Journal of Diabetes Science and Technology
Volume 7, Issue 6, November 2013

ORIGINAL ARTICLE

Role of Interleukin-1/Interleukin-1 Receptor Antagonist Family of Cytokines in Long-Term Continuous Glucose Monitoring *In Vivo*

Ulrike Klueh, Ph.D.,[1,2] Omar Antar, M.S., M.B.A.,[1,2] Yi Qiao, M.D.,[1,2] and Donald L. Kreutzer, Ph.D.[1,2]

Abstract

Background:

Glucose-sensor-induced tissue reactions (e.g., inflammation and wound healing) are known to negatively impact sensor function *in vivo*. The roles of cytokine networks in controlling these tissue reactions (i.e., sensor biofouling) is not understood. In the present study, we investigated the role of interleukin-1 receptor antagonist (IL-1Ra), a key anti-inflammatory antagonist of the proinflammatory interleukin-1 cytokines [i.e. interleukin-1 (IL-1) alpha and IL-1 beta] in controlling continuous glucose monitoring (CGM).

Methods:

To investigate the role of IL-1Ra in long-term CGM *in vivo*, we compared CGM in transgenic mice that overexpress IL-1Ra [interleukin-1 receptor antagonist overexpresser (IL-1Ra~OE), B6.Cg-Tg*(IL1rn)1Dih/J*] or are deficient in IL-1Ra [interleukin-1 receptor antagonist knockout (IL-1Ra~KO), B6.129S-*IL1rn*^{tm1Dih}*/J*] with mice that have normal levels of IL-1Ra (C57BL/6) over a 28-day time period.

Results:

Mean absolute relative difference (MARD) analysis of CGM results among the mice of varying IL-1Ra levels demonstrated that during the first 21 days, IL-1~KO mice had the greatest tissue inflammation and the poorest sensor performance (i.e., higher MARD values) when compared with normal or IL-1Ra~OE mice. By 28 days post-sensor implantation, the inflammatory reactions had subsided and were replaced by varying degrees of fibrosis.

Conclusions:

These data support our hypothesis on the importance of the IL-1 family of agonists and antagonists in controlling tissue reactions and sensor function *in vivo*. These data also suggest that local delivery of IL-1Ra genes or recombinant proteins (anakinra) or other IL-1 antagonists such as antibodies or soluble IL-1 receptors would suppress sensor-induced tissue reactions and likely enhance glucose sensor function by inhibiting inflammation and wound healing at sensor implantation sites.

J Diabetes Sci Technol 2013;7(6):1538–1546

Author Affiliations: [1]Center for Molecular Tissue Engineering, University of Connecticut School of Medicine, Farmington, Connecticut; and [2]Department of Surgery, University of Connecticut School of Medicine, Farmington, Connecticut

Abbreviations: (CGM) continuous glucose monitoring, (IL-1) interleukin-1, (IL-1a) interleukin 1 alpha, (IL-1B) interleukin-1 beta, (IL-1RI) interleukin-1 receptor I, (IL-1RII) interleukin-1 receptor II, (IL-1Ra) interleukin-1 receptor antagonist, (IL-1Ra~KO) interleukin-1 receptor antagonist knockout, (IL-1Ra~OE) interleukin-1 receptor antagonist overexpresser, (MARD) mean absolute relative difference

Keywords: angiogenesis, biosensor, continuous glucose monitoring, diabetes, fibrosis, inflammation

Corresponding Author: Ulrike Klueh, Ph.D., Center for Molecular Tissue Engineering, University of Connecticut School of Medicine, Farmington, CT; email address klueh@nso.uchc.edu