



## ROLE OF INTERLUKIN 1 IN DIABETES MELLITUS

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### ARTICLE INFO

#### Article History:

Received 18<sup>th</sup> February, 2017

Received in revised form 2<sup>nd</sup> March, 2017

Accepted 5<sup>th</sup> April, 2017

Published online 28<sup>th</sup> May, 2017

#### Key words:

Interlukin, Metabolising Tissues

### ABSTRACT

Interleukin-1 (IL-1) family comprises of 11 cytokines, which plays central mediator of innate immunity and inflammatory response, are key regulators of multiple inflammatory diseases. Diabetes is a metabolic disease that occurs when pancreatic islets fail to produce sufficient insulin or the sensitivity of glucose metabolising tissues to insulin decreases. Diabetes is classified in to diabetes type 1 and diabetes type 2. Interleukin 1 beta has direct effect on diabetes mellitus, resulting in beta dysfunction and impaired in insulin secretion.

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## INTRODUCTION

### Interlukin 1

Interleukin-1 (IL-1) family comprises of 11 cytokines, which plays central mediator of innate immunity and inflammatory response, are key regulators of multiple inflammatory diseases<sup>[1]</sup>. Interleukin 1 (IL 1) is a polypeptide that is produced after infection, injury, or antigenic challenge<sup>[2]</sup>. IL-1 $\alpha$  is a unique member in the cytokine family which is synthesized as a 31kDa precursor protein, ProIL-1 $\alpha$ <sup>[3]</sup>. IL-1 $\beta$  is primarily synthesized as an immature 31 kDa protein called Pro-IL-1 $\beta$ <sup>[4]</sup>. Interleukin 1 $\alpha$  (IL-1 $\alpha$ ) and IL-1 $\beta$  are equally potent inflammatory cytokines that activate the inflammatory process, and their deregulated signaling causes devastating

Table 1 The interleukin family<sup>[8]</sup>.

Types	Properties
IL-1 $\alpha$	Proinflammatory
IL-1 $\beta$	Proinflammatory
IL-1Ra	Antagonist for IL-1 alpha, IL-1 beta
IL-18	Proinflammatory
IL-36Ra	Antagonist for IL-36 alpha, IL-36 beta, IL-36 gamma
IL-36 $\alpha$	Proinflammatory
IL-37	Anti-inflammatory
IL-36 $\beta$	Proinflammatory
IL-36 gamma	Proinflammatory
IL-38	Unknown
IL-33	Th2 response, proinflammatory

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diseases manifested by severe acute or chronic inflammation<sup>[5]</sup>. IL-1 $\beta$  plays an important role in lipid metabolism by regulating insulin levels and lipase activity under physiological conditions<sup>[6]</sup>. In the past decades, it had been well established that inflammatory cytokines including IL-1 $\beta$  play a critical role in the pathogenesis of type 1 diabetes, although its role in type 2 diabetic are still not completely elucidated<sup>[7]</sup>. This current review focuses on role of interleukin 1 in Diabetes mellitus.

### Classification of interleukin 1

#### Mode of Action

When binding to cells, IL-1 induces several biochemical and signaling pathway such as multiple protein phosphorylation and activation of phosphatases during the first 2 to 5 min<sup>[9]</sup>. There is no sequential order has been identified. The IL-1 signaling events are prominent in different cells with post receptor mechanisms providing cellular specificity.

### Diabetes mellitus

Diabetes is a metabolic disease that occurs when pancreatic islets fail to produce sufficient insulin or the sensitivity of glucose metabolising tissues to insulin decreases<sup>[7]</sup>. The pathophysiological hallmarks of type 2 diabetes mellitus are insulin resistance and beta cell dysfunction<sup>[10]</sup>. Beta cells function is mainly destructed by autoimmune-mediated apoptosis, leading to the loss of insulin production. Inflammatory cytokines play important role in this process<sup>[11]</sup>.

### Diabetes Mellitus is categorized into the following groups

Type 1 diabetes mellitus (T1DM) includes 5-10% of diabetic patients. Cellular-mediated autoimmune destruction of the

beta-cells of the pancreas results in T1DM. It classically occurs in juveniles and affected patients are dependent on insulin injection in their lifetime and are very prone to diabetic Ketoacidosis<sup>[12]</sup>

Type 2 diabetes mellitus (T2DM) includes 90-95% of patients with diabetes. Patients with type 2 diabetes may be asymptomatic for long period of time. Vascular complications such as nephropathy, neuropathy, retinopathy, and cardiovascular disease may develop in these patients. The impact of genetic component appears to be stronger in T2DM compared to T1DM<sup>[12]</sup>

### Role of Interlukin in Dm

IL- 1 activity is more important in the pathology of diabetes type 2 by mediating obesity induced inflammation and directly aggravating insulin resistance<sup>[13]</sup>. Eizadi Mojtaba *et al.*, 2011 reported that Serum IL-1 $\beta$  concentrations were significantly higher in the type 2 diabetics than in the healthy subjects. Proinflammatory cytokines secreted by adipose tissue and the other tissues can cause insulin dysfunction in adipose tissue, skeletal muscle and liver by inhibiting insulin signal transduction<sup>[14]</sup>. Sauter NS *et al.*, 2008 suggested that the diseases related to metabolic syndrome are characterized by abnormal cytokine production, including elevated circulating IL-1 $\beta$ <sup>[15]</sup>. A number of studies have demonstrated that low concentration of IL-1 $\beta$  stimulates insulin release and proliferation in rat and human islets<sup>[16-17]</sup>. A recent study states that increased IL-1 $\beta$  levels is accompanied with impaired insulin secretion, decreased cell proliferation and apoptosis of pancreatic beta cells<sup>[18]</sup>. Ehses JA *et al.*, 2009 reported that IL-1 $\beta$  may drive tissue inflammation that impacts on both beta cell functional mass and insulin sensitivity in type 2 diabetes<sup>[19]</sup>. For over 25 years, the cytotoxic effects of IL-1 $\beta$  for the insulin-producing pancreatic beta cell have been studied (Mandrup-Poulsen T *et al.*, 2010)<sup>[20]</sup>. Subsequently, it was shown that high concentrations of glucose stimulated IL-1 $\beta$  production from the beta-cell itself<sup>[19]</sup> implicating a role for IL-1 $\beta$  in type 2 diabetes<sup>[21]</sup>. Gene expression for IL-1 $\beta$  was over one hundred-fold higher in beta cells from type 2 patients compared to non-diabetic patients. The clinical proof of a role for IL-1 $\beta$  in the pathogenesis of type 2 diabetes came from a randomized, placebo controlled study of anakinra for 13 weeks<sup>[22]</sup>. Type-2 diabetes is a chronic IL-1- mediated disease and could be classified as an auto-inflammatory disease in which IL-1 $\beta$ - mediated inflammation progressively destroys the insulin-producing beta cells.

### CONCLUSION

From the findings of various studies, it has been shown that interleukin 1 beta has direct effect on diabetes mellitus, resulting in beta dysfunction and impaired in insulin secretion. Hence novel therapeutic agents like anti-cytokines therapy for interleukin 1 can be used for the control of diabetes mellitus.

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**How to cite this article:**

Bhavani G and Priyalochana Gajendran (2017) ' Role Of Interlukin 1 In Diabetes Mellitus', *International Journal of Current Advanced Research*, 06(05), pp. 3852-3854. DOI: <http://dx.doi.org/10.24327/ijcar.2017.3854.0381>

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