regulation of bioactive properties.

The excess of free fatty acids causes lipotoxicity, whereas adipose-origin inflammatory cytokines, named adipokines, also contribute to this situation. Tumor Necrosis Factor (TNF)- α and Interleukin (IL)-6 are classical cytokines secreted by various cells, including macrophages and adipocytes during a chronic inflammatory state. They are classical ligands of TLR4, thus decreasing the translocation and activity of Glucose Transporter (GLUT)1 and GLUT4 to the cell membrane in skeletal muscle, leading to insulin resistance [12]. Interestingly, it is reported that blocking IL-6 signaling does not improve insulin resistance, despite the prevention of macrophage recruitment, which may be attributed to adipose-origin IL-6 secretion [13]. Leptin, resistin and adiponectin are classical adipokines linked to adipocyte metabolism and cytokine secretion network, generated from adipose tissue. Among these, leptin is reported to ameliorate insulin resistance in lipodystrophic mice independent of hepatocyte leptin receptors, and increases insulin sensitivity through activating the AMPK signaling pathway [14,15]. However, in obese subjects, leptin resistance usually exists. Several studies conducted recently claim that increased circulating resistin is associated with insulin resistance in type 2 diabetes mellitus [16,17]. Leptin resistance usually appears alongside insulin resistance, whilst the promotion of TLR4 mediated lipotoxicity, and inhibition of resistin is shown to reduce TLR4 signaling, thus ameliorating insulin resistance [18,19]. Adiponectin is an anti-inflammatory adipokine. It is reported that adiponectin suppresses TLR4/MyD88 signaling in a rat model, contributing to prevent insulin resistance [20]; increased resistin and TLR4 are linked with down-regulation of adiponectin, thus contributing towards insulin resistance [21]. Adipokines are closely linked to insulin resistance, whilst the function of TLR4 plays a key, but complimentary role in the above sessions.

Anti-Inflammatory and Anti-Diabetes Effect of Exercise through Regulation of TLR4

Endurance exercise has complicated interactions with the immune system and inflammation, including the dynamics of stress hormones, systematic cytokine release and neutrophil activation, which was narrated by Suzuki and colleagues, and then extended by followers [22-24]. The anti-inflammatory effects of acute and chronic exercise have been also reported in recent years [23-26]. Obesity induces a phenotypic switch in adipose tissue macrophage polarization, whilst aerobic exercise reverses this switch, partly by regulating TLR4 expression in adipocytes and macrophages, or by down-regulating the overexpression of TLR4, TLR2, MyD88 and NF- κ B [26]. On the other hand, resistance-trained elderly women displayed significantly

lowered TLR4 expression [27]. Muscular cell-origin IL-6 is reported to possess inflammatory regulation abilities; exercise with concurrent IL-6 infusion inhibits endotoxin-induced TNF- α production [28,29]. It is reported that the increase of TLR4 by ligands may decrease with the increase of the stimulation, therefore multiple exercise bouts may decrease the amount of activated TLR4 [30]. The reduction of free fatty acids in the blood by exercise may also contribute to the anti-inflammatory function (Figure 1). Reduced circulating monocytes by regular exercise is another probability for the exercise-induced anti-inflammatory phenomenon, since monocytes are one of the main cells to express TLR4 [31]. In a recent study, both acute and chronic exercise indirectly activated the leptin-AMPK-ACC signaling pathway and increased insulin sensitivity in the liver of type 2 diabetic rats through TLR4 mediation [32]. Exercise is reported to decrease resistin; therefore TLR4 may also be down-regulated by exercise. Figure 1 concisely describes the pathway how exercise is interacted with TLR4 through regulation of bioactive properties.

The effect of exercise on adiponectin is contradictory, with some reports of no influence, and other reports of increased adiponectin concentrations, despite the belief of exercise to improve insulin sensitivity [34-37]. Therefore, the interaction between TLR4, exercise, and various adipokines is an intriguing area of research, requiring further investigation [38-40].

Conclusion

The relationships between TLR4 and inflammation, and exercise and anti-inflammation are undeniably strong; TLR4 may be the key link between these relationships. The immediate function of adipokines requires in depth investigations. However, as TLR4 is extensively expressed in various cell types, tissue-specific knock-out models may be useful to study which tissue(s) and their magnitudes contribute to exercise-induced TLR-4-dependent anti-inflammation responses.

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