Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

AGER (advanced glycosylation end product-specific receptor)

Geetha Srikrishna, Barry Hudson

Sanford-Burnham Medical Research Institute, 10901 North Torrey Pines Road, La Jolla, California 92037, USA (GS), Columbia University Medical Center, 630 West 168th St. New York, NY 10032, USA (BH)

Published in Atlas Database: June 2010

Online updated version : http://AtlasGeneticsOncology.org/Genes/AGERID594ch6p21.html
DOI: 10.4267/2042/44975

Identity

Other names: MGC22357; RAGE

HGNC (Hugo): AGER

Location: 6p21.32

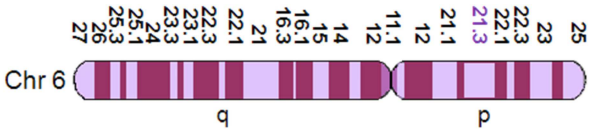

Figure 1. Schematic of human chromosome 6.

DNA/RNA

Description

The human AGER (RAGE) gene lies within the major histocompatibility complex class III region on chromosome 6, which contains genes involved in immune responses, such as TNFalpha, lymphotoxin, complement components and homeobox gene HOX12. It comprises 11 exons and 10 introns, and a 5' flanking region that regulates its transcription. The resulting transcribed mRNA of ~1.4 kb with a short 3'UTR is alternatively spliced, and nearly twenty isoforms have been identified in different tissues such as lung, liver, kidney, smooth muscle, endothelial cells and brain. The different RAGE gene splice variants have been named RAGE, RAGE_v1 to RAGE_v19 according to the Human Gene Nomenclature Committee. RAGE is composed of a number of distinct protein domains; an extracellular region (aa 1-342) composed of a signal peptide (aa 1-22), followed by three immunoglobulin-like domains, a V-type domain, (aa 23-116) and two C type domains (C1: aa 124-221 and C2: 227-317), a single transmembrane domain (aa 343-363), and a short cytoplasmic domain (aa 364-404) necessary for signaling. The prevalent isoforms of RAGE are full length RAGE, RAGE_v1 or endogenous secretory (es RAGE) which lacks the cytosolic and transmembrane domains and therefore can be secreted into the extracellular space, and N-terminal truncated RAGE (RAGE_v2) which lacks N-terminal V domain and therefore cannot bind ligands. RAGE_v2 does not form mature protein. Through its ability to scavenge RAGE ligands, soluble RAGE isoforms (sRAGE) are believed to act a decoy receptor by regulating signaling mediated by activation of full length RAGE. Expression of isoforms is tissue specific, suggesting tight tissue-specific regulation of expression. sRAGE can also be formed by ectodomain cleavage by ADAM10/MMP9.

A number of NF-kappaB sites have been identified in the RAGE 5' regulatory region. In addition, transcription is also controlled by other pro-inflammatory transcription factors such as SP-1 and AP-2.

At least 30 polymorphisms are known, most of which are single nucleotide polymorphisms (SNP). A Gly to Ser change at an N-glycosylation sequon at position 82, and two 5' flanking polymorphisms at position -374 and -429 lead to altered function and expression of RAGE.

Protein

Description

The V and C1 domains in the extracellular region of RAGE form an integrated structural unit, while C2 is fully independent, attached to VC1 through a flexible linker. RAGE was originally identified as a receptor for advanced glycation end products, but it also interacts with other structurally unrelated ligands including HMGB1, several members of the S100 family, amyloid-beta peptide, transthyretin and beta2 integrin Mac-1. By virtue of its multi-domain structure and ability to recognize different classes of ligands, RAGE behaves as a pattern recognition receptor (PRR) akin to innate immune receptors such as Toll-like receptors (TLRs) in orchestrating immune responses. However, unlike other PRRs that predominantly bind exogenous ligands, RAGE binds endogenous ligands, especially those considered to be damage associated molecular pattern molecules (DAMPs). AGEs, HMGB1, Abeta peptides, S100B, S100A1, S100A2 and S100A5 bind to the V domain, S100A12 binds to V-C1 domains, and S100A6 interacts with V-C2 domain. Studies on S100 protein-RAGE interactions also suggest that multimerization of ligand and receptor occurs and that formation of these higher ordered complexes may be essential for signal transduction. In addition to contribution by protein interaction domains, post-translational modifications such as glycosylation of the receptors, or acetylation or phosphorylation of ligands could also play important roles in defining specificity of interactions, multimerization and downstream signaling. RAGE has two N-glycosylation sites on the V-domain and both sites are occupied by complex and hybrid or high mannose N-glycans. A subpopulation is modified by carboxylated glycans, which promote interaction with HMGB1, S100A8/S100A9 and S100A12. In addition, the quaternary structure of RAGE might also account for the diversity of ligand recognition. Though the cytoplasmic domain lacks endogenous kinase activity or any other known signaling motif, studies indicate that the cytoplasmic domain is essential for intracellular signaling.

Expression

RAGE is highly expressed during embryonic development, especially in the brain, but levels decrease in adult tissues. RAGE is found at low levels in neurons, endothelial cells, mononuclear phagocytes, smooth muscle cells, and constitutively expressed at high levels in the lung.

Localisation

- Full length: membrane: single pass type I membrane protein.
- Isoforms: secreted.

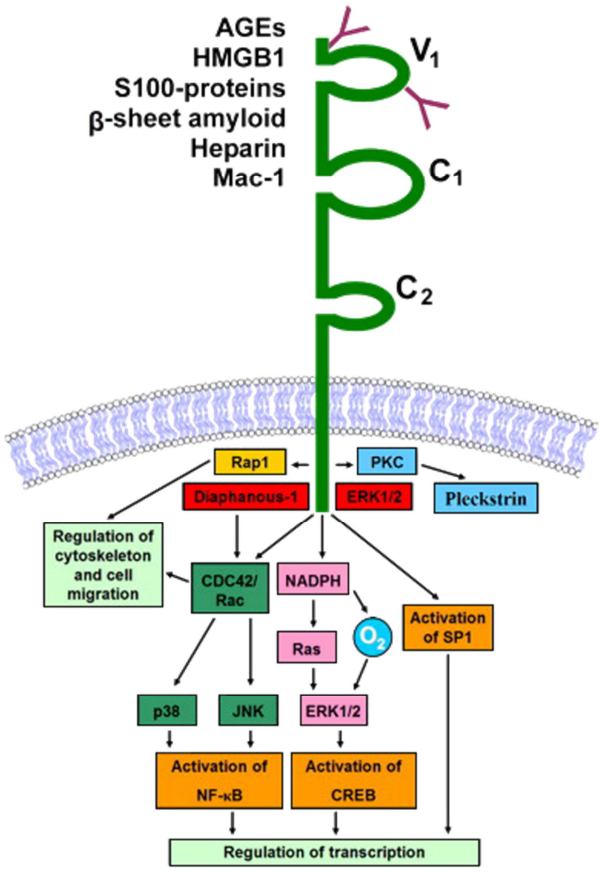

Figure 2. Schematic of RAGE protein and its domains. RAGE is a multi-ligand receptor consisting of three Ig-domains (V, C1 and C2), a transmembrane domain and a cytosolic tail required for RAGE-mediated intracellular signaling. The V and C1 domains in the extracellular region of RAGE form an integrated structural unit, while C2 is fully independent, attached to VC1 through a flexible linker. Many ligands bind to the V domain, while some also interact with the V-C1 or V-C2 domains. The V domain has N-glycosylation sites both of which are modified. Ligand binding activates multiple signaling pathways and regulates gene expression through the transcription factors NF-kappaB, CREB and SP1 (From Rauvala H, Rouhiainen A. Biochim Biophys Acta. 2010 Jan-Feb;1799(1-2):164-70. Reproduced with permission from publishers).

Function

Normal physiological functions of RAGE include embryonal neuronal growth, myogenesis, mobilization of dendritic cells, activation and differentiation of T cells, stem cell migration and osteoclast maturation. HMGB1 interaction of RAGE results in stimulation of myogenesis. RAGE mediates trophic and toxic effects of S100B on embryonal neurons, and promotes neurite outgrowth and neuronal regeneration promoted by HMGB1. RAGE also plays an important role in the regulation of osteoclast maturation and function, and bone remodeling.

Ligand interaction promotes activation of intracellular signaling pathways including the MAPK pathway, RAC-1 and CDC42, NADPH oxidase, PI3 kinase and

JAK/STAT pathway, and activation of NF-kappaB. RAGE expression is induced in inflammatory settings, since its transcription is controlled by several transcription factors as mentioned above. Thus a positive feed-forward loop evolves in ligand rich inflammatory settings, perpetuating the pathology. sRAGE is believed to regulate signaling mediated by activation of full length RAGE. Binding of RAGE to HMGB1 induces RAGE shedding by ADAM10 metalloprotease, thus possibly representing another pathway for negatively regulating RAGE mediated cellular activation.

Implicated in

Gastric cancer

Note

RAGE is constitutively expressed in human gastric carcinoma cell lines, and poorly differentiated human gastric carcinomas preferentially express RAGE. Strong RAGE expression is seen in cells at the invasive edge of tumors and correlates with invasion and lymph node metastasis. Studies in Chinese population show that Gly82Ser polymorphism on RAGE is associated with increased risk for gastric cancer.

Colon cancer

Note

RAGE expression is increased in advanced colon tumors. Co-expression of RAGE and its ligands HMGB1 and S100P is strongly associated with invasion and metastasis of human colorectal cancer. RAGE appears to be at the interface of inflammation and colon cancer, since RAGE deficient mice are resistant to the onset of colitis associated colon cancer.

Pancreatic cancer

Note

Expression of RAGE is strongest in pancreatic cancer cells with high metastatic ability, and RAGE may play an important role in the viability of pancreatic tumor cells against stress-induced apoptosis. RAGE ligand S100P is overexpressed in pancreatic cancer.

Prostate cancer

Note

RAGE and ligands are highly expressed on prostate cancer cell lines, untreated prostate cancer tissue and hormone-refractory prostate cancer tissue, and RAGE promotes growth and invasion of prostate cancer cells in response to ligand activation.

Oral squamous cell cancer

Note

RAGE expression closely associates with histologic differentiation, invasiveness, angiogenesis and recurrence of oral squamous cell carcinoma.

Common bile duct cancer

Note

RAGE is expressed on human biliary cancer cells, and expression correlates with their invasive ability.

Glioma

Note

HMGB1/RAGE signaling pathways promote the growth and migration of human glioblastoma cells. Inhibition of RAGE-HMGB1 interactions decreases growth and metastases of gliomas in mice.

Skin cancer

Note

RAGE is expressed in human melanoma cells and promotes ligand-dependent growth and invasion. RAGE null mice are resistant to the onset of inflammation mediated skin tumors in mice.

Lung cancer

Note

RAGE, as well as its ligands, is highly expressed in normal lung, but unlike other cancers, RAGE is markedly reduced in human lung carcinomas. Down-regulation correlates with advanced tumor stages, suggesting that RAGE may have tumor suppressive functions in lung cancer.

Tumor microenvironment

Note

Many RAGE ligands are expressed and secreted not only by cancer cells but also by cells within the tumor microenvironment, including myeloid derived cells and vascular cells. These ligands interact with the receptor in both autocrine and paracrine manners, promoting tumor growth, invasion, angiogenesis and metastasis.

Inflammation and immune responses

Note

RAGE and its ligands are highly enriched in immune and inflammatory foci and their interaction promotes upregulation of inflammatory cytokines, adhesion molecules and matrix metalloproteinases. They are therefore implicated in many inflammatory conditions including colitis and arthritis. RAGE is upregulated in synovial tissue macrophages and its ligands are abundant in inflamed synovial tissue. Activation leads to increased stimulation of chondrocytes and synoviocytes, promoting ongoing inflammation and autoimmunity in arthritis. RAGE mediates HMGB1 activation of dendritic cells in response to DNA containing immune complexes, contributing to autoimmune pathogenesis. Blockade of RAGE interactions suppresses myelin basic protein induced experimental autoimmune encephalomyelitis. Inhibition of RAGE-ligand interactions or RAGE deletion protects mice from septic shock induced by

caecal ligation and puncture. RAGE null mice are also resistant to skin and colon inflammation and inflammation-based tumorigenesis.

Diabetes

Note

RAGE, as a receptor for advanced glycation end products and other pro-inflammatory ligands, contributes to micro and macrovascular changes in diabetes. RAGE over-expression in transgenic mice is associated with increased vascular injury, diabetic nephropathy and neuropathy, while RAGE deletion confers partial protection from these diabetes-associated changes.

Atherosclerosis and ischemia

Note

Increased RAGE expression is found in endothelial cells in non-diabetic patients with peripheral occlusive vascular disease. sRAGE reduces atherosclerotic lesions and inflammation in normoglycemic Apo E null mice, and reduced neointima expansion in wild type mice following femoral artery injury. Studies on ischemia-reperfusion injury of the heart in wild type and RAGE null mice show that infarct size and severity of tissue damage is dependent on HMGB1-RAGE interactions following necrotic cell death.

Neuronal degeneration

Note

RAGE is expressed on neurons, microglia and endothelial cells in the brain, and binds the multimeric form of amyloid-beta peptide. Binding leads to activation of NADPH oxidase, generation of reactive oxygen species, activation of NF-kappaB and CREB, and upregulation of cytokines and chemokines, thus promoting neuroinflammation. The associated up-regulation and release of other RAGE ligands such as HMGB1 and S100 proteins further amplifies this cascade, leading to neuronal degeneration. sRAGE has been shown to be beneficial in animal models of Alzheimer's disease. RAGE null mice are also partially protected from diabetes-induced loss of neuronal function.

References

Bierhaus A, Humpert PM, Morcos M, Wendt T, Chavakis T, Arnold B, Stern DM, Nawroth PP. Understanding RAGE, the receptor for advanced glycation end products. J Mol Med. 2005 Nov;83(11):876-86

Bierhaus A, Humpert PM, Stern DM, Arnold B, Nawroth PP. Advanced glycation end product receptor-mediated cellular dysfunction. Ann N Y Acad Sci. 2005 Jun;1043:676-80

Ding Q, Keller JN. Splice variants of the receptor for advanced glycosylation end products (RAGE) in human brain. Neurosci Lett. 2005 Jan 3;373(1):67-72

Andrassy M, Igwe J, Autschbach F, Volz C, Remppis A, Neurath MF, Schleicher E, Humpert PM, Wendt T, Liliensiek B, Morcos M, Schiekofer S, Thiele K, Chen J, Kientsch-Engel R, Schmidt AM, Stremmel W, Stern DM, Katus HA, Nawroth PP, Bierhaus A. Posttranslationally modified proteins as mediators of sustained intestinal inflammation. Am J Pathol. 2006 Oct;169(4):1223-37

Bierhaus A, Stern DM, Nawroth PP. RAGE in inflammation: a new therapeutic target? Curr Opin Investig Drugs. 2006 Nov;7(11):985-91

Zhou Z, Immel D, Xi CX, Bierhaus A, Feng X, Mei L, Nawroth P, Stern DM, Xiong WC. Regulation of osteoclast function and bone mass by RAGE. J Exp Med. 2006 Apr 17;203(4):1067-80

Dattilo BM, Fritz G, Leclerc E, Kooi CW, Heizmann CW, Chazin WJ. The extracellular region of the receptor for advanced glycation end products is composed of two independent structural units. Biochemistry. 2007 Jun 12;46(23):6957-70

Donato R. RAGE: a single receptor for several ligands and different cellular responses: the case of certain S100 proteins. Curr Mol Med. 2007 Dec;7(8):711-24

Leclerc E, Fritz G, Weibel M, Heizmann CW, Galichet A. S100B and S100A6 differentially modulate cell survival by interacting with distinct RAGE (receptor for advanced glycation end products) immunoglobulin domains. J Biol Chem. 2007 Oct 26;282(43):31317-31

Logsdon CD, Fuentes MK, Huang EH, Arumugam T. RAGE and RAGE ligands in cancer. Curr Mol Med. 2007 Dec;7(8):777-89

Ostendorp T, Leclerc E, Galichet A, Koch M, Demling N, Weigle B, Heizmann CW, Kroneck PM, Fritz G. Structural and functional insights into RAGE activation by multimeric S100B. EMBO J. 2007 Aug 22;26(16):3868-78

Xie J, Burz DS, He W, Bronstein IB, Lednev I, Shekhtman A. Hexameric calgranulin C (S100A12) binds to the receptor for advanced glycated end products (RAGE) using symmetric hydrophobic target-binding patches. J Biol Chem. 2007 Feb 9;282(6):4218-31

Gebhardt C, Riehl A, Durchdewald M, Németh J, Fürstenberger G, Müller-Decker K, Enk A, Arnold B, Bierhaus A, Nawroth PP, Hess J, Angel P. RAGE signaling sustains inflammation and promotes tumor development. J Exp Med. 2008 Feb 18;205(2):275-85

Hudson BI, Carter AM, Harja E, Kalea AZ, Arriero M, Yang H, Grant PJ, Schmidt AM. Identification, classification, and expression of RAGE gene splice variants. FASEB J. 2008 May;22(5):1572-80

Turovskaya O, Foell D, Sinha P, Vogl T, Newlin R, Nayak J, Nguyen M, Olsson A, Nawroth PP, Bierhaus A, Varki N, Kronenberg M, Freeze HH, Srikrishna G. RAGE, carboxylated glycans and S100A8/A9 play essential roles in colitis-associated carcinogenesis. Carcinogenesis. 2008 Oct;29(10):2035-43

Xie J, Reverdatto S, Frolov A, Hoffmann R, Burz DS, Shekhtman A. Structural basis for pattern recognition by the receptor for advanced glycation end products (RAGE). J Biol Chem. 2008 Oct 3;283(40):27255-69

Bierhaus A, Nawroth PP. Multiple levels of regulation determine the role of the receptor for AGE (RAGE) as common soil in inflammation, immune responses and diabetes mellitus and its complications. Diabetologia. 2009 Nov;52(11):2251-63

Kalea AZ, Schmidt AM, Hudson BI. RAGE: a novel biological and genetic marker for vascular disease. Clin Sci (Lond). 2009 Apr;116(8):621-37

Leclerc E, Fritz G, Vetter SW, Heizmann CW. Binding of S100 proteins to RAGE: an update. Biochim Biophys Acta. 2009 Jun;1793(6):993-1007

Lin L, Park S, Lakatta EG. RAGE signaling in inflammation and arterial aging. Front Biosci. 2009 Jan 1;14:1403-13

Maillard-Lefebvre H, Boulanger E, Daroux M, Gaxatte C, Hudson BI, Lambert M. Soluble receptor for advanced glycation end products: a new biomarker in diagnosis and prognosis of chronic inflammatory diseases. Rheumatology (Oxford). 2009 Oct;48(10):1190-6

Ramasamy R, Yan SF, Schmidt AM. RAGE: therapeutic target and biomarker of the inflammatory response--the evidence mounts. J Leukoc Biol. 2009 Sep;86(3):505-12

Riehl A, Németh J, Angel P, Hess J. The receptor RAGE: Bridging inflammation and cancer. Cell Commun Signal. 2009 May 8;7:12

Schmidt AM, Sahagan B, Nelson RB, Selmer J, Rothlein R, Bell JM. The role of RAGE in amyloid-beta peptide-mediated pathology in Alzheimer's disease. Curr Opin Investig Drugs. 2009 Jul;10(7):672-80

Sparvero LJ, Asafu-Adjei D, Kang R, Tang D, Amin N, Im J, Rutledge R, Lin B, Amoscato AA, Zeh HJ, Lotze MT. RAGE (Receptor for Advanced Glycation Endproducts), RAGE ligands, and their role in cancer and inflammation. J Transl Med. 2009 Mar 17;7:17

Srikrishna G, Freeze HH. Endogenous damage-associated molecular pattern molecules at the crossroads of inflammation and cancer. Neoplasia. 2009 Jul;11(7):615-28

Yan SD, Bierhaus A, Nawroth PP, Stern DM. RAGE and Alzheimer's disease: a progression factor for amyloid-beta-induced cellular perturbation? J Alzheimers Dis. 2009;16(4):833-43

Yan SF, Ramasamy R, Schmidt AM. Receptor for AGE (RAGE) and its ligands-cast into leading roles in diabetes and the inflammatory response. J Mol Med. 2009 Mar;87(3):235-47

Yan SF, Ramasamy R, Schmidt AM. The receptor for advanced glycation endproducts (RAGE) and cardiovascular disease. Expert Rev Mol Med. 2009 Mar 12;11:e9

Yan SF, Yan SD, Ramasamy R, Schmidt AM. Tempering the wrath of RAGE: an emerging therapeutic strategy against diabetic complications, neurodegeneration, and inflammation. Ann Med. 2009;41(6):408-22

Zhang L, Postina R, Wang Y. Ectodomain shedding of the receptor for advanced glycation end products: a novel therapeutic target for Alzheimer's disease. Cell Mol Life Sci. 2009 Dec;66(24):3923-35

Rauvala H, Rouhiainen A. Physiological and pathophysiological outcomes of the interactions of HMGB1 with cell surface receptors. Biochim Biophys Acta. 2010 Jan-Feb;1799(1-2):164-70

Rojas A, Figueroa H, Morales E. Fueling inflammation at tumor microenvironment: the role of multiligand/RAGE axis. Carcinogenesis. 2010 Mar;31(3):334-41

Sims GP, Rowe DC, Rietdijk ST, Herbst R, Coyle AJ. HMGB1 and RAGE in inflammation and cancer. Annu Rev Immunol. 2010 Mar;28:367-88

Srikrishna G, Nayak J, Weigle B, Temme A, Foell D, Hazelwood L, Olsson A, Volkmann N, Hanein D, Freeze HH. Carboxylated N-glycans on RAGE promote S100A12 binding and signaling. J Cell Biochem. 2010 Jun 1;110(3):645-59

Yan SF, Ramasamy R, Schmidt AM. Soluble RAGE: therapy and biomarker in unraveling the RAGE axis in chronic disease and aging. Biochem Pharmacol. 2010 May 15;79(10):1379-86

This article should be referenced as such:

Srikrishna G, Hudson B. AGER (advanced glycosylation end product-specific receptor). Atlas Genet Cytogenet Oncol Haematol. 2011; 15(3):239-243.