

# Toll-Like Receptors and Targeted Therapy in Diabetes Mellitus

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## Abstract

Role of immune system in diabetes mellitus (DM) has been emerged for a long time. Since then, the majority of focus has been toward the role of adaptive immunity, while little thoughts credited a role for innate immunity in this process. By the emerging role of innate immunity in DM pathogenesis, especially toll-like receptors (TLRs) superfamily, it is expected that therapeutic approaches target these components in future of pharmaceutical research in diabetes.

**Keywords:** Diabetes mellitus, Innate immunity, Toll-like receptor

## Diabetes Mellitus and Immune System

Diabetes mellitus (DM) is characterized with low grade inflammatory status. The inflammation within islet cells is considered a major determinant in beta cell dysfunction.<sup>1</sup> This inflammatory state contributes to the pathogenesis of DM. However, the extent of the contribution, the mediators, and the potential role of targeting anti-inflammatory therapies are not well understood. Toll-like receptors (TLRs) are major receptors expressed on a variety of immune cells. The role of TLRs in the pathogenesis of DM has started to be unveiled in recent years. Attenuation of TLR-2 expression in the inflammatory cells of diabetic patients has been noted in association with modulated inflammatory state in these patients.<sup>2</sup> It has been hypothesized that the release of large entities of damage-associated molecular pattern (DAMP) in DM can result in the persistent activation of TLR-2 signaling.<sup>3</sup> TLRs-derived signaling pathways have been recognized among 11 major signaling routes activated in DM type 2.<sup>4</sup> Immunotherapy of DM targeting innate immunity components is a new approach in treatment of the disease.<sup>5</sup> Specially, therapies aimed at targeting TLR-4 signaling pathway rendered a potential intriguing candidate.<sup>6</sup> There are accumulating evidence that TLRs signaling may participate in DM complications and progression.<sup>7-9</sup> Linagliptin, an anti-glycemic therapeutic agent, has been shown to exert its beneficial effects on

blood cerebrovascular circulation partly through the inhibition of TLR-2 activity.<sup>10</sup> In addition, it has been noted that insulin exerts its effects in part by inhibition of TLR-4 derived signaling pathways.<sup>11</sup> This is interesting that the same signaling route involving TLR-4, inhibited by insulin-mediated actions, is involved in the development of insulin resistance.<sup>12</sup> In line with this, downregulation of TLR-4 has been a part of protective measures in animal models of diabetes. Herbal extract of *Urtica dentata* containing coumarin was shown to exert diabetes protective role through the suppression of TLR-4 signaling pathways.<sup>13</sup> Despite these substantial evidence on the role of TLRs family in DM pathogenesis, pharmaceutical studies targeting these pathways have not been appropriately credited. Regarding the sufficiency of immune therapies targeting adaptive and cell mediated immunity in the treatment and prevention of DM during past decades, it seems that therapies have been oriented towards innate immunity to take the place of adaptive counterparts in this area.

## Ethical Approval

Not applicable.

## Competing Interests

None.

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