The NRSE smRNA specifies the fate of adult hippocampal neural stem cells

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ABSTRACT

Recently we found that the nuclear localized small modulatory double-stranded (ds) RNA (smRNA) coding NRSE sequences triggered activation of transcription of NRSE genes in adult hippocampal neural stem cells. NRSE smRNA, which are non-coding dsRNAs about 20 bp in length, reside in the nucleus and play a critical role in mediating neuronal differentiation. These smRNAs carry the sequence of NRSE/RE1, which is recognized by the NRSE/REST transcription factor. The NRSE sequences are embedded widely in the genomic region, typically in promoters of neuron-specific genes. The mechanism of action appears to be mediated through a specific interaction between dsRNA and DNA/protein interaction, rather than through siRNA or miRNA. The discovery of smRNAs extends the important contribution of non-coding RNAs as key regulators of cell fate choice for adult neurogenesis.

INTRODUCTION

Small modulatory dsRNAs, smRNAs, trigger gene expression of neuron-specific genes containing NRSE sequences through an interaction with NRSE/REST. The NRSE sequences are embedded widely in the genomic region, typically in promoters of neuron-specific genes, including ion channels, neurotransmitter receptors and their synthesizing enzymes, receptor-associated factors, neurotrophins, synaptic vesicle proteins, growth-associated and cytoskeletal and adhesion molecule factors involved in axonal guidance, transport machinery, and transcription factors and cofactors (1, 2). NRSE/REST mediates the transcription repression of neuron-specific genes through the association of histone deacetylase (HDAC) complex or MBD1 in non-neuronal cells, but the appearance of NRSE smRNAs in an early stage of neurogenesis in the adult hippocampus leads to the initiation of transcription of NRSE genes by modulating the function of NRSE/REST from repressor to activator (3).

![Figure 1. Schematic illustration of NRSE smRNA-mediated transcription activation of neuronal specific gene (NRSE-gene).](image-url)
suggesting it can function as an endogenous inducer of neuronal differentiation. The apparent gene activation effects of the NRSE dsRNA clearly distinguish it from the gene silencing effects of cellular miRNA/siRNAs and suggest a novel function for non-coding RNAs.

RESULTS AND DISCUSSION

The NRSE smRNAs appear during a relatively short period in neuroblasts, specifically during the transition from adult hippocampal neural stem cells to their neuronal cell fate. The smRNAs localize only in the nucleus to function as RNA transcription modulators during early neurogenesis. When cells differentiate into more mature neurons, the smRNAs gradually disappear from the cells. This transient appearance of the smRNA (non-coding RNA) seems to be important and sufficient for neuronal differentiation both in vitro and in vivo.

The NRSF/REST is conserved between *Xenopus laevis*, *Danio rerio*, *Fugu rubripes*, mouse, rat, chicken, sheep, and human, but not conserved in *Drosophila*. Recent bioinformatics analysis revealed that more than 1,800 NRSE targets exist in the human and mouse genomes (4). The expression of NRSF/REST was detected in many cases in non-neuronal cells during embryonic development, to restrict neuronal gene expression to the nervous system by silencing genes in non-neuronal cells (5, 6). While, in fact, NRSE/REST is expressed in adult mammalian CNS neurons (7, 8). The mRNA expression level is elevated in response to ischemic or epileptic insults (6, 7). During cell fate choices from adult hippocampal neural stem cells, the up-regulation of mRNA of NRSE/REST is detected (3). Together with our finding that NRSF/REST has a second function as a transcription activator with NRSE smRNA during cell fate choice from adult neural stem cells, these recent findings of NRSF/REST in the adult CNS suggest multiple roles for NRSF/REST in functional mature neurons.

Genes important for functional neurons contain the NRSE sequence, which is recognized by the protein NRSF/REST, and require NRSE smRNAs on their genomic loci to change the function of NRSF/REST from repressor to activator at a critical period during early neurogenesis in adult brain. We further assess this smRNA as a new type of regulatory RNA (non-coding RNAs from our genome) to understand complicated and changeable adult brain function.

REFERENCES