Study on file RAGE signaling in vascular cells - a novel mechanism of the development of diabetic vascular complications

2002 Fiscal Year Final Research Report Summary

Study on file RAGE signaling in vascular cells - a novel mechanism of the development of diabetic vascular complications

Research Project

Project/Area Number

13670113

Research Category

Grant-in-Aid for Scientific Research (C)

Allocation Type

Single-year Grants

Section

一般

Research Field

General medical chemistry

Research Institution

Kanazawa University

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Project Period (FY)

2001 – 2002

Keywords

diabetic complications / transgenic mouse / advanced glycation endproducts (AGE) / alternative splicing / endogenous soluble receptor / receptor for AGE (RAGE) / esRAGE / gene knockout mouse

Research Abstract

In this research, we provide the first direct in vivo evidence that interactions between advanced glycation end products (AGE) and their receptor, RAGE, lead to diabetic vascular derangements. We also found the presence of a cytoprotective secretory form of RAGE (endogenous secretory RAGE, esRAGE) in human and identified new RAGE ligands, which are abundantly present in human circulation.

(1) We created transgenic mice that overexpress human RAGE in vascular cells. The diabetic RAGE transgenic mice exhibited an accelerated development of diabetic nephropathy. This transgenic mouse will be a useful animal model that shows the renal changes seen in humans.
(2) We also created transgenic mice that overexpress human RAGE in the heart and obtained evidence suggesting that the AGE and RAGE could play an active role in the development of diabetes-induced cardiac dysfunction.
(3) We created RAGE gene-knockout mice and showed that the advanced diabetic nephropathy was significantly suppressed in the diabetic knockout mice.
(4) We demonstrated that human vascular endothelial cells (EC) and pericytes express a novel splice variant encoding a novel secretory form of RAGE (esRAGE). The AGE induction of ERK phosphorylation and vascular endothelial growth factor in EC and of the growth and cord-like structure formation of EC was perfectly abolished by this RAGE variant, indicating that esRAGE is cytoprotective against AGE. The findings may contribute to our understanding of the molecular basis for the diversity of cellular responses to AGE and for individual variations in susceptibility or resistance to diabetic vascular complications.
(5) We identified glyceraldehyde- and glycolaldehydee-derived AGE as new RAGE ligands. The AGE fractions increased VEGF mRNA levels in human EC as well as cell growth. These results suggested that glyceraldehyde- and glycolaldehyde-derived AGE participate in vascular injury in diabetes.

Research Products (36 results)

All Other

All Publications

[Publications] Yamamoto, Y., et al.: "Development and prevention of advanced diabetic nephropathy in RAGE-overexpressing mice"J.Clin.Invest.. 108. 261-268 (2001)

[Publications] Wu, P., et al.: "Hypoxia down-regulates endostatin production by human microvascular endothelial cells and pericytes"Biochem.Biophys.Res.Commun.. 288. 1149-1154 (2001)

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[Publications] Harada, S., et al.: "Effects of ELF high magnetic fields on enzyme-catalyzed DNA and RNA synthesis in vitro and on a cell-free DNA mismatch repair"Bioelectromagnetics. 22. 260-266 (2001)

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