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Mini Review

AGE-RAGE System and its Application in Stem Cell Therapy

Delger Bayarsaikhan#, Govigerel Bayarsaikhan# and Bonghee Lee*

Center for Genomics and Proteomics, Lee Gil Ya Cancer and Diabetes Institute, School of Medicine, Gachon University, Incheon City, Republic of Korea

#Equal Contribution

Abstract

Functionally improved cell therapy has brought enormous benefits for patients suffering from serious illnesses. With the advances in biomedical science, numerous diseases are known for their correlation with post-translational modification of proteins, such as glycation, which leads to the formation of toxic Advanced Glycation End Products (AGEs). Themortality and morbidity rates of toxic AGE-induced diseases are continuously increasing globally. Due to growing concerns over these diseases, researchers are intensively discovering and synthesizing thousands of therapeutic molecules as scavengers for AGEs. Among them, soluble receptor for AGE (sRAGE) could beone of the promising candidates; its mode of action and efficacy has been demonstrated in hundreds of *in vitro* and *in vivo* studies. Recent progress in this field includes the generation of sRAGE secreting stem cells, showing promising efficacy in the treatment of various diseases, such as cardiovascular, metabolic, and neurodegenerative disorders.

Keywords: AGE; Disease; Gene therapy; sRAGE; Stem cell

Introduction

The translation of stem cells is showing their therapeutic strength for a wide range of intractable and chronic diseases in both clinical and academic studies [1]. However, the efficiency of stem cells relies on cell survivability *in vivo*, and current genome editing technologies have enabled the production of functionally improved cell lines that secrete not only biologically active growth factors, cytokines, or unstable therapeutic molecules owing to their short half-life, but are also able to demonstrate high homing and survivability due to their genetic alterations, such as artificial matching of human leukocyte antigens between donor and recipients [2].

One example of a gene-edited cell line isthe soluble receptor for advanced glycation end product (sRAGE) secreting stem cells, and much attention is paid to the remedial role of sRAGE molecules in advanced glycation end product (AGE)-associated disorders [3-6]. The advantages of sRAGE secretion by stem cells can be explained by the instability of the molecule itself; their combination with stem cells is among the best alternatives for their continuous generation *in vivo*. At the same time, sRAGE is known to compete for RAGE, the main receptor for AGEs, and it has been shown that their interaction contributes to cell apoptosis, as discussed in this review.

Gene silencing or knockout enables understanding of the role of a specific gene and associated mechanisms in certain disease conditions. To reveal the role of RAGE signaling in AGE-dependent disorders, RAGE knockout cell lines and transgenic animals have been intensively studied [7-10]. Consequently, it has been found that AGEs and their interaction with RAGE are implicated in the pathophysiology of a variety of diseases. However, there is no comprehensive explanation for the mechanism underlying the cell damage caused by AGE-RAGE interaction due to the diversity of AGEs, but it is definite that AGEs bind to the RAGEs locatedon the cell surface and corresponding signaling leads to cell death [11,12]. Furthermore, AGE-RAGE stress-induced complications have been reported for a wide range of diseases, including neurodegenerative disorders such as alcoholic brain damage, Parkinson's and Alzheimer's diseases, cardiovascular diseases, secondary complications of damaged hepatocytes, some pulmonary diseases, and diabetes-related complications through macrophage activation [13]. On the other hand, it has been reported that compared to RAGE-knockout animals, wild type animals are more susceptible to these AGE-associated diseases, including acute inflammation and cancers caused by exogenous stimuli [14].

Recent studies have demonstrated that alternative therapeutic strategies for patients with AGE-associated diseases involve AGE-RAGE signaling inhibitors that include synthetic chemical drugs or bioactive natural compounds capable of destroying harmful pathological molecules induced by immune responses during AGE-RAGE interaction [15]. In contrast to drugs, the administration of sRAGE into animal models generated for AGE-related diseases has been shown to obstruct the cellular AGE-RAGE interaction by competing with RAGE and contribute to disease suppression and precluding cell death [16].

Principally, the current biomedical applications of sRAGE are divided into two major groups: therapeutic agents and potent biomarkers for AGE-linked diseases. Thus, we aimed to investigate the potential application and current progress of sRAGE secreting stem cells in AGE-associated diseases. Furthermore, the circulating

***Corresponding author:** Bonghee Lee, Center for Genomics and Proteomics, Lee Gil Ya Cancer and Diabetes Institute, Gachon University, Incheon 21999, Republic of Korea, Tel: +82 328996582; Fax: +82 328996519, E-mail: bhlee@gachon.ac.kr

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level of sRAGE is liable to unpredictable variation depending on the type or progress of disease focalization; it may increase or decrease in different pathological states, as discussed below. Therefore, this article was designed to describe whether the effectiveness of sRAGE secreting stem cell therapy is dependent on the underlying role of sRAGE in different pathologic processes.

Biomarker Potential of sRAGE in AGE-linked Disorders

sRAGE is implicated in various biochemical reactions *in vivo* not only during regular metabolic processes but also in AGE-associated pathological conditions. For example, these molecules have anti-inflammatory and antioxidant properties and thus are known for their important regulatory and protective rolesin the maintenance of homeostasis within the cell and body of living organisms [17]. Based on the AGE scavenging activity of circulating sRAGE, numerous human and animal studies have measured sRAGE levels in biological samples. However, the results demonstrated that making a comprehensive conclusion on their biomarker potential in diseases caused by toxic AGEs is complicated for several reasons. One of the main reasons can be their widely diverse structures and properties, and along with these dissimilarities, organisms respond to them via distinctive pathways. Thus, scientific arguments are stillbeing conferred among researchers, and it is shown that considering the low level of sRAGE as a universal biomarker for AGE-associated disease is unconvinced. Additionally, sRAGE levels may be exaggerated by confounding factors, such as smoking and exacerbation [18]. Nevertheless, recent studies have demonstrated promising alternative indicators, including a strong correlation between disease risk and elevated AGEs/sRAGE ratio [19,20].

Probably, the up and down changes of sRAGE level during the AGE-induced pathogenic process is showing their disease specific - distinctive role not only depending on the generation of AGEs. For example, as shown in table 1, the level of advanced glycation end products of albumin was typically increased with the development of chronic diseases, and there was no conjoint pattern found for sRAGE circulating in human blood. The literature shows that compared to healthy subjects, the patients showed increased levels of sRAGE in lung consolidation, diabetes mellitus, multiple myeloma, ST-segment elevation myocardial infarction, kidney diseases and transplantations, trauma, and chronic heart failure. At the same time, it was decreased in various respiratory and dermatological disorders, cardiovascular diseases, metabolic disorders, and autoimmune disorders (Table 1). This implies that considering sRAGE as a universal biomarker for all AGE-associated diseases is a controversial issue as it cannot demonstrate a comparable pattern even in a single organ system. However, it should be noted that such differences are caused by variations in external and internal factors, such as disease stage, sampling method, subject's lifestyle, the specificity of applied analytical methods, and ethnic or gender differences.

Disease	Sample	sRAGE level, ng/mL		AGE albumin level, ng/mL		Ref.
		Control	Patient	Control	Patient	
Atopic Dermatitis	serum	High	low	32.87	28.97	[21]
Lung consolidation	serum	1.13	1.58	-	-	[22]
Respiratory disease	serum	1.46	1.07	-	-	
Combined pulmonary fibrosis & emphysema	serum	-	0.59±0.29	-	-	[23]
Chronic obstructive pulmonary disease	serum	-	0.75±0.43	-	-	
Diabetes mellitus	plasma	-	1.97	-	9.3	[24]
Diabetes mellitus	plasma	-	0.2	-	21.63	[25]
Diabetes mellitus	plasma	0.85	1.25	-	-	[26]
Inflammation in Silicosis	serum	24.4	14.8	-	-	[27]
Resistant Hypertension	serum	0.00019	0.06	< 38,280	184,300	[28]
Multiple Myeloma	serum	0.94	1.68	1,520	1,400	[29]
Rheumatoid arthritis	serum	0.29	1.00	-	-	[30]
Rheumatoid arthritis	serum	1.29	0.87	-	-	[31]
Osteoarthritis	plasma	880.8	698.1	485.9	460.3	[32]
Adult-onset Still's disease	plasma	1.05	Active: 0.63; Inactive: 0.86	9,800	Active: 16,750; Inactive 7,002	[33]
Systemic lupus erythematosus	plasma	1.05	Active: 0.77; Inactive: 1.48	9,800	Active: 14,800; Inactive: 6,490	[33]
ST-segment elevation myocardial infarction (day 0)	venus blood	~17.0	~23.0	~ 240	~ 280	[34]
Non-ST - segment elevation myocardial infarction	serum	1.31	0.80	-	-	[35]
Kidney transplantation (day10)	blood	0.77	2.11	-	-	[36]
Kidney disease	plasma	0.12 (mild)	1.26 (Severe)	-	-	[37]
Low muscle mass	serum	0.87	0.76			[38]
Trauma	serum	0.75 (survived)	1.69 (non surviver)	-	-	[39]
AMI	plasma	125.68AU	72.87AU	-	-	[40]
Chronic heart failure	plasma	1.06	1.64	20.2 ± 12.0	23.7 ± 12.5	[41]
Non-alcoholic fatty liver disease	serum	1.00	1.35	-	-	[42]

Alzheimer's disease	plasma	1.39	0.58	-	-	[43]
Mild cognitive impairment	serum	1.05 ± 0.52	0.87 ± 0.35	2.71 ± 1.18 U/ml	3.54 ± 1.27 U/ml	[44]

Table 1: Recent findings for sRAGE level in human sample.

On the other hand, it has been shown that the beneficial effect of sRAGE administration to the patient is highly conditionalonthe specificity of developed diseases. In other words, if, by any chance, the increase in sRAGE disrupts the balance of the cell/tissue and supports the disease development process via an unknown pathway yet, exogenously injected sRAGE may accelerate the severity of the disease. The other drawbacks of recombinant sRAGE treatment include their limited binding ability to all family of AGEs and increased levels of RAGE due to their active counteract with AGEs competing with cellular RAGE [45]. However, compared to these limitations, their remedial mode of actions and advantages have been proven ina wide variety of AGE-associated diseases using the short-term intake of sRAGE in human and animal subjects, according to reports registered in the PubMed database.

Therapeutic Applications of sRAGE Secreting Stem Cells

The sRAGE secreting stem cells have been introduced recently, and thus far, a limited number of scientific articles have been published in peer-reviewed journals. In the beginning, researchers studied how AGEs damage stem cells during long-lasting diabetes and found that an increased level of AGEs led to decreased proliferation of endothelial progenitor cells (circulating levels dropped from 7.4 x 10^7 to 3.9 x 10^7cells/event) and that serum levels of sRAGE were significantly (3.8 vs 4.6 ng/mL) higherin young patients compared to control group [46].

In 2015, Wang and colleagues investigated the therapeutic activity of sRAGE against the high mobility group box chromosomal protein 1-induced immune response and inflammatory reactions in acute liver failure through co-injection with Mesenchymal Stem Cells (MSCs) in Sprague - Dawley rat models [47]. It was observed that appropriate expression of sRAGE could be sustained by 3x10^6 numbers of sRAGE secreting MSCs in ALF rats and that sRAGE secreted from this number of MSCs was comparable to the direct injection of 400 µg/kg of sRAGE. Furthermore, sRAGE and sRAGE secreting MSCs resulted in significant improvements in health indicators, such as enhanced liver functions, less hepatocyte necrosis, and decreased immune-inflammatory responses. In this study, the survival rate was increased by six and five times upon treatment with sRAGE and sRAGE secreting MSCs after three days. Compared to the sole injection of sRAGE, its combination with stem cells showed slightly weaker activity in severely conditioned rats. This could be related to the time taken for adjustment and homing of injected cells *in vivo*, and the result was observed only in short-term intervals. In this regard, follow-up studies for a longer period may provide valuable information.

The cellular mechanism of sRAGE has been considered to accelerate the healing of diabetic wounds. An example includes research work by Olekson and colleagues in 2016. They noted that deficiency of growth factors, such as stromal cell-derived factor -1 (SDF-1), led to slow remediation of diabetic wounds and studied the correlation of sRAGE and SDF-1 growth factor using human leukemia - 60 and mouse peripheral blood mononuclear cells designated to express the CXCR-4 receptor for SDF-1. The diabetic condition was artificially developed in cell culture media, and cellular RAGE was blocked by exogenously supplemented sRAGE to investigate its role in the secretion of therapeutically active growth factors. Through this study, it was reported that cellular response to exogenously exposed sRAGE improves the activity of exogenous growth factors, such as SDF-1, under hyperglycemic conditions [48].

Compared to other types of stem cells, knockin of sRAGE secreting gene into MSCs is superior due to several reasons including their differentiation capacity into wide range of cell types comprising the cardiovascular system, such as smooth muscle cells, cardiomyocytes, and vascular endothelial cells [49]. Additionally, various cytokines and growth factors that support cardiovascular function are secreted and synthesized by MSCs, and the therapeutic effects of MSC-derived exosomes have been shown to have cardiac repair activity [50,51]. Therefore, Son and colleagues conducted a study to determine whether the combined injection of MSCs and sRAGE protects against muscle cell death caused by AGE albumin-induced post-ischemic reperfusion injury [52]. This strategy of co-injection can be considered as the simplest way to disclose the therapeutic effects of sRAGE secreting stem cells *in vivo*, since genome engineering is highly expensive. The results demonstrated that injection of human bone marrow-derived MSCs supplemented with sRAGE enhanced the survival rate of skeletal muscle cells and decreased the incidence of secondary adverse effects of post-ischemic reperfusion injury - critical limb ischemia in mice. Additionally, the authors suggested an explanation for the protective mechanism of sRAGE against AGE albumin-induced cell death. It was proposed that post-ischemic reperfusion leads to activation of M1 macrophage cells, and these activated cells start to intensively synthesize AGEs. Subsequently, AGEs bind to the cell through their cellular receptor, RAGE, and the stress, such as oxidative stress, caused by AGE-RAGE breaks the "ground state" of cell and stimulates the cell death pathways [52,53]. Based on this explanation we may consider sRAGE as an AGE albumin trapping molecule, and it can be said that sRAGE secreting stem cellsmay be one of the promising strategies for preventing or suppressing the AGE dependent aggressive progress in any disease.

On the other hand, sRAGE secreting stem cells have been introduced for gene therapy of autoimmune diseases, such as arthritis [54]. One of the typical patterns observed among these diseases is that inflammation plays a crucial role in the pathogenesis and fate of the patients [55]. Furthermore, integration of the sRAGE gene into MSCs showed unexpected consequences in that the secretion level of pro-inflammatory molecules was decreased while expression of immunomodulatory molecules was increased when knockin the sRAGE gene into the adipose tissue-derived human MSC cell line. Additionally, sRAGE knockin led to an increased potential for stem cell migration [54]. In this study, overexpression of sRAGE by MSCs demonstrated its novelty in cell therapy against rheumatoid arthritis.

The authors suggested that the restorative mechanism of their injected cell line was interrelated to prolonged stability of cell balance maintained by sRAGE-MSCs via increasing regulatory T cells and decreasing IL-17-producing T helper (Th17) cells in IL-1RA-knockout mice. In the same year, Kikodze and colleagues summarized the role of T regulatory and TH17 cells in the pathogenesis of chronic autoimmune inflammation of joints through their review article. They proposed that inflammation in rheumatoid arthritis can be controlled by modulating the activity of regulatory T cells and secretion of pro-inflammatory IL-17, which is synthesized through Th17 cell cycle [56]. On the other hand, Th17 cells are involved in the pathogenesis of various inflammatory or autoimmune disorders and thus, discovering their suppressor molecules and cells, which synthesize and secrete regulatory cytokines in acute and chronic inflammations, will be advantageous [57].

Several studies have reported that AGEs are involved in microglial cell death and contribute to damage to the neurological system and development of disorders such as Parkinson's disease and Alzheimer's disease [58,59]. Consequently, it is reasonable to consider that sRAGE secreting stem cells should demonstrate their therapeutic effects in chronic neurodegenerative disorders, and there have been several related studies in this field. Most of these studies involved transfection of the sRAGE gene into MSCs, which can be explained by not only their multipotent features, but also their capacity to support the maintenance of neurons through the synthesis and secretion of neurotrophic exosomes and growth factors, such as vascular endothelial growth factor, glial cell-derived neurotrophic factor, and brain-derived neurotrophic factor [60].

A recent study demonstrated that *in vivo* generation of sRAGE through MSC secretion inhibits the death of neurons by suppressing the RAGE-related inflammation and accumulation of T lymphocytes. In addition, compared to wild type, sRAGE knock in MSCs have been shown to exhibit persistent survivability in amyloid beta (1-42) induced Alzheimer's rat model [61]. A similar study was conducted on Alzheimer's disease model; 5xFAD generated in mice [62]. Comparing these results, we may respond to the question - Does sRAGE secreting stem cell therapy affectthe pathogenesis of Alzheimer's disease depending on its developed pathway; however, the difference can be varied by dissimilarity between experimental conditions and other factors. In the rat model, Alzheimer's disease was generated by oxidative stress under the accumulation of amyloid beta (1-42), and these molecules are known for their lethal toxicities to the neurons as well as for accelerating the synthesis and secretion of RAGE by inducing the activation in microglial cells [63]. In the latter case, the Alzheimer disease model was typically developed using genome engineering techniques. Therefore, in transgenic animals, disease models can be generated accurately and precisely, and it is highly comparable to the results obtained from various groups of similar animals; for example, investigation of therapeutic effects of druggable molecules. In addition, the duration of disease was different between these two kinds of animals. When a disease is generated by exposure to chemicals, the therapeutic study is conducted immediately and in transgenic mice, it takes at least several weeks until the initiation of the research experiments on them. However, similar results were obtained for the therapeutic effects of umbilical cord blood driven sRAGE-MSCs against inflammation during Alzheimer's disease in 5xFAD transgenic mouse models. In other words, cell viability was increased due to sRAGE secretion by MSCs, and the secreted sRAGE showed a protective role for RAGE against RAGE ligands, such as AGEs [62].

In our recent study, we also demonstrated the potential use of sRAGE – MSCs in the treatment of Parkinson's disease [64]. The cell line was obtained using the CRISPR/Cas9 system and transplanted to PD mice after oral exposure to rotenone for one month. It was observed that such functional improvement of the MSCs resulted in protection against neuronal cell death via competing with AGEs near microglial cells during the pathogenesis of Parkinson's disease in mouse [64].

However, there are no human data regarding injection of sRAGE secreting stem cells. Animal studies have demonstrated the incredible curative effects of functionally improved stem cells (especially, sRAGE-MSCs) for the treatment of AGE-induced diseases, including cardiovascular, metabolic, and neuronal disorders. Considering the inconsistencyin circulating levels of sRAGE in various diseases, no definitive explanation can be providedfor the therapeutic effects of stem cells overexpressing sRAGE. For example, serum sRAGE level was decreased in patients with Alzheimer's disease and acute myocardial infarction, but increased in thosewith diabetes mellitus (Table 1). Though, sRAGE secreting stem cells have been proven to be beneficial in the treatment of all these diseases, as shown above. In addition, from a toxicological perspective, the safety of final yields of the therapy must be considered, and recent studies have reported the possibility of cancer-promoting activity of AGE-RAGE [53]. Thus, further studies should be performed to define safe and efficient doses of sRAGE, and in this case, the secondary effect can be avoided by a suicide gene to control the fate of the injected cells.

Conclusion

Thus far, sRAGE secreting stem cell based cell therapies have been shown their promising benefits for several disorders, including cardiovascular disorders, diabetes related obstacles, some autoimmune and neuronal complications in animal studies. The common feature of these disorders is that they are all associated with toxicity of glycated albumins, whereas changes in circulating sRAGE level during these conditions were in dynamic pattern, it was increased in some of them, while showing decreases for others, according literature data. Nevertheless, there is no comprehensive explanation for up and down changes of sRAGE during certain disorders, but it is seen that increases and decreases in sRAGE level is playing crucial role and significant correlation with fate of disease progress. In this case, exogenously adding of sRAGE into a biological system damaged by illness, which is associated with increased level of sRAGE, may bring negative outcome to the therapeutic effects of this therapy in long and short term interventions. However, the study results demonstrated that sRAGE secreting stem cells have universal therapeutic effects against the AGE - linked disorders, without depending on irregular changes of sRAGE level and showing their anti-AGE-RAGE defensive activity. The future researches should be extended to more different disorders, since AGEs are associated with variety of organ systems. Additionally, we believe that increasing the therapeutic effects of this therapy without damaging the other healthy systems and focusing on determination of safety dose for sRAGE secreted by stem cells in *in vivo*, will definitely bring the enormous benefits to the patients, suffered by AGEs.

Conflict of Interest

The authors have no conflict of interest.

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