

## Editorial

# Alternative Splicing, Selective Cell Death and Antagonistic Pairing Model of Gene Regulation

**Haiyan Zhu and Qunxing Ding\***

Department of Biological Sciences, Kent State University at East Liverpool, East Liverpool, OH, USA

**\*Corresponding author:** Qunxing Ding, Department of Biological Sciences, Kent State University at East Liverpool, East Liverpool, OH, USA**Received:** December 10, 2015; **Accepted:** December 11, 2015; **Published:** December 14, 2015

## Editorial

Alternative Splicing (AS) occurs in the majority of human genes with high tissue specificity and is an effective way to increase protein diversity [1]. Literatures indicated that more than 90% of human genes have AS isoforms [2] and the majority of AS involved in genomic evolution, physiological development and pathogenesis [3]. For example, the AS isoform Stat3 $\beta$  contributed to constitutive Stat3 activation in oncogenesis [4], and the AS isoforms could increase the sensitivity of G-protein dependent calcium channels which involved in pain control [5]. It has been proposed that the process of AS and related isoforms of a certain gene is highly involved in selective cell death such as that in neurodegenerative disorders, which is termed antagonistic pairing model [6]. Previous studies have suggested that the expression of AS isoforms were tissue specific [7,8] which indicates the specific regulation of trans-acting factors in different tissue and even different cells. Splicing is processed by a complex named spliceosome and more than 200 human genes are involved in the function of spliceosome [1,9]. Interestingly, these spliceosome related genes also have AS isoforms themselves [1]. A well-studied example is receptor for advanced glycation end products (RAGE), which is a member of immunoglobulin (Ig) super family, normally located on cytoplasm membrane, has multiple AS isoforms [7,8]. This receptor binds to multiple ligands including  $\beta$ -amyloid ( $A\beta$ ), calgranulin, high-mobility group box-1 (HMGB1) and DNA fragments to trigger immune response and inflammatory signaling pathways that associate with neurodegeneration, diabetic pathogenesis and vascular disorders [10-12]. Recent study indicated that the expression of AS isoform RAGE $\Delta$  and sRAGE $\Delta$  were even brain-region specific (different cells of same tissue). It's clear that RAGE $\Delta$  and sRAGE $\Delta$  expressed at different levels in different brain regions including hippocampus, inferior parietal, superior mid temporal gyrus and cerebellum. Such specificity indicated comprehensive roles of these AS isoforms in physiological and pathological processes especially in aging and aging associated conditions. Previously the cerebellum was regarded as a relatively neglected area in neurodegenerative brain, here for the cerebellum in Alzheimer's Disease (AD) subjects showed significant lower sRAGE $\Delta$  level than that in control subjects. Indeed, synaptic study indicated the cerebellum region in AD had different behavior from other regions like hippocampus and superior temporal gyrus [13] but increased evidence indicated the involvement of cerebellum

in neurodegeneration [14]. More importantly, the expression of RAGE $\Delta$  and sRAGE $\Delta$  were associated with pathological conditions, both of them showed lower expression levels in multiple brain regions of AD subjects compared with control subjects [6]. Certainly the decreased expression of RAGE $\Delta$  and sRAGE $\Delta$  might not be the causal factors of neuro degeneration, the tight association between AD and the expression levels of RAGE $\Delta$  and sRAGE $\Delta$  elucidated the highly involvement of RAGE $\Delta$  and sRAGE $\Delta$  during neurodegeneration in regard to the pivotal role of RAGE signaling in neurodegeneration [15,16]. Thus the question should be asked is, how does these AS isoforms involve in neurodegenerative processes?

RAGE $\Delta$  had a deletion in the intracellular domain which may significantly change the normal interaction in signal transduction [15]. sRAGE had been reported as an decoy to regulate the signal transduction of full length RAGE and may play a protective role in early stage of neurodegeneration with decreased expression in AD patients [17,18]. sRAGE was proposed to antagonize the RAGE inflammation signaling by binding to the ligands and reduce their circulating concentration [19]. Similarly, RAGE $\Delta$  may also bind ligands without delivering the signals into cytoplasm due to the deletion of 16 amino acids in intracellular domain. So the decreased expression of RAGE as well as sRAGE in AD may result in impaired regulation of RAGE signaling. The AS isoform sRAGE had a lower expression level in AD subjects and could work as another regulatory isoform to deal with RAGE signaling: binding to different ligands and/or binding to ligands in different way in extracellular space due to the deletion in C2 domain. Loss of sRAGE in AD brain might interrupt the regulatory machinery of normal RAGE signaling. We propose that AS isoforms in genes like RAGE are produced in antagonistic pairs and regulate the gene function to keep the balance, and the pairing setting might be varied in different tissues, which harmonizes its tissue specificity. The pairs of RAGE/RAGE, and sRAGE/sRAGE in this study could be explained with this hypothesis. In fact, such pairing examples could be found in many genes [20-23]. For example, p53 is a well-documented tumor suppressor gene and one of the p53 AS isoforms antagonistically regulated the function of normal p53 [24]. Synuclein  $\alpha$  (SNCA) is a protein interacting with membrane phospholipids and promote the assembling of SNARE complex [25]. It have multiple AS isoforms in human cell especially nervous cells. SNCA and its' AS isoforms are involved in the pathogenesis of Parkinson's Disease (PD) and Dementia with Lewy body. One AS isoform SNCA-126 misses exon 3, has elevated expression level in substantia nigra region in PD patients compared with control subjects. Coincidentally the expression of SNCA AS isoforms are also brain region specific [25]. These facts could fit in the antagonistic pairing model, and the pairing setting meets the yin-yang theory which can explain the balanced regulation of gene expression and protein function, interruption of such balance and regulation will result in pathogenesis. Due to the individual profiles of AS expression pattern in individual cells, the selective cell

death (such as neurons in hippocampus of AD brain and neurons in substantia nigra of PD brains) could be well explained.

## Reference

- Barbosa-Morais NL, Irimia M, Pan Q, Xiong HY, Gueroussov S, Lee LJ, et al., The evolutionary landscape of alternative splicing in vertebrate species. *Science* 2012; 21: 338: 1587-1593.
- Shakola F, Suri P, Ruggiu M. Splicing Regulation of Pro-Inflammatory Cytokines and Chemokines: At the Interface of the Neuroendocrine and Immune Systems. *Biomolecules* 2015; 5: 2073-2100.
- Athanassiou-Papaefthymiou M, Papagerakis P, Papagerakis S. Isolation and Characterization of Human Adult Epithelial Stem Cells from the Periodontal Ligament. *J Dent Res* 2015; 94: 1591-1600.
- U Bharadwaj, MM Kasembeli, TK Eckols, M Kolosov, P Lang, K Christensen, et al., Monoclonal Antibodies Specific for STAT3 $\beta$  Reveal Its Contribution to Constitutive STAT3 Phosphorylation in Breast Cancer. *Cancers (Basel)* 2014; 6: 2012-2034.
- Raingo J, Castiglioni AJ, Lipscombe D. Alternative splicing controls G protein-dependent inhibition of N-type calcium channels in nociceptors. *Nat Neurosci* 2007; 10: 285-292.
- Zhu H, Ding Q. Lower expression level of two RAGE alternative splicing isoforms in Alzheimer's disease. *Neurosci Lett* 2015; 597: 66-70.
- Lopez-Diez R, Rastrojo A, Villate O, Aguado B. Complex tissue-specific patterns and distribution of multiple RAGE splice variants in different mammals. *Genome Biol Evol* 2013; 5: 2420-2435.
- Hudson BI, Carter AM, Harja E, Kalea AZ, Arriero M, Yang H, et al., Identification, classification, and expression of RAGE gene splice variants. *FASEB J* 2008; 22: 1572-1580.
- Barbosa-Morais NL, Carmo-Fonseca M, Aparicio S. Systematic genome-wide annotation of spliceosomal proteins reveals differential gene family expansion. *Genome Res* 2006; 16: 66-77.
- L Park, KG Raman, KJ Lee, Y Lu, LJ Ferran, WS Chow, et al., Suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation endproducts. *Nat. Med.* 1998; 4: 1025-1031.
- TM Wendt, N Tanji, J Guo, TR Kislinger, W Qu, Y Lu, et al., RAGE drives the development of glomerulosclerosis and implicates podocyte activation in the pathogenesis of diabetic nephropathy. *Am. J. Pathol.* 2003; 162: 1123-1137.
- CM Sirois, T Jin, AL Miller, D Bertheloot, H Nakamura, GL Horvath, et al., RAGE is a nucleic acid receptor that promotes inflammatory responses to DNA. *J Exp Med.* 2013; 210: 2447-2463.
- SS Tiwari, MD Orange, C Troakes, BN Shurovi, O Engmann, W Noble, et al., Evidence that the presynaptic vesicle protein CSPalpha is a key player in synaptic degeneration and protection in Alzheimer's disease. *Mol Brain.* 2015; 1: 6.
- G Sh Burbaeva, IS Boksha, EB Tereshkina, LI Starodubtseva, OK Savushkina, EA, TA Prokhorova. Glutaminase in the cerebellum of patients with Alzheimer's disease: a postmortem brain study. *Zh Nevrol Psikhiatr Im S S Korsakova.* 2013; 113: 71-75.
- Ding Q, JN Keller. Evaluation of rage isoforms, ligands, and signaling in the brain. *Biochim Biophys Acta.* 2005; 1746: 18-27.
- CLv, L Wang, X Liu, S Yan, SS Yan, Y Wang, et al., Multi-faced neuroprotective effects of geniposide depending on the RAGE-mediated signaling in an Alzheimer mouse model. *Neuropharmacology.* 2014; 89: 175-184.
- Hernanz, M De la Fuente, M Navarro, A Frank. Plasma aminothiol compounds, but not serum tumor necrosis factor receptor II and soluble receptor for advanced glycation end products, are related to the cognitive impairment in Alzheimer's disease and mild cognitive impairment patients. *Neuroimmunomodulation.* 2007; 14: 163-167.
- F Liang, J Jia, S Wang, W Qin, G Liu. Decreased plasma levels of soluble low density lipoprotein receptor-related protein-1 (sLRP) and the soluble form of the receptor for advanced glycation end products (sRAGE) in the clinical diagnosis of Alzheimer's disease. *J Clin* 2013; 20: 357-361.
- Srikanth V, A Maczurek, T Phan, M Steele, B Westcott, D Juskiw, G Münch. Advanced glycation endproducts and their receptor RAGE in Alzheimer's disease. *Neurobiol Aging.* 2011; 32: 763-777.
- M Zavolan, EV Nimwegen. The types and prevalence of alternative splice forms. *Curr Opin Struct Biol.* 2006; 16: 362-367.
- K Buchmann. Evolution of Innate Immunity: Clues from Invertebrates via Fish to Mammals. *Front Immunol.* 2014; 5: 459.
- J Raingo, AJ Castiglioni, D Lipscombe. Alternative splicing controls G protein-dependent inhibition of N-type calcium channels in nociceptors. *Nat Neurosci.* 2007; 10: 285-292.
- H Shi, T Tao, D Huang, Z Ou, J Chen, J Peng. A naturally occurring 4-bp deletion in the intron 4 of p53 creates a spectrum of novel p53 isoforms with anti-apoptosis function. *Nucleic Acids Res.* 2015; 2: 1035-1043.
- Burre J, Sharma M, Sudhof TC. Alpha Synuclein assembles into higher-order multimers upon membrane binding to promote SNARE complex formation. *Proc Natl Acad Sci U S A* 2014; 111: 4274-4283.
- McLean JR, Hallett PJ, Cooper O, Stanley M, Isacson O. Transcript expression levels of full-length alpha-synuclein and its three alternatively spliced variants in Parkinson's disease brain regions and in a transgenic mouse model of alpha-synuclein overexpression. *Mol Cell Neurosci* 2012; 49: 230-239.