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Contents

Monthly Volume 15 Number 10 October 15, 2024

EDITORIAL

REVIEW

ORIGINAL ARTICLE

Retrospective Study

Observational Study

World Journal of Diabetes

Monthly Volume 15 Number 10 October 15, 2024

Contents

World Journal of Diabetes

Monthly Volume 15 Number 10 October 15, 2024

Contents

ABOUT COVER

Peer Review of *World Journal of Diabetes*, Tao-Hsin Tung, PhD, Researcher, Director, Epidemiologist, Evidence-based Medicine Center, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Taizhou 317000, Zhejiang Province, China. dongdx@enzemed.com .

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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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LETTER TO THE EDITOR

Interleukin-35: A key player managing pre-diabetes and chronic inflammatory type 1 autoimmune diabetes

Ratul Chakraborty, Ashis Kumar Mukherjee, Asis Bala

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Abstract

Interleukin-35 (IL-35) is a novel protein comprising IL-12α and IL-27β chains. The IL12A and *EBI3* genes are responsible for its production. The study of IL-35 has experienced a substantial increase in interest in recent years, as demonstrated by many research papers. Recent clinical studies have shown that individuals who do not have a C-peptide have notably reduced amounts of IL-35 in their blood serum. This is accompanied by a drop in the percentage of IL-35$^+$ Treg cells, regulatory B cells, and CD8$^+$ FOXP3$^+$ cells that produce IL-35. This article emphasizes the potential significance of IL-35 expression in governing the immune response and its involvement in chronic inflammatory autoimmune diabetes in pancreatic inflammation. It demonstrates IL-35's ability to regulate cytokine proportions, modulate B cells, and protect against autoimmune diabetes. However, further investigation is necessary to ascertain the precise mechanism of IL-35, and meticulous planning is essential for clinical studies.

Key Words: Interleukin-35; Chronic inflammatory type diabetes; Autoimmune diabetes; Pancreatic inflammation; Gene disease association

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Core Tip: Studies suggest interleukin (IL)-35 protects against prediabetes and autoimmune diabetes by regulating immune system function. Development of type 1 diabetes (T1D) can be influenced by various cytokines produced by immune and pancreatic cells. Some cytokines, such as IL-10, transforming growth factor beta (TGF-β), IL-5, IL-4, IL-2, IL-15, IL-33, and IL-35, can stimulate regulatory cells in the immune system, releasing anti-inflammatory cytokines. Regulatory dendritic cells release IL-7, important for maintaining Tregs. In T1D, Tregs express IL-7Rα. Inhibiting TGF-β and activating IFN-γ can increase TC, Th1, and Th17 cells, while TGF-β can stimulate Runx1 expression to convert Th1 cells into Th17 cells.

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TO THE EDITOR

The study by Ping *et al*[1], published in 2024 in the *World Journal of Diabetes*, elucidates the etiology of prediabetes and its corresponding treatment medications. Nevertheless, the role of interleukin (IL)-35 in regulating the progression of prediabetes has not been investigated, which deserves due attention.

IL-35 has garnered considerable interest in recent years as a potential pivotal controller of diabetes, namely in prediabetes and chronic inflammatory autoimmune diabetes, which are progressively impacting children and adolescents across various locations globally[2,3]. Two separate genes encode IL-35 called IL12A and Epstein–Barr virus-induced 3 (EBI3)[4,5]. Both the genes IL-12A and EBI3 are networked with various diseases, as represented in Figure 1. The data in the PubMed database indicated a direct correlation between IL-35 and EBI3 genes in many immune-inflammatory, autoimmune, cancer, and endocrine diseases[6-8].

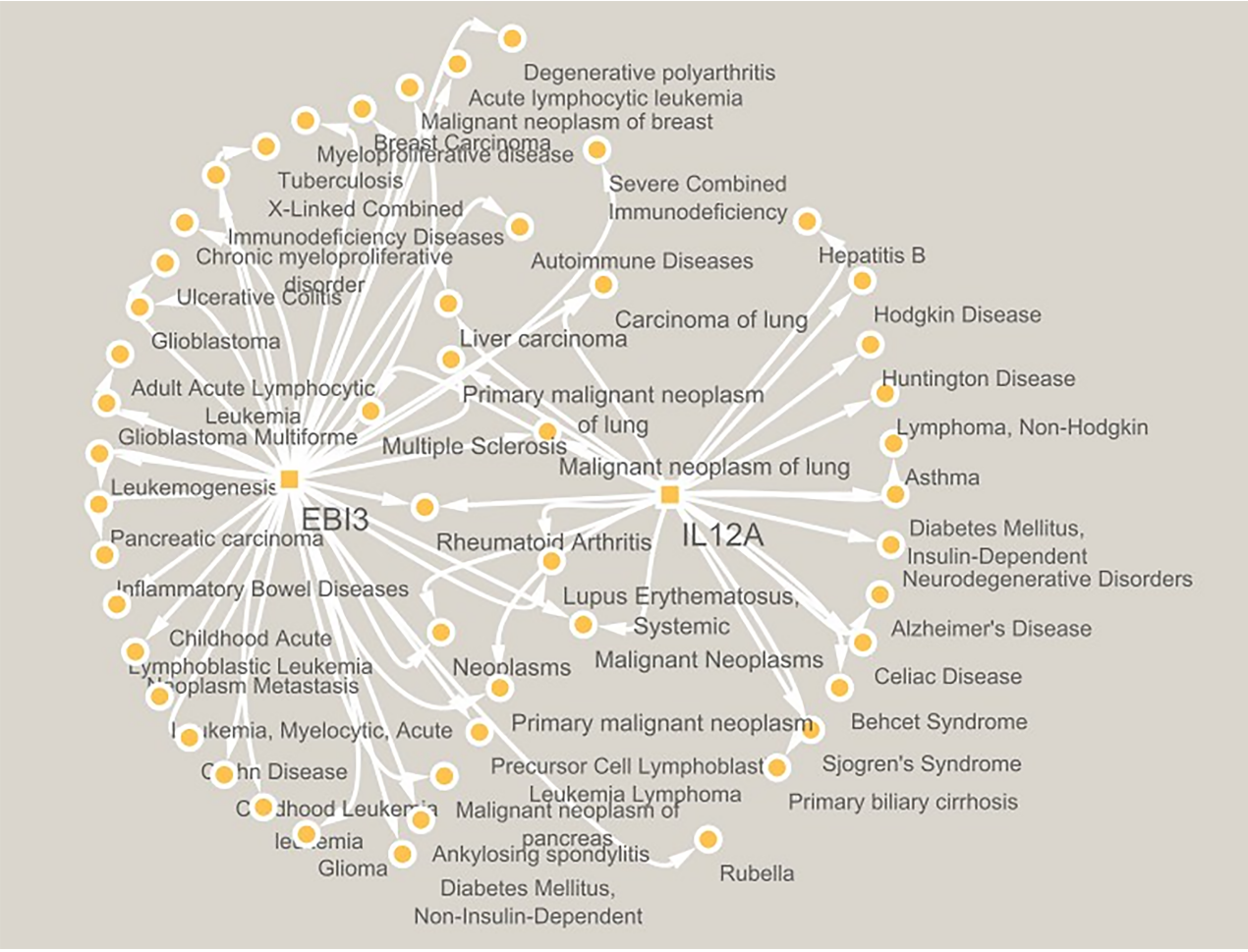

Figure 1 Schematic representation of interleukin-12A and Epstein–Barr virus-induced 3 individually and mutually networked with

different diseases by white solid lines. Data were collected from the PubMed database. The disease-gene association is searched in the DisGeNET database v 7.0 for gene-disease associations, whereas the "N_PMIDs (citation)" ≥ 3 were considered, and a gene-disease target network was created and analyzed using CYTOSCAPE version 3.10.0. Schematic representation of networking in Figure 1, in which interleukin-12A and Epstein–Barr virus-induced 3 are found to be individually and mutually networked by solid white lines.

Further, we selected 5 protein/enzyme markers clinically identified with IL12A and EBI3 from the PubMed database. We then searched for their UniProt ID and human gene names in the UniProt databases and looked for their disease associations in the DisGeNET database v7.0. Gene-disease associations with N_PMIDs (citation) greater than or equal to 10 were considered. Finally, we created a gene-disease target network using CYTOSCAPE version 3.10.0[9]. The schematic representation of networking of the total of five genes named ADIPOQ, CRP, IL18, IL1RN, and SERPINE1 encodes the protein Progestin and adipoQ receptor family member 3, C-reactive protein, IL-18, IL-1 receptor antagonist protein, and SERPINE1 mRNA-binding protein 1, respectively are shown in Figure 2.

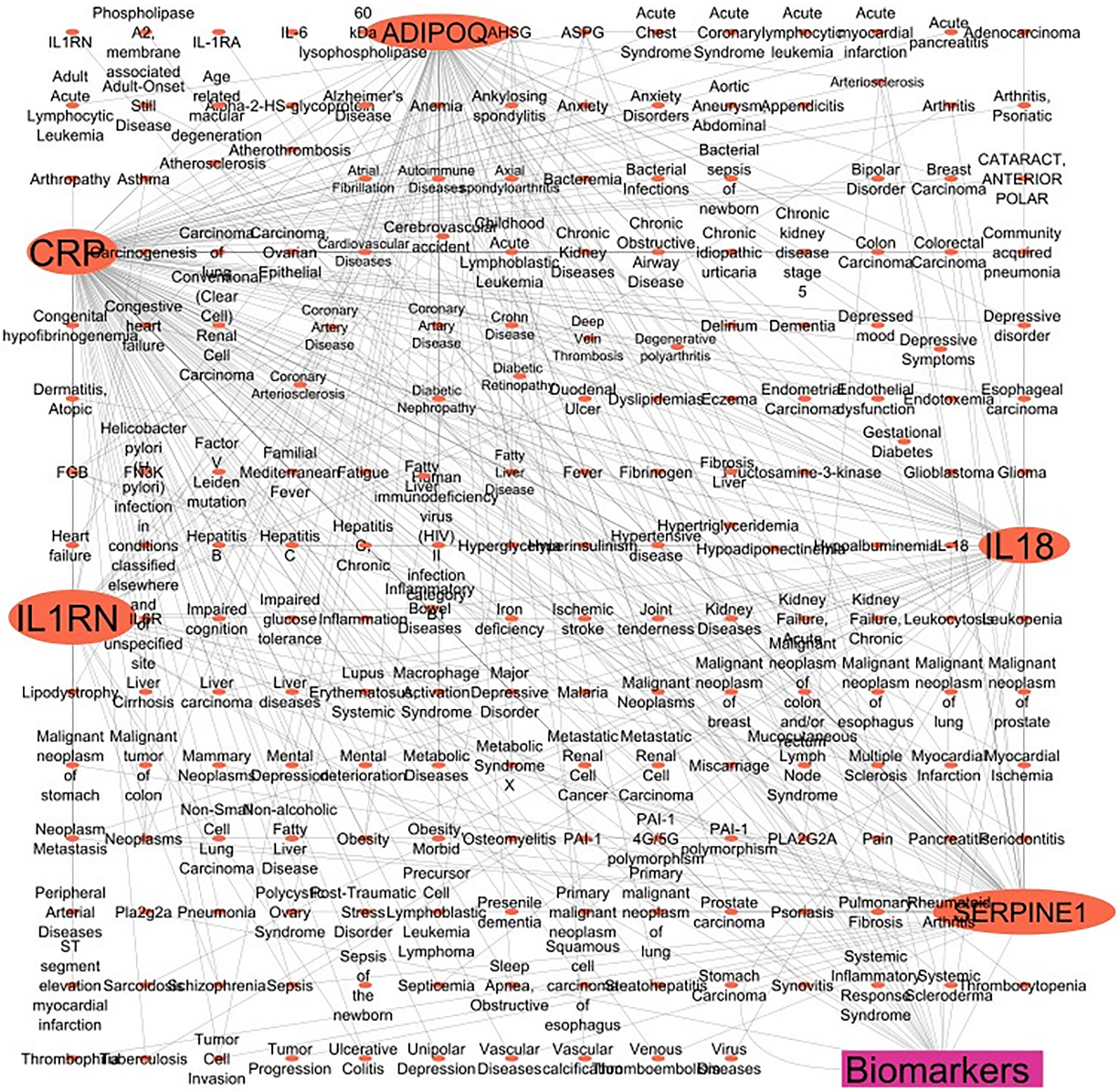

Figure 2 Schematic representation of networking of the 5 genes encodes 5 unique protein/enzymatic markers. A total of 5 clinically identified protein/enzyme markers were identified from the PubMed database. Next, their UniProt ID and human gene names were searched in the UniProt databases, and their disease associations were found in the DisGeNET database v7.0. A note on gene-disease associations with N_PMIDs (citation) greater than or equal to 10 was taken. Lastly, the gene-disease target network was constructed and analyzed using CYTOSCAPE version 3.10.0.

The network pharmacological analysis revealed that these five genes, highlighted in the figure, exhibited the most significant interaction with the disease. The PubMed database establishes a correlation between 5 genes and various disorders, encompassing immune-inflammatory, autoimmune, cancer, and endocrine diseases.

Based on several PubMed literature searches, there is a direct correlation between proinflammatory mediators such as CRP and IL-6R, which has been re-validated through networking. As a result, IL-35, an anti-inflammatory immune suppressant, may help counteract the proinflammatory signals that occur during prediabetes, diabetes, and its complications.

KEY POINTS

IL-35 is a protective factor against prediabetes and plays a significant role in macrophage polarization[10]. Treg and Th1 cells are crucial for this protection[11]. Studies on non-obese diabetic mice have revealed that IL-35 expression reduces conventional T cells, dendritic cells, and Treg cells against beta cells[12]. The administration of IL-35 also reduces the number of Th1 and Th17 cells and IFN-γ or IL-17A-expressing CD8+ T cells[13]. Thereby, IL-35 plays a critical regulatory role in T1D by decreasing the infiltration of mononuclear cells in the islets[14,15]. Clinical research has provided additional insights, indicating that C-peptide-negative patients exhibit markedly lower serum levels of IL-35[8-13]. This decrease is associated with a simultaneous reduction in the proportion of IL-35+ Treg cells, IL-35+ regulatory B cells, and IL-35-producing CD8+ FOXP3+ cells[15,16].

CONCLUSION

The results above emphasize the possible importance of IL-35 expression in regulating the immune response and its involvement in the autoimmune mechanisms underlying type 1 diabetes. Immunotherapy with IL-35 has demonstrated encouraging outcomes in combating the consequences of prediabetes and diabetes. Research indicates that IL-35 can alter the balance of cytokines, modulate the activity of B cells, and offer defense against autoimmune diabetes. Nevertheless, additional investigation is necessary to ascertain the precise mechanism of action, accompanied by meticulous design of clinical studies.

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FOOTNOTES

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