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Opinion Article

Alternative Splicing and Gene Antagonistic Pairing Model

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DESCRIPTION

Alternative splicing (AS) occurs in most human genes with high tissue specificity and is an effective way to increase protein diversity. Literature indicates that more than 90% of human genes have AS isoforms, and the majority of AS are involved in genomic evolution, physiological development, and pathogenesis. For example, the AS isoform Stat3β contributes to constitutive Stat3 activation in oncogenesis, and AS isoforms may increase the sensitivity of G protein-gated calcium channels involved in pain control. The AS process and associated isoforms of specific genes have been suggested to be strongly involved in selective cell death such as that in neurodegenerative disorders, termed antagonistic pairing model. Previous studies have suggested that the expression of AS isoforms is tissue-specific, indicating differential regulation of transacting factors in different tissues and even different cells. Splicing is handled by a complex called the spliceosome, and over 200 human genes are involved in spliceosome function. Interestingly, these spliceosome-associated genes also have AS isoforms themselves. A well-studied example is the Receptor Advanced Glycation End product (RAGE), a member of the Immunoglobulin (Ig) superfamily, which is normally localized to the cytoplasmic membrane and has multiple AS isoforms. This receptor binds multiple ligands, including β-amyloid (Aβ), calgranulin, High Mobility Group Box 1 (HMGB1), and DNA fragments, and is associated with neurodegeneration, diabetes etiology, and vascular disease. Recent studies have shown that the expression of the AS isoforms RAGE and sRAGE is even specific to brain regions. It is clear that RAGE and sRAGE are expressed at different levels in different brain regions, including the hippocampus, inferior parietal lobe, superior middle temporal gyrus, and cerebellum. Such specificity points to the widespread role of these AS isoforms in physiological and pathological processes, particularly aging and age-related conditions. Previously considered a relatively neglected region of the neurodegenerative brain, the cerebellum showed significantly lower sRAGE levels in Alzheimer's Disease (AD) patients than in controls. Indeed, although synaptic studies have shown that cerebellar regions in Alzheimer's disease are distinct from other regions such as the hippocampus and superior temporal gyrus, there is growing evidence implicating the cerebellum in neurodegeneration. More importantly, RAGE and sRAGE expression are associated with pathological conditions, both showing lower levels of expression in multiple brain regions in AD subjects compared to controls. Indeed, decreased expression of RAGE and sRAGE may not be causative factors for neurodegeneration. The tight association between AD and the expression levels of RAGE and sRAGE elucidated the highly involvement of RAGE and sRAGE during neurodegeneration in regard to the pivotal role of RAGE signaling in neurodegeneration.

RAGE has deletions in its intracellular domain that can significantly alter its normal interactions in signaling. sRAGE has been described as a decoy that regulates full-length RAGE signaling and may play a protective role in early-stage neurodegeneration with reduced expression in AD patients. sRAGE has been suggested to antagonize RAGE inflammatory signals by binding ligands and reducing their circulating levels. Similarly, due to the deletion of 16 amino acids in the intracellular domain, RAGE can also bind ligands without signaling to the cytoplasm. Therefore, downregulation of RAGE and sRAGE in AD may lead to dysregulation of RAGE signaling. The AS isoform sRAGE is expressed at low levels in AD patients and may serve as another regulatory isoform to address RAGE signaling. Binding to different ligands and/or binding to ligands differently in the extracellular space due to deletion of C2 domain. Loss of sRAGE in AD brains may disrupt the regulatory mechanisms of normal RAGE signaling.

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