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Sponsor: New York University School of Medicine
Dates: August 1, 2014 to July 31, 2015
Amount: \$70,412

Targeting RAGE-mDia1 in Diabetic Complications: Mechanisms and Therapeutics

Types 1 and 2 diabetes are on the rise in the United States and world-wide¹⁻³. The long-term consequences of diabetes ensue from the direct and indirect effects of hyperglycemia. Diabetes attacks the macro- and microvasculature and is well-established as a leading cause of heart attacks and stroke, blindness, renal failure, amputations, and peripheral neuropathies. The strong epidemiological links between diabetes and Alzheimer's disease raise the possibility that devastating loss of quality and duration of life in the form of irreversible chronic disease often accompany diabetes. Despite significant advances in the treatment of hyperglycemia, definitive means to prevent these most common forms of diabetes are not yet on the immediate horizon. Indeed, rigorous control of hyperglycemia, particularly in older individuals, may be fraught with significant sequelae, such as striking hypoglycemia, seizures, and cardiac ischemia and death⁴⁻⁶.

The products of nonenzymatic glycation and oxidation of proteins and lipids, the advanced glycation endproducts (AGEs), form and accumulate to accelerated degrees in hyperglycemia⁷. AGEs may be detected in the plasma, urine, skin and other tissues of diabetic subjects and their presence has been linked to the development of complications of diabetes. AGEs impart their effects both by non-receptor mediated mechanisms, such as by cross-linking of the body's proteins, particularly those that are long-lived such as in basement membranes. AGEs also exert their effects by receptor-dependent mechanisms; the chief receptor for AGE is the receptor for AGE or RAGE. Extensive evidence reveals that expression of RAGE, a member of the immunoglobulin superfamily of cell surface molecules, is increased in animal model and human diabetic tissues, such as in the macro- and microvascular tissues. RAGE is a multi-ligand receptor and the finding that RAGE binds at least certain members of the pro-inflammatory S100/calgranulin family and high mobility group box 1 (HMGB1) indicated that inflammatory mechanisms contribute integrally to the pathogenesis of complications. Indeed, non-AGE RAGE ligands also accumulate in human and animal model diabetic tissues⁸⁻⁹. Once thought highly unlikely, the role of inflammation in at least certain forms/stages of diabetic complications is now widely appreciated.

Pharmacological and genetic approaches by multiple laboratories, working independently, have provided very strong support for roles for RAGE in the pathogenesis of diabetic complications. For example, administration of antibodies to RAGE or soluble RAGE (the latter the extracellular ligand binding domain of RAGE) or genetic deletion of RAGE significantly reduces accelerated diabetic atherosclerosis in mice; ischemia/reperfusion injury in the diabetic hearts; pathological and functional indices of nephropathy; pathological and functional indices of neuropathy; and improves wound healing in diabetic animals⁸⁻⁹. Accumulating evidence reveals that levels of soluble RAGEs (cell surface cleaved RAGE and the endogenous secretory (splice variant)) may be biomarkers of diabetes and its complications in human subjects; levels of soluble RAGEs appear to be modulated by therapeutic interventions, thereby raising the significance of measuring these forms of circulating RAGE. It is well-appreciated that RAGE is a multi-ligand receptor and hence simply targeting the ligand families of RAGE as a therapeutic target in diabetic complications would be extraordinarily challenging, as: (1) there are multiple ligands and ligand families; many of which have been shown to be increased in human and animal model tissues. Hence, how to directly target the pathogenic ligands would be a challenge; (2) use of soluble RAGE strategies might block potential adaptive non-RAGE dependent actions of the ligands. Therefore, we strongly believe that alternative strategies are essential to bring to fruition and “full circle” the powerful evidence linking RAGE and its signaling to the understanding of diabetic complications and to the development of novel therapeutic strategies.