

RAGE-DEPENDENT MECHANISMS & MOLECULAR IMPRINTING IN THE PATHOGENESIS OF DIABETIC COMPLICATIONS

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UPREGULATION OF RECEPTOR FOR ADVANCED GLYCATION ENDPRODUCTS (RAGE) & ITS LIGANDS...

A Mechanism for Hyperglycemia-mediated Chronic Perturbation and Molecular Imprinting in Diabetes

THE FAMILY OF SIGNAL TRANSDUCING LIGANDS OF RAGE

Advanced Glycation Endproducts
(carboxymethyl (lysine) adducts)

- Diabetes, Renal Failure
- Inflammation (Myeloperoxidase Pathway)
- Oxidant Stress
- Aging

Amyloid β -peptide &
 β -sheet fibrils

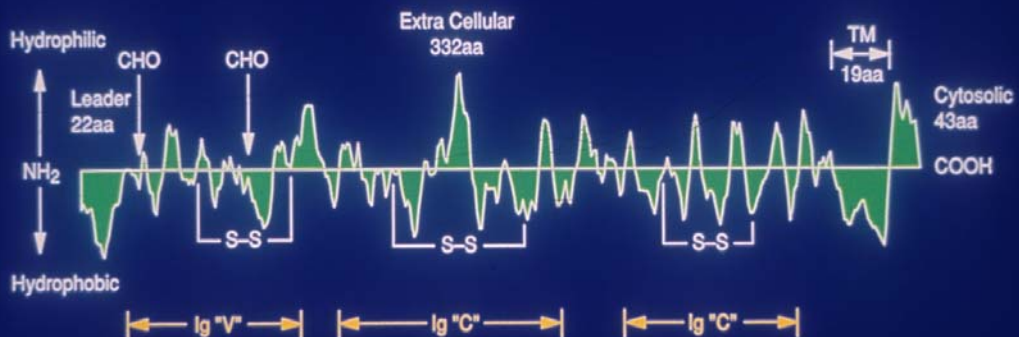
- Alzheimer's Disease
- Amyloidoses

S100/calgranulins

- Inflammation

Amphoterins

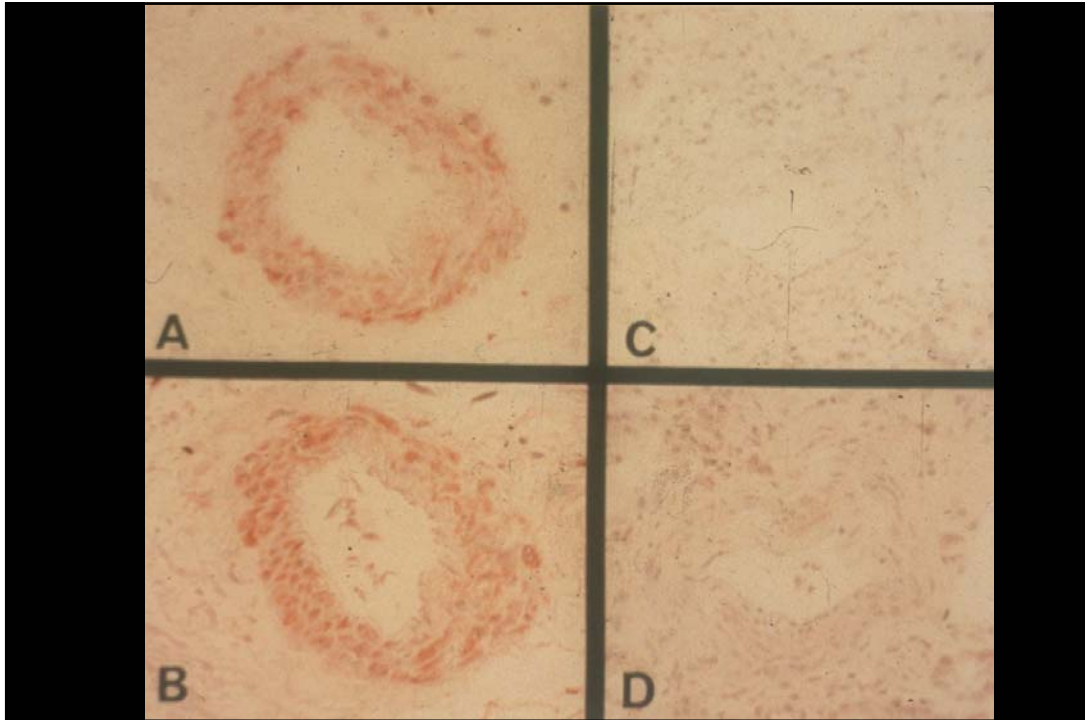
- Inflammation
- Development & Neurite Outgrowth
- Cellular Motility & Neoplasia



Ligand engagement of RAGE in endothelium, vascular smooth muscle cells, mononuclear phagocytes, lymphocytes, neurons, glomerular epithelial cells (podocytes) and transformed cells modulates cellular properties...

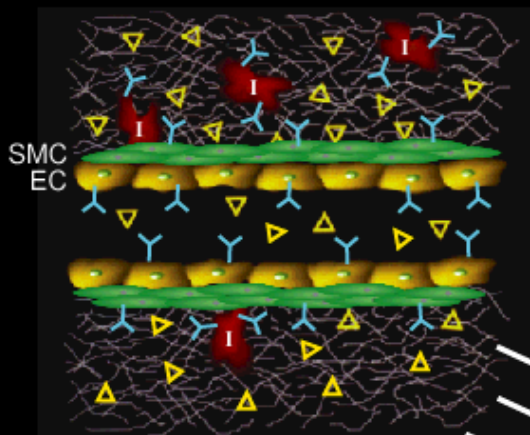
- Upregulates expression of proinflammatory and prothrombotic molecules
- Enhances cellular proliferation and migration
- Upregulates levels and activity of MMPs
- Triggers activation of distinct signalling pathways such as p44/p42, p38 and SAPK/JNK MAP kinases; JAK/STAT; NF- κ B; cdc42/rac; and PI-3 kinase

RAGE and the Vascular Complications of Diabetes



STAGE 1: Ligand - RAGE Interaction

STAGE 2: Superimposed Vascular Stress



- Modified lipoprotein accumulation (atherosclerosis)
- Injury (angioplasty)
- Hypoxia
- Ischemia / Reperfusion

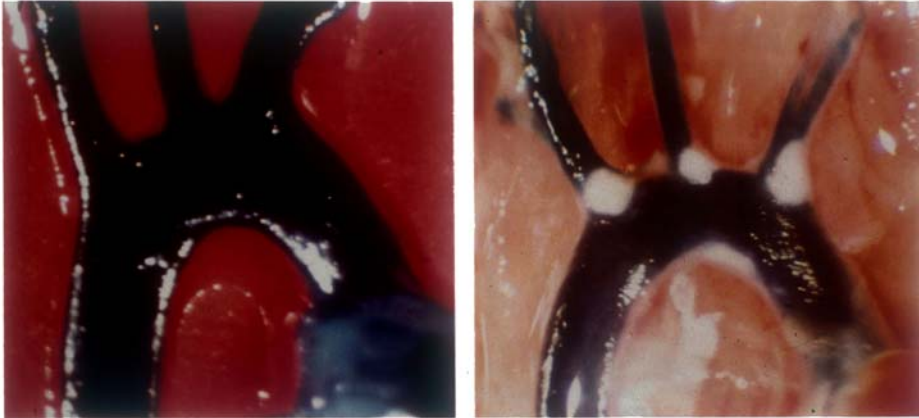
MAGNIFICATION OF VASCULAR STRESS AND DYSFUNCTION

Ligand  RAGE  Inflammatory cell 

Apo E null mice

euglycemic

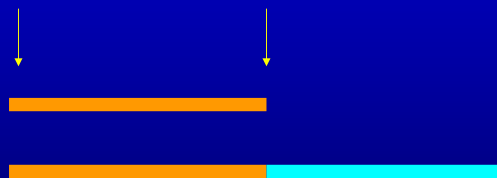
diabetic



STZ
or
Citrate
6 weeks old

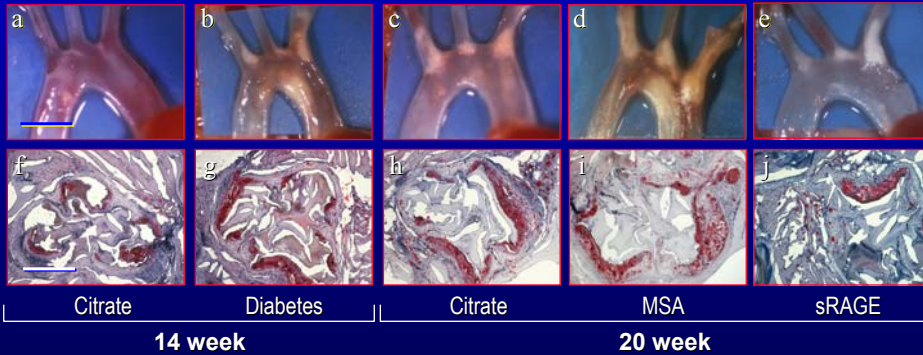
Sac Diabetic and
Non Diabetic
14 weeks old

Sac Diabetic
and Non Diabetic
at 20 weeks

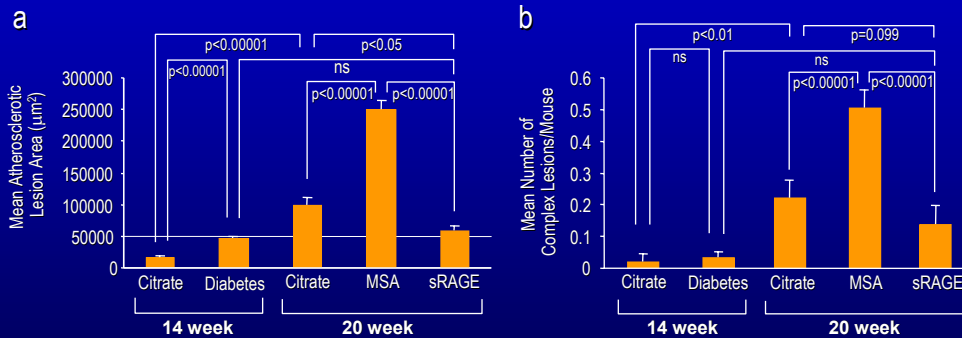


sRAGE or MSA
treatment

BLOCKADE OF RAGE STABILIZES ESTABLISHED ATHEROSCLEROSIS



BLOCKADE OF RAGE STABILIZES ESTABLISHED ATHEROSCLEROSIS



IN PARALLEL WITH DECREASED ATHEROSCLEROTIC LESION AREA AND COMPLEXITY, BLOCKADE OF RAGE IN DIABETIC MICE...

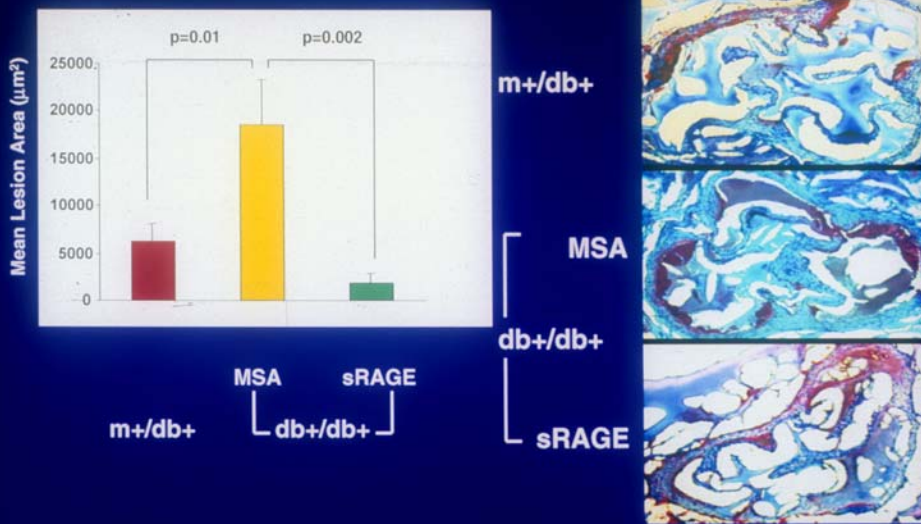
- Decreased MP & SMC migration/proliferation
- Decreased vascular expression of JE-MCP-1, VCAM-1; and antigen/activity of MMP-9
- Decreased vascular oxidant stress: decreased expression of cox-2 and nitrotyrosine epitopes
- Decreased phospho-p38 MAP kinase and activation of NF- κ B in the vasculature
- Decreased vascular expression of tissue factor

BLOCKADE OF RAGE IN DIABETIC ATHEROSCLEROSIS...

- Highlights a lipid- and glycemia-independent facet in the pathogenesis of accelerated atherosclerosis
- Hold promise for multi-target therapy in diabetic vascular disease

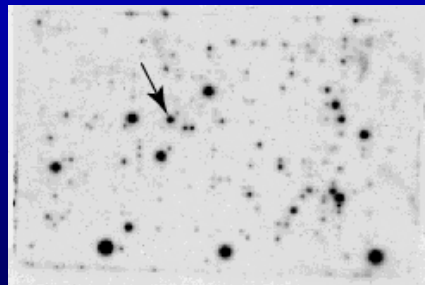
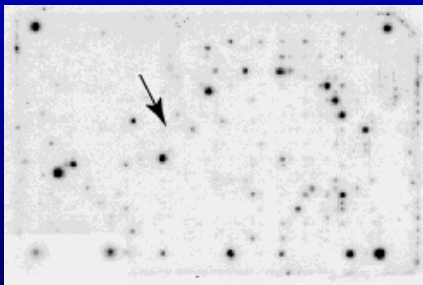
To Extend These Concepts to a Murine Model of Type 2 diabetes, Apo E null Mice were Bred into the db/db Background

Apo E Null db/db Mice Display Enhanced Atherosclerosis: Dependence on RAGE



Induction of Hypoxic Stress in Diabetic Apo E Null Mice and Modulation of Gene Expression

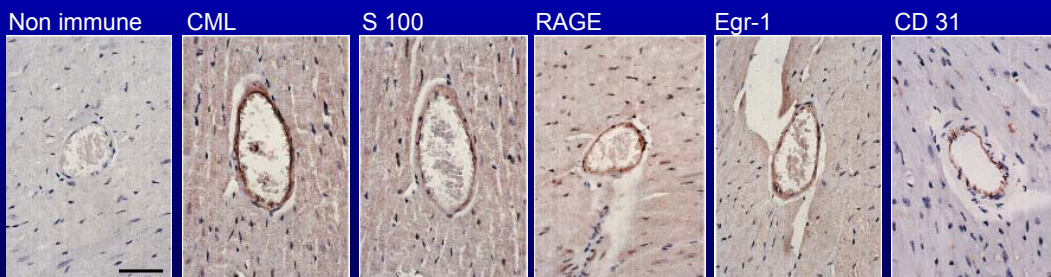
**APO E NULL DB/DB MICE DISPLAY STRIKING
UPREGULATION OF EGR-1 IN HYPOXIA:
MICROARRAY ANALYSIS OF HEART TISSUE**



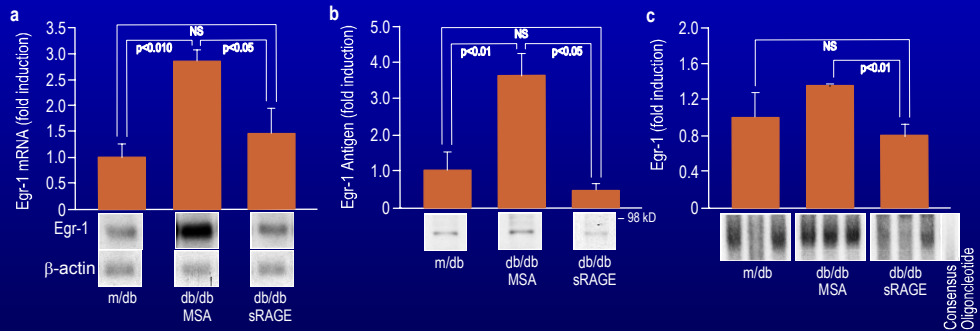
EARLY GROWTH RESPONSE (Egr-1)...

- Zinc finger transcription factor
- Homeostasis... Important role in LH transcription
(Egr-1 null mice are infertile)
- Stress...
regulates expression of a wide range of inflammatory and prothrombotic molecules in hypoxia

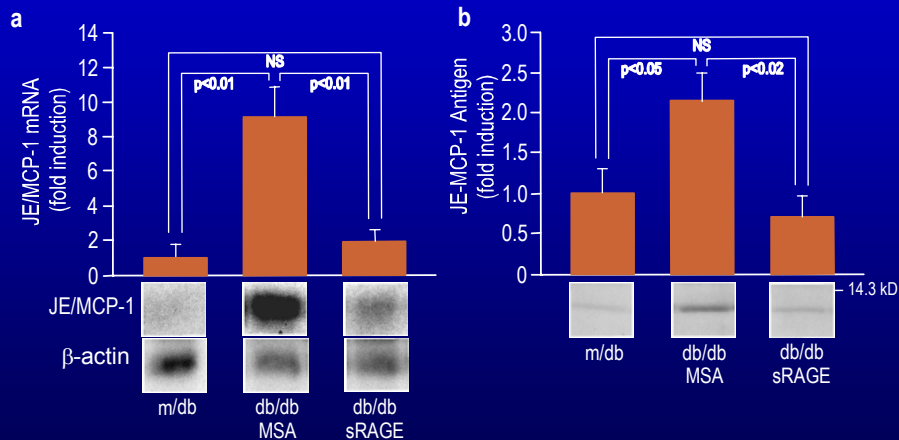
EGR-1 IS UPREGULATED IN ENDOTHELIUM IN HEARTS OF APO E NULL DB/DB MICE: ENHANCED EXPRESSION CO-LOCALIZES WITH RAGE AND CD31



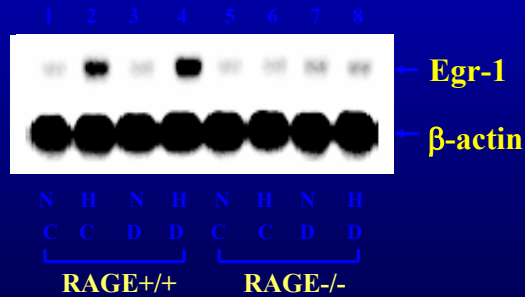
HYPOXIA UPREGULATES EGR-1 TRANSCRIPTS, ANTIGEN AND NUCLEAR TRANSLOCATION IN DIABETIC HEARTS: IMPACT OF RAGE BLOCKADE



HYPOXIA UPREGULATES JE-MCP-1, A TARGET GENE OF EGR-1: IMPACT OF RAGE BLOCKADE

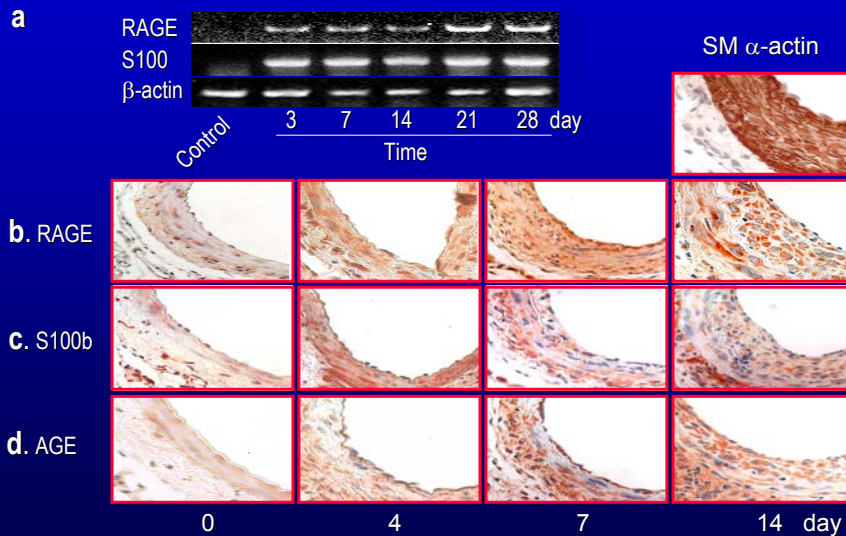


RAGE Null Mice Fail to Display Upregulation of Egr in the Heart Upon Induction of Hypoxic Stress

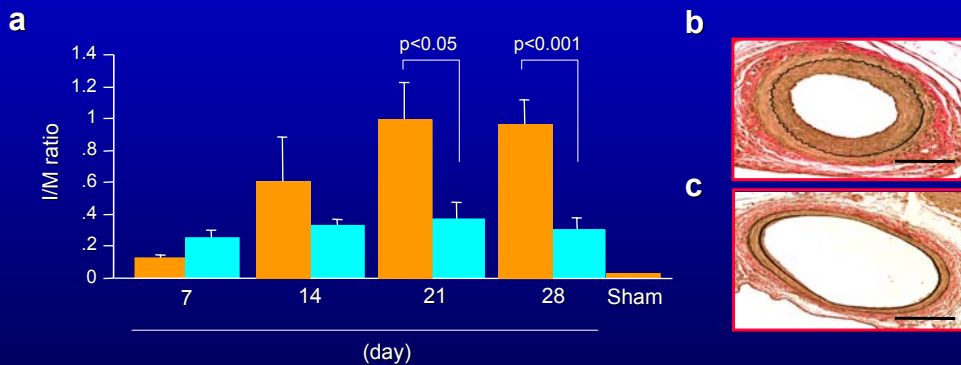


RAGE AND MECHANISMS OF VASCULAR REPAIR

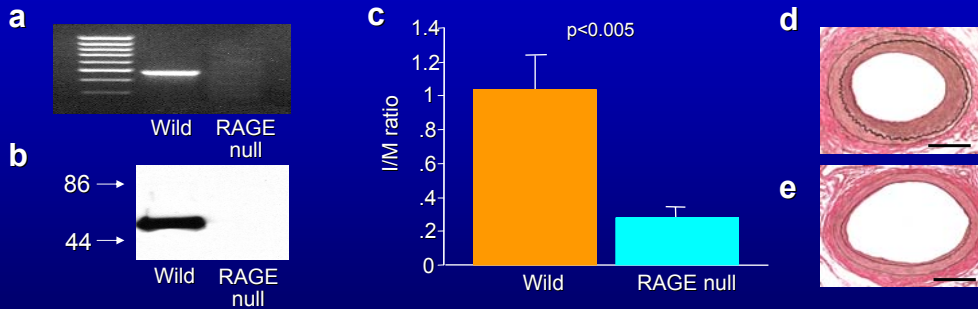
RAGE and its Ligands are Expressed in the Injured Vessel Wall



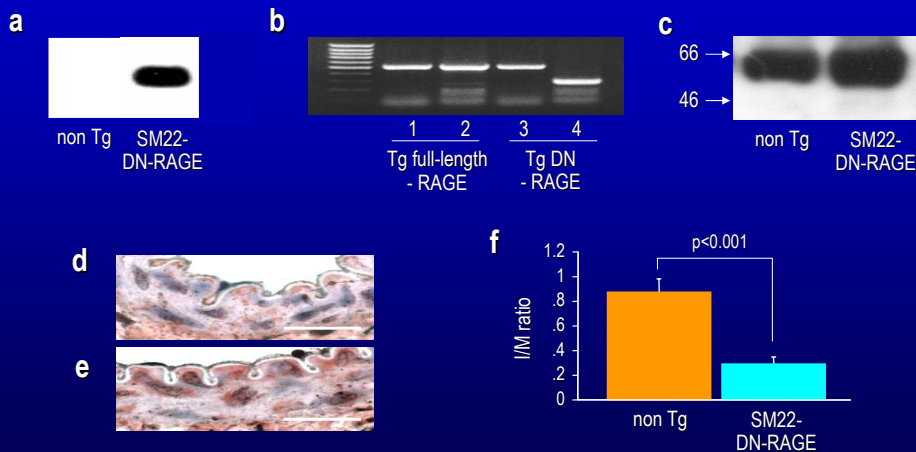
Blockade of RAGE Suppresses Exaggerated Neointimal Expansion after Arterial Injury



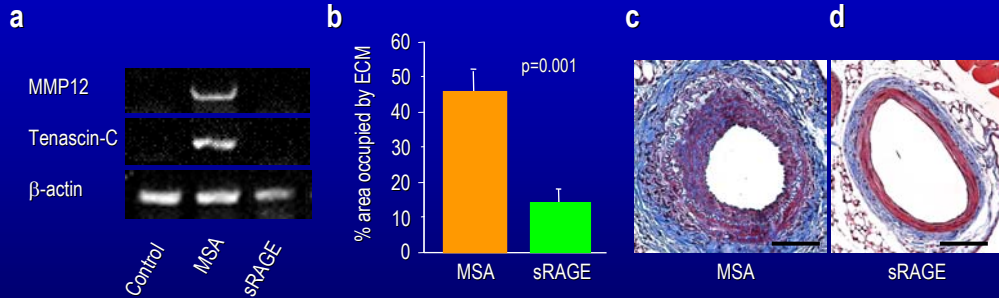
RAGE Null Mice Display Diminished Neointimal Expansion after Arterial Injury



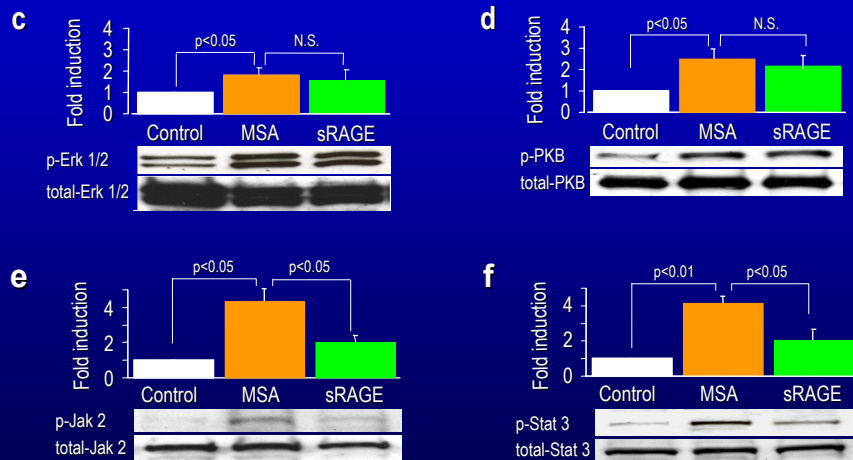
Transgenic Mice Expressing DN RAGE in SMC Display Diminished Neointimal Expansion after Arterial Injury



Blockade of RAGE Suppresses Expression of MMP12 and Tenascin-C in Arterial Injury



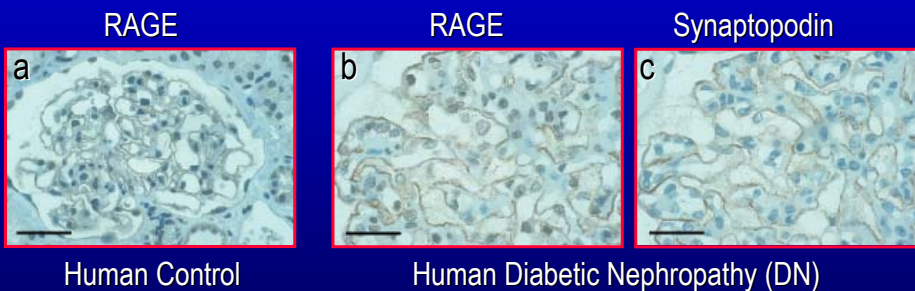
Activation of Jak2/STAT3 in the Injured Vessel Wall: Dependence on RAGE



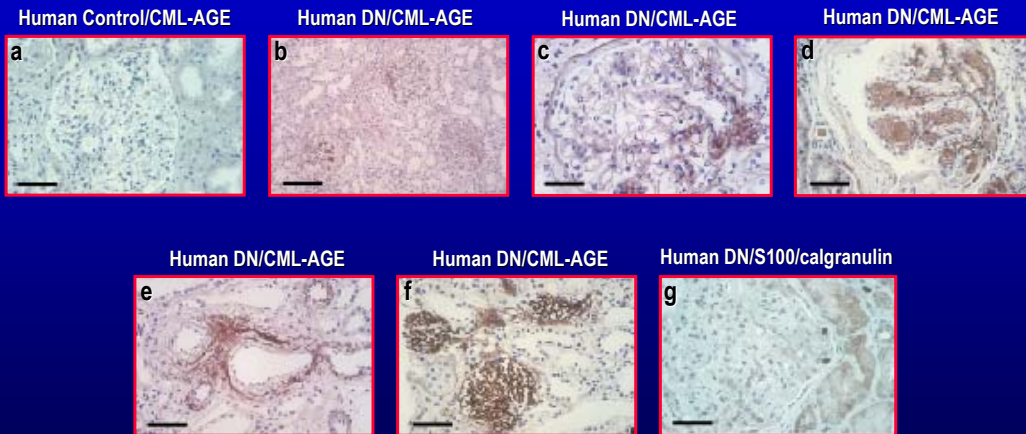
AGEs AND S100/CALGRANULINS ACCUMULATE IN DIABETIC GLOMERULI AND TUBULOINTERSTITIUM...

? Insights into Proinflammatory Mechanisms Linked to the Pathogenesis of Diabetic Nephropathy

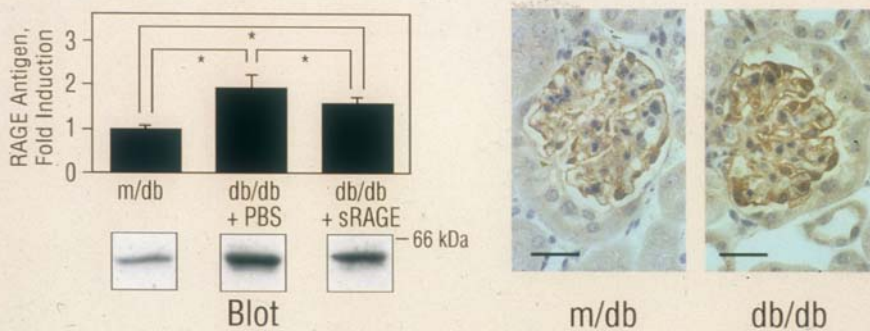
RAGE IS EXPRESSED IN PODOCYTES IN HUMAN KIDNEY: ENHANCED EXPRESSION IN DIABETES



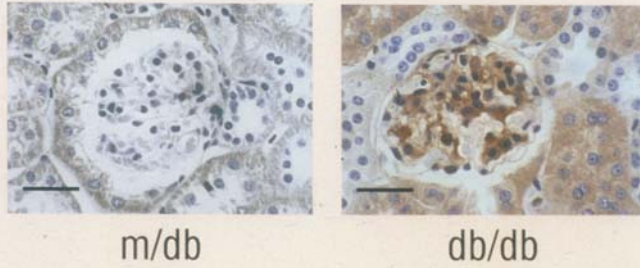
CML-AGE AND S100/CALGRANULINS: INCREASED EXPRESSION IN HUMAN DIABETIC KIDNEY



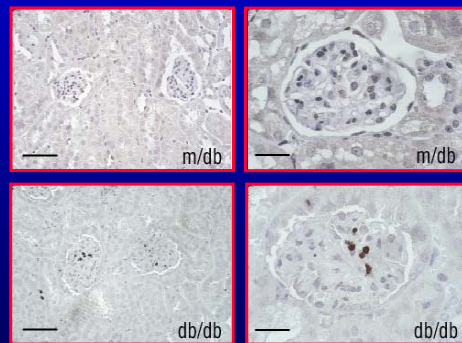
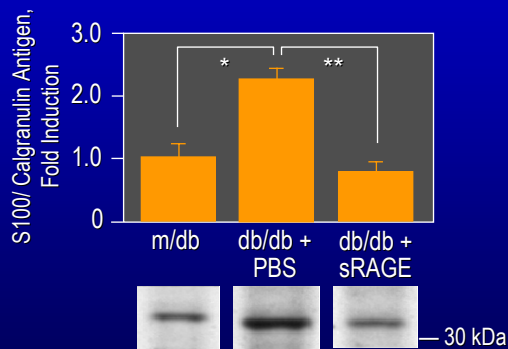
EXPRESSION OF RAGE IS INCREASED IN DIABETIC PODOCYTES IN THE db/db MOUSE KIDNEY: AGE 13 WEEKS



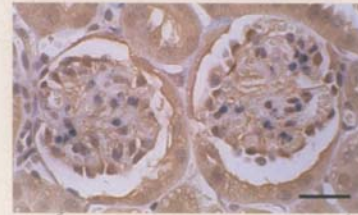
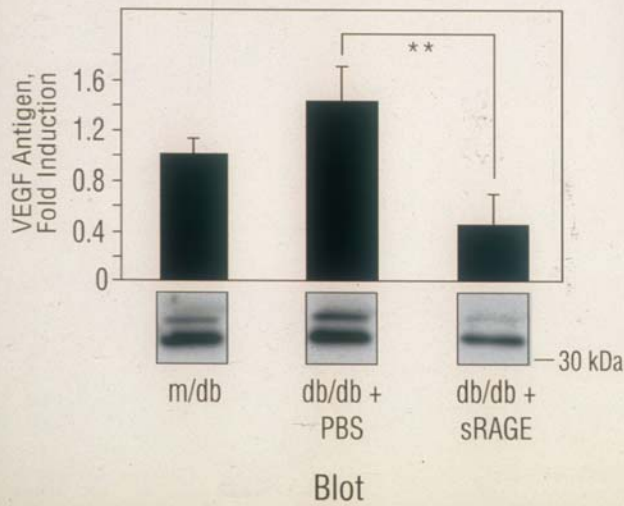
ACCUMULATION OF CML AGE EPITOPES IS INCREASED IN db/db MOUSE KIDNEY: AGE 13 WEEKS



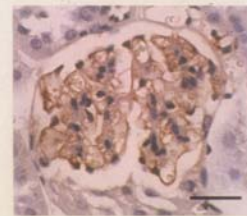
S100/CALGRANULINS: ENHANCED EXPRESSION IN db/db GLOMERULI



EXPRESSION OF VEGF IS INCREASED IN db/db MOUSE KIDNEY AND LOCALIZES TO THE PODOCYTE: AGE 13 WEEKS

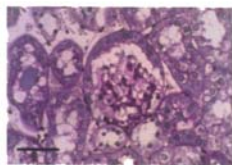
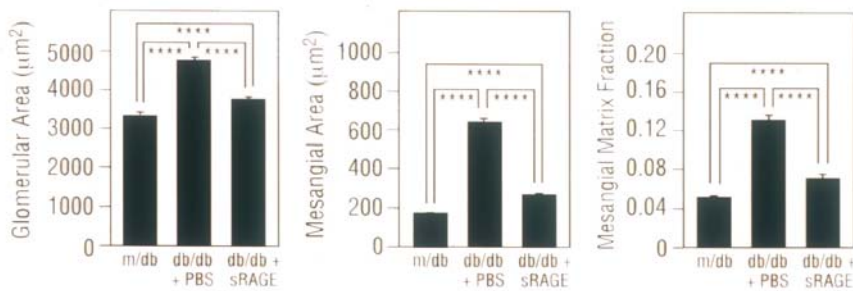


VEGF

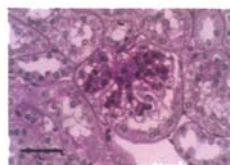


Synaptopodin

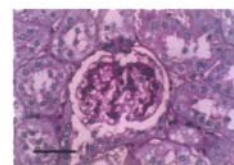
EXPANSION OF MESANGIAL MATRIX IN db/db KIDNEY AT AGE 26 WEEKS IS SUPPRESSED BY BLOCKADE OF RAGE



m/db

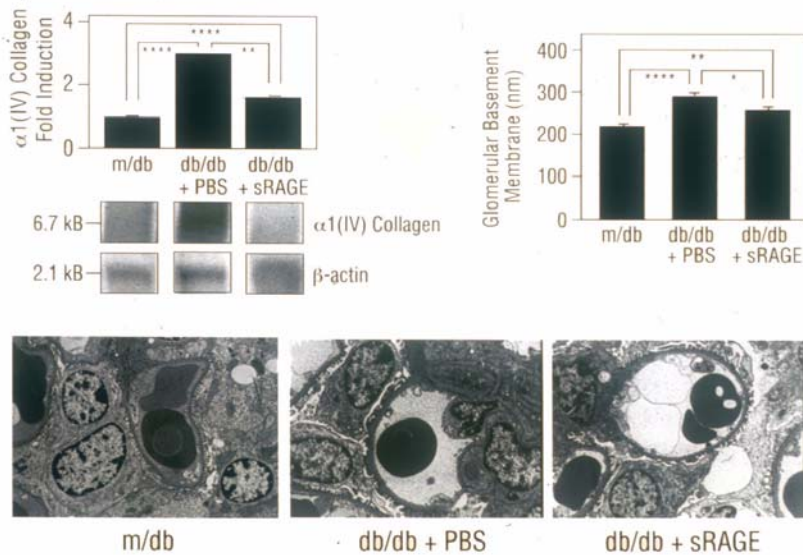


db/db + PBS

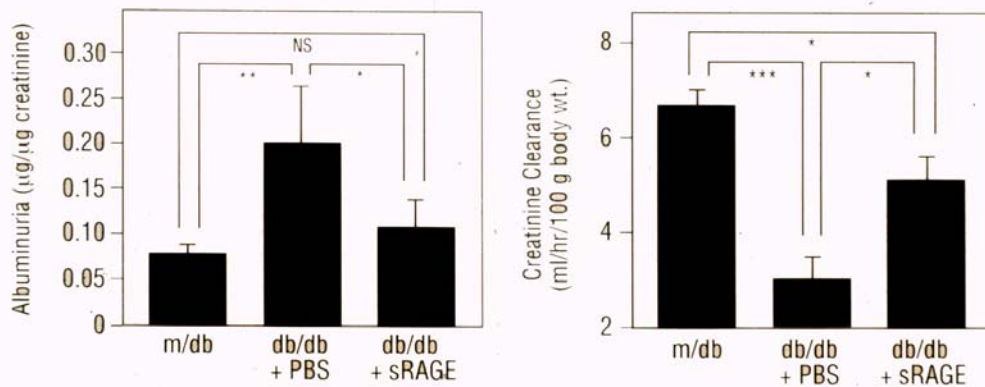


db/db + sRAGE

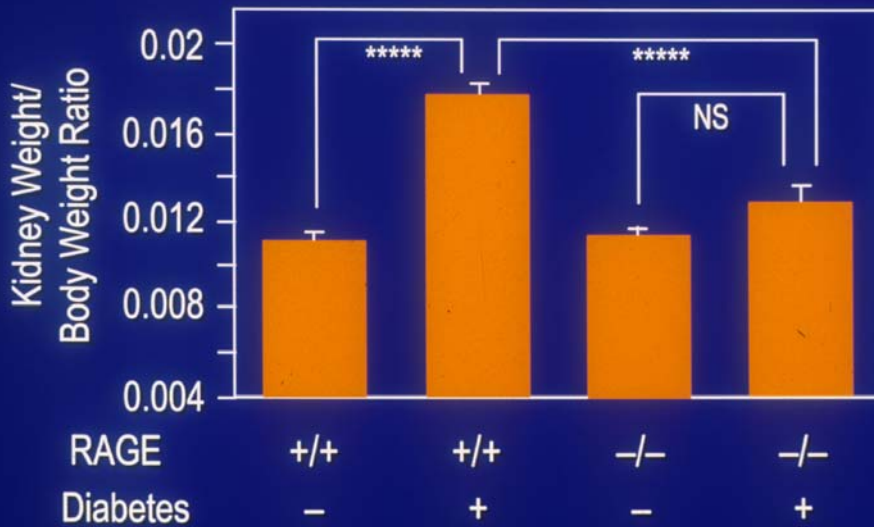
DIABETES-ASSOCIATED INCREASED EXPRESSION OF $\alpha 1(IV)$ COLLAGEN AND GBM THICKNESS IS SUPPRESSED BY BLOCKADE OF RAGE IN db/db MICE AT AGE 26 WEEKS



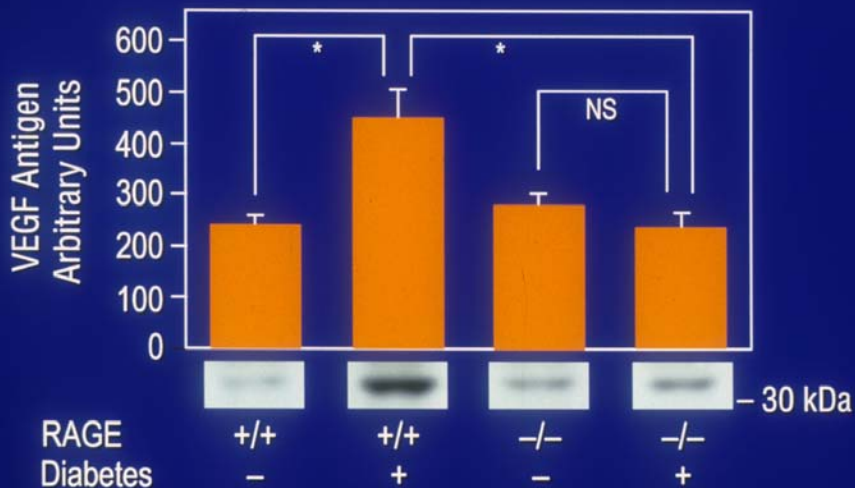
ALBUMINURIA IS DECREASED AND CREATININE CLEARANCE INCREASED IN db/db MICE BY BLOCKADE OF RAGE



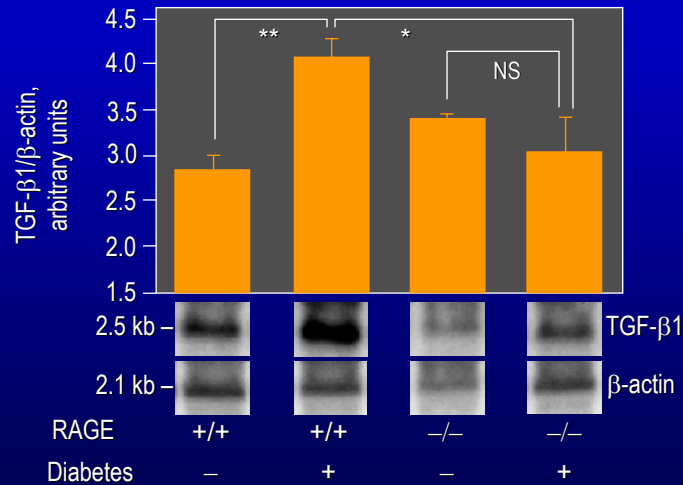
Diabetic RAGE Null Mice Do Not Display Increased Kidney/Body Weight Ratio



Diabetic RAGE Null Mice Do Not Display Increased Levels of VEGF Antigen in Renal Cortical Tissue



DIABETIC RAGE NULL MICE DO NOT DISPLAY INCREASED TRANSCRIPTS FOR TGF- β 1 IN THE RENAL CORTEX



CHRONIC UPREGULATION OF RAGE/RAGE LIGANDS IN DIABETIC TISSUE AMPLIFIES THE RESPONSE TO STRESS AND PROVIDES...

A Mechanism for Molecular Imprinting in the Pathogenesis of Diabetic Complications