Autoimmunity, June 2010; 43(4): 255–263

ISSN 0891-6934 print/1607-842X online
DOI: 10.3109/08916930903305641

informa
healthcare

REVIEW

Interleukin-1 receptor antagonist (IL-1Ra) and IL-1Ra producing mesenchymal stem cells as modulators of diabetogenesis

VLADISLAV VOLAREVIC[1], AHMED AL-QAHTANI[2], NEBOJSA ARSENIJEVIC[1], SLADJANA PAJOVIC[1], & MIODRAG L. LUKIC[1,2]

[1]*Faculty of Medicine, Center for Molecular Medicine, University of Kragujevac, Kragujevac, Serbia, and* [2]*Department of Microbiology and Immunology, Faculty of Medicine and Health Sciences, UAE University, Al Ain, United Arab Emirates*

(*Submitted 9 July 2009; revised 28 August 2009; accepted 2 September 2009*)

Abstract
The increase of pro-inflammatory cytokines and oxidative stress leads to β-cell damage and promotes β-cells apoptosis, in types I and II of diabetes mellitus. Therefore, blocking of pro-inflammatory cytokines should be an effective way for the treatment of diabetes mellitus. When IL-1 occupies its receptor, various pro-inflammatory events are initiated including the synthesis and releases of chemokines and these chemokines attract neutrophils, macrophages, and lymphocytes that cause tissue inflammation. IL-1Ra is a naturally occurring cytokine and is the inhibitor of IL-1. When IL-1Ra binds to the IL-1 receptor, binding of IL-1 is blocked by IL-1Ra and pro-inflammatory signal from IL-1 receptor is stopped. There are mounting evidences to suggest that anti-inflammatory IL-1Ra reduces the inflammatory effects of IL-1 and preserves cell function in both types of diabetes. Therefore, IL-1Ra maybe a new therapeutic agent for diabetes mellitus types I and II. Mesenchymal stem cells (MSCs) are self-renewable multipotent stromal cells that have immunomodulatory capacity. Recently, well characterized subpopulations of MSCs which express IL-1Ra have been described. IL-1Ra expressed by these MSCs effectively binds to IL-1 receptor and protects tissues from inflammation-induced injuries. It has been previously shown that bone marrow-derived MSC therapy could be considered for the treatment of diabetes mellitus type 1 and complications of diabetes mellitus. This review presents understanding of potential use of IL-1Ra and MSCs as modulators of diabetogenesis.

Keywords: *Interleukin-1 receptor antagonist, mesenchymal stem cells, diabetes mellitus, prevention, therapy*

Introduction

Destruction of β-cells in diabetes mellitus type 1 is proposed to be due to abnormal T-cell immune response [1]. Chronic hyperglycemia due to an imbalance between insulin production and insulin action is the key metabolic abnormality important in the pathogenesis of diabetes mellitus type 2 [2,3]. However, several lines of evidence suggest that there are shared mechanisms of β-cell dysfunction in both types of diabetes mellitus [4].

Different initial events characterize pathogenesis of diabetes mellitus type 1 and diabetes mellitus type 2 [1,2,4]. Nevertheless, the increase of pro-inflammatory cytokines and oxidative stress induced by glucotoxicity and lipotoxicity leads to β-cell damage and promotes β-cells apoptosis, in both types of diabetes [4].

Thus, blocking of pro-inflammatory cytokines should be an effective way for treatment of diabetes mellitus. One possible therapeutic agent for diabetes mellitus treatment appears to be interleukin 1 receptor antagonist (IL-1Ra), a member of the IL-1 cytokine family [4].

It has been shown that a subset of mesenchymal stem cells (MSCs) is an excellent source of IL-1Ra, which in addition to their regenerative capacity makes these cells a potential therapeutic agent in the treatment of diabetes mellitus [5]. Here, we review the present understanding of the potential use of IL-1Ra and MSCs as modulators of diabetogenesis.

IL-1Ra in type 1 diabetes mellitus

IL-1Ra is a naturally occurring cytokine that inhibits the IL-1 function [6]. When IL-1 binds to its receptor

Correspondence: Miodrag L. Lukic, MD, PhD, Professor and Chair, Department of Microbiology and Immunology, Faculty of Medicine and Health Sciences, UAE University, P.O. Box 17666, Al Ain, United Arab Emirates. Tel: + 971 3 7137516. Fax: + 971 3 7671966. E-mail: m.lukic@uaeu.ac.ae