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

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

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-1RaOE), B6.Cg-Tg(IL1rn1Dih/J)] or are deficient in IL-1Ra [interleukin-1 receptor antagonist knockout (IL-1RaKO), B6.129S-IL1rn1m1Dih/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-1KO mice had the greatest tissue inflammation and the poorest sensor performance (i.e., higher MARD values) when compared with normal or IL-1RaOE 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.


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