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Non-coding RNA transcripts: Sensors of neuronal stress, modulators of synaptic plasticity, and agents of change in the onset of Alzheimer's disease

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Abstract

Non-protein-coding RNAs (ncRNAs) play critical roles on many levels of cellular information processing and pervasive expression of ncRNAs in the nervous system could help explain brain complexity. ncRNAs are enriched in the central nervous system and are associated with specific neuroanatomical regions. Additionally, several recent publications have revealed an important role for deregulation of ncRNAs in various human neuropathologies, such as Alzheimer's disease, Parkinson's disease and Fragile X mental retardation. Herein, we summarize reports on functional ncRNA molecules involved in cellular stress response, particularly related to Alzheimer's disease. We conclude that ncRNAs have a prominent role in maintaining precise physiological levels of gene products directly implicated in Alzheimer's disease pathology.

Introduction

Accumulating evidence suggests that non-protein-coding RNAs (ncRNAs) play transformative roles as molecular information processors to enhance the performance of systems throughout the cell. This evidence led to the proposal that ncRNAs articulate high-density information flows between the many layers of functional networks, facilitating refined integration and concert of action among diverse molecular machineries¹. Across the expanse of cellular physiology, ncRNAs have the capacity, in principle, for information coupling between otherwise disparate systems, decisively impacting the behavioral dynamics of cells, tissues, and organisms.

At critical junctures in evolutionary history, genomic expansions of non-coding elements appeared simultaneously with large increases in organismal complexity. The transition from unicellular to multi-cellular organisms that occurred approximately 700 million years ago, the so called Precambrian Explosion, may only have been possible by the widespread incorporation of ncRNAs into the genomes of early multicellular organisms²⁻⁵. The same features that drove

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intensive incorporation of ncRNAs in the developmental pathways of multicellular organisms later facilitated their use in the mammalian stress response. An emerging theme now links the unique information processing features of ncRNAs to stress response and the onset of chronic diseases ⁶.

In neurophysiology, simultaneous stresses of many different types are the rule, not the exception. The wide dynamic ranges required for signaling and plasticity create a constant stream of challenges for molecular machineries, such as thermal dissipation in restricted microregions, and maintenance of order among rapidly changing synaptic inventories of molecular materials. The interplay between these phenomena and the demands of synaptic homeostasis has emerged as a focal point in the early stages of Alzheimer's disease pathogenesis. A mosaic of recent findings demonstrating functions of ncRNAs in stress response ⁶ together with their specific expression in the nervous system ⁷ now indicate important roles for ncRNAs in neurodegeneration. In this review, we provide a framework for discussion of this emerging theme in neurodegeneration, and we highlight recently discovered examples of ncRNA pathways in the molecular etiology of Alzheimer's disease. We seek to provide a glimpse of a still mysterious additional dimension of information flow through nervous system tissues, orthogonal to both electrophysiology and canonical protein interaction networks.

NcRNAs orchestrate complex nervous system functions

Even after almost a century of intensive investigations of the molecular architecture of neurons and synapses, ncRNAs had gone virtually unnoticed. Suddenly though, high throughput studies from multiple platforms have provided evidence for a striking nervous system wide pattern of ncRNA expression ⁷. Whole transcriptome cDNA libraries from hundreds of mouse and human tissues, created by the FANTOM Consortium ⁸⁻¹⁰, facilitated the search for spatially defined transcript expression in the nervous system ¹¹. Using this resource, Mercer *et al.* have shown widespread expression of long ncRNAs in mouse brain. They showed that the majority of ncRNAs, 849 out of 1328 examined, are expressed in the adult mouse brain in specific neuroanatomical regions, cell types, or sub-cellular compartments, suggesting that the majority of ncRNAs are expressed in the brain and play an important role in nervous system complexity ⁷. Although some of these RNAs may ultimately prove to result from the alternative splicing of previously unannotated 3' UTRs¹², the Mattick laboratory subjected input RNAs to a rigorous filter to eliminate these and other artifacts. Other studies have used *in situ* hybridization techniques to demonstrate articulate nervous system expression of many miRNAs ¹³. While low copy number and cell specific expression of ncRNAs result in sequence depth and localization issues, the advent of next generation sequencing technology now provides an improved approach to ncRNA discovery and expression mapping. The miRNA atlas has confirmed enhanced expression of many human miRNAs in brain tissue ¹⁴. Studies by Berezikov and colleagues also revealed hundreds of brain specific novel miRNAs, utilizing massively parallel sequencing approach ¹⁵. They also compared the miRNA between human and chimpanzee brains, and suggested that some of the new miRNAs are not conserved beyond primates, indicating their recent origin, and species specificity ¹⁵. The discovery of Human Accelerated RNA (HAR1) suggests very recent expansion events for functional ncRNAs in the human lineage, and illustrates important principles driving their evolution ¹⁶. This RNA, along with several dozen others identified, was strongly conserved from the chicken to the chimpanzee. In contrast, human HAR1 contains 14 base changes compared to chimpanzee, 8 of which are A to G transitions ¹⁶. HAR1 expression by in-situ hybridization mirrors that of Reelin in Cajal-Retzius cells suggesting a functional role (although not confirmed in the original publication by Northern blotting). Considering the rapid growth in nervous system complexity, the example of HAR1 highlights how non-conserved ncRNAs can serve important functions in rapidly evolving nervous system architectures ¹⁶.

NcRNAs as information mediators

Overall estimates of the number of distinct ncRNAs in the human genome have ranged from 450,000 to over 1,000,000 (Mattick, J.S. personal communication and ¹⁷, many of which may not have function ¹⁸, or await future data on function. Several informative recent reviews cover the expanding topic of ncRNA expression and function in the nervous system ^{1,19,20}, including the intriguing topic of ncRNA based intercellular communication in the nervous system ^{21, 22}, and transport of glial cell derived mRNAs to adjacent neuronal synaptic regions for translation ²³. While the nervous system environment features a spectacular range of diversity, functionality, and throughput, homeostasis hinges on the ability to maintain macromolecular order even under high stress levels. The unique information-coding and computational features of ncRNAs make them prime candidates for use in this demanding context. Unlike most proteins, ncRNAs usually function purely in the acquisition, processing, or delivery of information. Their rapidly evolvable information content couples analog to digital within the same molecule, allowing their interaction with protein networks through their secondary structure (analog information content), and with other nucleic acids through primary sequence homology (digital information content). In effect, ncRNAs serve as a bridge between the digital information universe of nucleic acids and the analog universe of cellular protein interactions ¹. Furthermore, ncRNAs can rapidly adapt to sensory inputs and alterations in their microenvironment by reversibly changing their secondary structure, so that their exposure to recent events orchestrates combinatorial changes in the presentation of their information content ¹. For example, in response to increased temperature, Heat Shock RNA (HSR) changes its secondary structure, allowing it to bind to Heat Shock factor (HSF) with high affinity, thereby activating the Heat Shock response. Cells treated with siRNA to HSR fail to induce a heat shock response even upon acute temperature shock ²⁴. Another illuminating and recently discovered example comes from the 3' UTR non-coding region of the vascular endothelial growth factor-A (VEGF-A) mRNA ²⁵. This region forms a functional switch between two different secondary structures, using analog information to sense the local concentrations of RNA binding proteins. The interaction of this non-coding region with one of its two cognate proteins forms an "AND NOT" circuit that only translates VEGF-A protein when the logical condition is satisfied ²⁵.

The typical long RNA binds co-transcriptionally to dozens, sometimes hundreds of RNA binding proteins, allowing a wide range of combinatorial interactions as the mature RNA emerges into its proper sub-cellular localization. Complex temporal and spatial interactions can occur between different sets of RNA binding or signaling proteins and information containing RNA binding motifs. These mechanisms create the potential for complex memory states, since each of the ncRNA-protein complexes within a cell can acquire, accumulate, process, and transmit an amount of information that only depends on the number of allowable states of the complex. Together the evidence now accumulating suggests that ncRNAs and their RNA-protein complexes compose a broad computational matrix that pervades all other layers of information processing within the cell. Using these features, ncRNAs increase the spatial and temporal density of macromolecular information processing in the limited space of the nervous system ¹.

Alzheimer's disease-modulated ncRNAs influence the diversity of LTP and LTD

With such a spectrum of computational features, ncRNAs can play a constructive role by increasing useful variation and semantic complexity, wherever increased information content might benefit biological networks. The regulatory networks that control synaptic plasticity provide a useful example, one that may localize to the epicenter of Alzheimer's disease. Finely tuned regulation of thousands of genes controls the spatio-temporally modulated patterns required for the coding of memory. Synaptic plasticity modulates the sizes, the locations, the macromolecular content, and other parameters of synapto-dendritic landscapes, producing

changes in the finely tuned heterogeneous connectivity landscape characteristic of memory and learning. Long-term potentiation (LTP) and long-term depression (LTD) operate prominently in the entorhinal cortex and the dentate gyrus during the acquisition of memory. Dereglulation occurs early in these regions during the cascade of Alzheimer's neurodegeneration, often resembling a loss of control in plasticity. Recent work demonstrated that synaptic release of beta amyloid (A β) soluble dimers produces reversible effects practically indistinguishable from LTD²⁶, consolidating a variety of previous findings on the early specific effects of A β . Soluble A β oligomers bind to a number of important targets in synaptic regions, producing specific and reversible effects including NMDA receptor endocytosis, excessive calcium influx^{27,28}, tau phosphorylation²⁹⁻³¹ and loss of mitochondrial potential^{32,33}. These events initiate a series of consequences that parallel the LTD pathway²⁶, strengthening an emerging hypothesis that Alzheimer's pathology begins with early events modulating synaptic plasticity.

With the discovery that components of LTP require local protein translation, a more holistic view of synaptic mechanisms and functions came into focus. Work by Susan Lindquist³⁴, Joel Richter³⁵, Eric Kandel³⁶ and others have suggested the possible existence of carefully modulated synaptic translational machinery, that responds to environmental and activity dependant inputs to regulate mRNA translation levels at each synapse. Translational scaffolds may contain RNA binding proteins such as FMRP, CPEB, and possibly prions, and likely interact with core elements of the Alzheimer's disease pathway. The cytoplasmic C-terminus of membrane bound APP binds to CPEB, thereby serving as a tethering and regulatory element for these highly programmed differential translation systems³⁷. Cleavage of APP then implies the un-tethering and eventual relocation of these complexes. On another level, APP mRNA itself associates with FMRP within these scaffolds, resulting in the regulation of its level of translation³⁸. Such a well articulated, interlocking servo loop (a control architecture using feedback from system output back to the input, to achieve a purpose, usually including a stable pattern of system behavior) likely influences the information content of individual synaptic regions, and utilizes this information to define individualized protein expression profiles at each synapse. With different synapses potentially composed of different concentrations of synaptic proteins, LTP and LTD can take on broadly heterogeneous characteristics, yielding a wider range of functional responses to stimuli. Some of the proteins translated by these machineries are likely themselves RNA binding proteins, whom in turn can capture different ncRNAs to establish information feedback mechanisms and provide changing information signals at different synapses.

The reversible effects of A β at synaptic sites occur well in advance of plaque formation, linking Alzheimer's disease onset downstream from the accumulation of unresolved stress in the machineries of synaptic plasticity. The ncRNA enhanced information flow between layers of these networks would allow system wide tuning, providing a compelling solution to stress challenges. A recent finding that ncRNA BC200 is significantly up-regulated in Alzheimer's disease highlights the potential nexus of connections between ncRNAs, synaptic plasticity, and Alzheimer's disease³⁹. In contrast to normal aging, Alzheimer's disease-affected brain regions show consistently higher levels of BC200 RNA than in age-matched controls. Expression levels corresponded proportionally to the progression of the disease state, suggesting a reactive or compensatory role for BC200 in Alzheimer's disease triggered synaptodendritic deterioration³⁹. BC1 RNA, the possible functional analog of BC200 RNA, locates to synaptic regions, interacts with key proteins in translational scaffold complexes, and regulates the synaptic translation of mRNAs critical for synaptic function, such as dopamine D2 receptor⁴⁰. BC1's modulation of the multiplexed synaptic translation scaffolding system has broad implications for homeostatic synaptic plasticity, and LTD/LTP (Figure-1). The mechanisms of action of the BC1 and BC200 RNAs illustrate the power and flexibility of ncRNAs in cellular

information processing in general, and specifically in the modulation of translational scaffolding systems in synaptic micro-regions.

Since primate BC200 is derived from member of the large family of ALU element derived RNAs known to undergo copious ADAR editing⁴¹, their secondary structures (analog information content) must cluster into large related families, suggesting that ALU derived RNAs other than BC200 could interact with scaffolds and regulate translation of specific subsets of synaptic mRNAs. Such machineries would integrate information content from synaptic activity, axonal transport, RNA processing, and transcriptional regulation, offering a molecular circuit for differentially shaping the contours of individual synaptic proteomes. So intriguing is the potential for ncRNAs to add to the semantic complexity of memory processing, that some authors have argued that ncRNAs must function directly in the process of memory formation⁴². While this suggestion remains open for future studies, the involvement of ncRNAs in local synaptic translation underlines the complexity of synaptic plasticity associated servo loop systems involved, the intriguing roles ncRNAs play in these servo loops, and the overlap between such mechanisms and actions of A β at the synapse. The dynamics and mechanisms of servo loop deregulation represent key questions for understanding the etiology of Alzheimer's disease.

NcRNA based servo loops in the service of nervous system robustness

When connected to molecular sensors and other components, servo loops serve a vital function for avoiding disease pathogenesis and the achievement of biological “robustness.” The Systems Biology concept of robustness defines a quality of responsiveness to changing environmental conditions and activity levels; the more timely and accurate the information moving through the servo loops, the greater the robustness of a complex system. As Kitano points out, information content marshaled for the purpose of enhancing robustness often overcomes known forms of network perturbations, such as thermal noise⁴³ to maintain homeostasis. The benefits include better articulation and fine-tuning of network functional resources (systems) under known conditions. The costs include greater sensitivity to unusual perturbations not previously presented to the systems during their evolution. In the case of sporadic Alzheimer's disease, these unusual perturbations can include lipid metabolic effects, chronic alterations in glucose signaling, and aging related antagonistic pleiotropy^{44,45}, among others.

Robustness in turn permits expansion of the dynamic range of a system, which, when taken to its natural limit, evolves into an increasing capability for dynamic plasticity. A system that has exceeded its static dynamic range may resort to temporarily augmenting its physical extent in response to peak demand. The ability of macromolecular systems to achieve these levels of functionality depends on their precise temporal and spatial coupling of energy and information. We argue that a correspondence exists between these advantageous features of higher complexity and the unique molecular information coding features of ncRNAs, leading to their recruitment and incorporation into existing gene expression machineries and protein interaction pathways^{4,46,47}.

With the ability to form complex computational modules and interact with multiple different layers of protein machineries in the cell, ncRNAs serve to increase information flow into feedback loops, and to extend the cell's ability to maintain homeostasis. The heterogeneous and distributed functions of miRNA machineries provide an excellent example of servo loops and systems control in neurophysiological systems. We recently reported details of one such servo loop: miRNA-mediated feedback loop that function to maintain NMDA receptor homeostasis⁴⁸. In this case, administration of an acute antagonist to NMDA receptors rapidly reduces the synaptic concentration of miR-219. MiR-219 targets CAMKIIgamma mRNA among others, a known direct downstream effector of the NMDA signaling cascade. Treatment with acute antagonist reduces miR-219 repression of target mRNAs, causing an increase in

CAMKII γ protein, and an increase in the NMDA receptor signaling cascade set point⁴⁸. Transient blockade of miR-219 by specific anti-miR application very rapidly reproduces the same increase in the set point of the NMDA receptor cascade.

Another useful example further illustrates the strong partnership between miRNAs and adaptive feedback loops. Alcohol stress responsive miRNA (miR-9) rapidly increases after alcohol treatment of neurons and strongly regulates ALCOREX exon inclusion, leading to alcohol adaptation in the large-conductance calcium- and voltage-activated potassium channel (BK) channels, known as an important element in behavioral and molecular alcohol tolerance⁴⁹. The short timescale of response illustrates a key principle in ncRNA function in the nervous system. The unique sensory and information processing features of ncRNAs enhance their participation in multiple layered feedback loops focused on homeostasis, stress response, and the maintenance of robustness of physiological resources. Thus while these molecules are not the cause of disease pathology, their function includes the early response to stress vectors that drive disease onset if not adequately resolved or fully neutralized by the response machineries.

In synaptic tissues, achieving homeostasis is only the beginning of the challenge. The demands of spike activity and synaptic plasticity require control architecture able to evaluate functional states far beyond the range of homeostasis. Perturbations of miRNAs in disease onset may represent regulatory signals designed to preserve nervous system function. Numbers of key transcripts in Alzheimer's disease pathways are regulated by miRNAs, such as APP⁵⁰, BACE1^{51,52}, and others. Non-dividing cells maintain tighter miRNA control of over translation than their rapidly dividing peers, due to their global transcription profiles. Indeed, mRNAs in these transcriptomes contain significantly longer 3'UTRs than those of dividing cells, which in turn serve as targets for many more miRNAs⁵³. The tendency for Alzheimer's disease neurons to change their expression landscapes towards cell division may also produce a transcriptome less regulated by miRNAs. The early events in the etiology of Alzheimer's disease involve synaptic changes in the parameters of plasticity networks, suggesting a connection between plasticity, stress, and robustness on the pathway to the onset of Alzheimer's disease.

Non-coding-RNAs mediate key stress response pathways in Alzheimer's disease

By using servo loop information flow to make intelligent defensive changes, biological robustness establishes barriers to the onset of chronic diseases. As long as the information flow remains uncompromised, the ongoing computation seeks to optimize the responses necessary for neutralization of the acute reversible phases of stress before they emerge as chronic irreversible phases. In this fashion cells and tissues avoid the progressive, irreversible loss of information content from cellular networks, and the subsequent corruption of functional systems, especially those of robustness and stress response themselves, that can occur as a prelude to chronic disease. Nervous system tissues, in particular, require a veritable arsenal of stress response pathways to move functional networks back into reversible zones of phase space, where behavior, regulation, and homeostasis are robust.

Accumulated stress often produces saturation of protein interaction pathways, making them no longer able to absorb new information^{54,55} and thus unable to properly process or communicate information to downstream effectors. In these situations, ncRNAs permit enhanced information flow to stress response systems in the face of ongoing perturbations. Roles for ncRNAs in cellular stress responses include sensory transduction, integration, and distribution of regulatory signals. For a relatively low entropic cost, ncRNAs add orthogonal information content to these networks, permitting among other things; the fine-tuned and carefully measured responses to stresses and perturbations encountered by the organism. As the examples discussed below demonstrate, sensing the onset and accumulation of stress in macromolecular networks represents a particularly critical role for ncRNAs in the pathways of disease.

A number of groundbreaking examples have brought ncRNA mechanisms to the forefront of mammalian stress response. Sensory transduction roles of ncRNAs in cellular stress responses include evaluating temperature levels in the heat shock response by Heat Shock RNA (HSR)²⁴, sensing DNA damage⁵⁶, and regulating the hypoxia response through HIF1alpha^{57,58}. The 3'UTR of human VEGF-A mRNA contains an RNA switch to integrate signals from stressors such as interferon gamma and hypoxia, and regulate VEGF-A translation²⁵. Other ncRNAs such as hsr-omega transcripts function in neurodegeneration and stress response pathways in *Drosophila*⁵⁹, while vault RNAs in humans appear to participate in detoxification and innate immunity⁶⁰. In the inflammation system a variety of RNA sensing proteins such as RIG, NOD, PKR, and OAS play roles suggestive of RNAs as endogenous sensors of molecular order, with regulatory and signaling impact of broad significance, orthogonal to any pathogenic RNAs.

Consistent with their usefulness in stress response, recent evidence implies that ncRNAs mediate key events in neuropathology. We documented ncRNA-mediated regulation of PTEN induced putative kinase 1 (PINK1), a key signaling protein in Parkinson's disease⁶¹. Our group and others previously reported the deregulation of long ncRNA's in Fragile X mental retardation and an associated neurological disease, fragile X-associated tremor ataxia syndrome (FXTAS)^{62,63}. Many brain disorders result in dysregulation of miRNAs, such as Tourette's syndrome⁶⁴, schizophrenia⁶⁵ and mental disorders⁶⁶.

An excellent example of ncRNA involvement in both nervous system stress and Alzheimer's pathology comes from our recent report on natural antisense-mediated regulation of beta-secretase-1 (BACE1) in Alzheimer's disease pathogenesis⁶. This somewhat surprising result highlights ncRNA involvement in Alzheimer's disease, illustrates how ncRNA features facilitate higher order signal integration in this disease, and provides insight on how ncRNAs could play decisive roles in Alzheimer's disease pathology (Figure-2). The BACE1 mediated cleavage of APP represents a defining early step in the onset of Alzheimer's disease. Yet, loss of BACE1 results in numerous behavioral and physiological deficits, including memory loss⁶⁷, emotional deficits⁶⁸, myelination defects in peripheral nerves^{69,70} and loss of synaptic plasticity⁶⁸. BACE1 activity increases in response to a series of specific neuronal stresses including A β itself. In effect, the subtle but crucial boundaries between BACE1 physiology and pathology indicate that BACE1 expression must be tightly regulated, allowing the enzyme to perform its physiological functions while avoiding the serious consequences of over- or under-expression. In contrast to the classic siRNA and miRNA mechanisms, the natural antisense transcript, BACE1-AS, forms a duplex with its cognate BACE1 mRNA, and stabilizes the mRNA for increased translation⁶. The example illustrates a growing diversity of mechanisms for ncRNAs that provide finely tuned regulation of neurodegeneration-associated pathways of gene expression.

Other stress responsive genes also use antisense transcripts to respond to stress, such as HIF1alpha⁷¹, Neuronal nicotinic receptor (CHRNA3 & CHRNA5)⁷² and neuronal nitric oxide synthase (nNOS)⁷³. Growth arrested DNA-damage inducible gene 7 (gadd7) represents a stress responsive ncRNA involved in a feed forward loop⁷⁴. Similar to BACE1-AS, Gadd7 appears to aggravate palmitate induced ROS accumulation and subsequent ER stress during conditions of lipotoxic stress. BACE1-AS, Gadd7, and HIF1alpha-AS exhibit commonalities in their functions, and together illustrate a ncRNA systems biology principle: as long as the cell remains within normal ranges of environmental variation, multi-layered regulatory systems take advantage of information flows from ncRNAs to increase robustness and enhance functional diversity. However, these systems proceed at the expense of stability when variation falls outside the intended range of functionality.

A systems perspective on Alzheimer's disease from the non-coding transcriptome

The above results imply that certain types of changes in synaptic conditions, loosely labeled “stress” by biologists, modulate the cleavage of APP and the production of A β , through a ncRNA mechanism. In turn A β rapidly modulates a series of synaptic parameters that appear to have physiological importance for stress response, as they establish a feed forward loop. With many other ncRNAs active early in stress response, and with their multilayered impact on cellular networks, interesting issues arise regarding integration and synthesis of these signals. In a dynamic synaptic environment, potentially hundreds of RNA mediated information flows interact to produce a resolved set of signals that will define phase state changes. The coupling and resolution of disparate signals may represent a challenge that may not always have a happy ending in complex networks. The resolution of disparate signals may depend on some type of internetwork coherence established as a result of redundancy in information flows from many sources. In this regard, information accumulated in existing ncRNA - protein complexes may allow real time comparisons with previously registered information flows. Logical conflicts that arise may trigger sensors or signal alarms to recruit resolution machineries. In this context, the idea of “internetwork coherence”, or coupled coherence of networks⁷⁵, proposes that in healthy neurophysiology, these conflicts are routinely resolved by systems of information coupling and synthesis. The result would include a resonance between these multilayered networks, such that the loss of information from one or a few of them, would be compensated for by the other network elements containing the same or resonant information (a little like a hologram).

The above-cited studies on the multilayered and finely tuned regulation of BACE1, together with many others at different gene loci, increase our awareness of the importance of multiple nested layers of feed forward, and feedback servo loops in the biology of neurodegeneration. ncRNAs enhance the connectivity of biological networks, and the information flow constantly occurring between them. The higher the quality of information flow, the greater the dynamic range, plasticity, and robustness of the system itself. The high performance environment of the mammalian nervous system features an increased range of diversity, greater functionality, and higher throughput than most other tissues and organisms. These features require the maintenance of order of synaptic molecular materials even under the increased stress levels typical of synaptic environments. Alzheimer's disease now appears to recapitulate some of these patterns, where the participation of many more ncRNAs in these processes may be expected.

Conclusion

The advent of systems biology marks the culmination of a century of reductionism, and the beginning of an era of conceptual integration in disease biology. During this transition, the non-coding transcriptome will continue to play a formative role by emphasizing the flow of information through large macromolecular networks, as well as the continuing impact of information on their dynamic behavior during stress response. The classic aqueous biochemical behavior of protein complexes occupies a smaller part of a larger context where information theory and computational integration define the state of functional systems. Disease onset occurs only when accumulated stresses on molecular machineries overpower the capabilities of multiple layers of servo loops supporting system robustness. As the servo loops falter, their dysfunctionality results in distortion and corruption of information flows, which propagate radially like waves, across the interconnected macromolecular networks from the epicenter of disorder. The health of the tissue fails as a function of the loss of molecular order, the loss of quality in its information content. A progressive loss of information quality represents an unfortunate consequence of multiple nested servo loops pushed beyond their robustness limits.

Understanding ncRNAs brings with it clarity for these servo loops and the map of their evolved information flows.

The establishment and maintenance of synaptic machineries in precise spatio-temporal coordinates require intricate order and robust control. While servo loops provide a useful and widely used architecture for achieving these requirements, they depend on the flow of information content often provided by ncRNAs. Thus ncRNAs highlight the information content of molecular machineries. The complexity of the Alzheimer's disease process reaches many cellular pathways from the dendritic spine, to the cell body, and back to the presynaptic terminal. Expanding the repertoire of ncRNAs associated with Alzheimer's disease will lead the way to a systems biology understanding of this complex disease. New insights into the unique and multifaceted functions of ncRNAs will reveal how complex systems use digital and analog information content to make molecular computations, which enhance robustness, and respond to stress. Perhaps with these insights Alzheimer's disease will be remapped as a descending cascade of corrupted information content within a landscape of information flows, servo loops, and multilayered control functions dedicated to robust synaptic functionality and plasticity.

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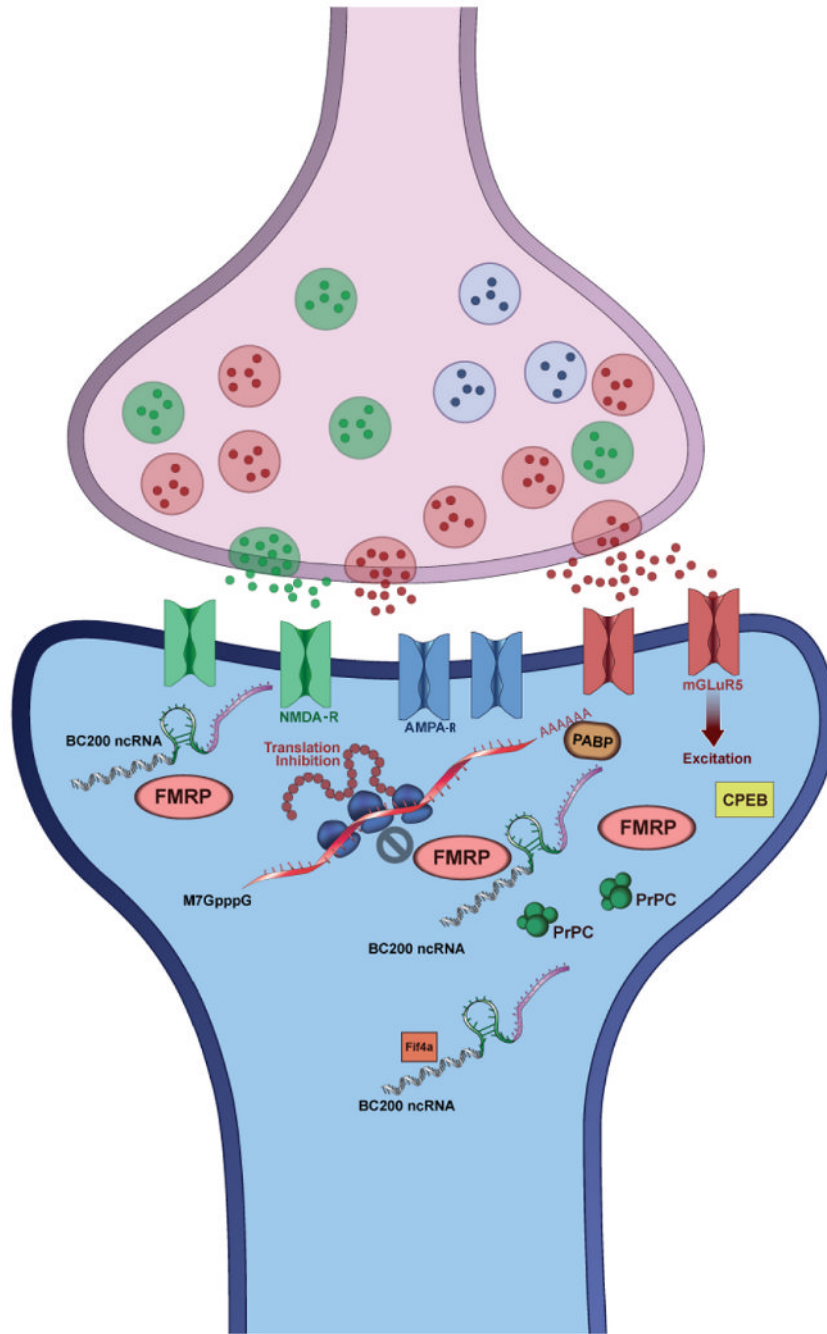


Figure-1. Synaptic protein translation scaffolds contain heterogeneous and multiplexed information content; role of BC200 ncRNA

BC1 and BC200 ncRNAs, which suggested as local translational regulators, are selectively localized in somatodendritic domains of neurons. Originally discovered in 1991, by Tiedge and coworkers ⁷⁶, BC1 and BC200 RNAs occupy a strategic position within the molecular machineries of synaptic plasticity. These RNAs regulate protein translation in the synaptic region through three proposed mechanisms of action. In the first mechanism, the analog information content of the RNA allows it to bind to Fragile X mental retardation protein (FMRP), while its digital information allows it to base pair with certain FMRP target mRNAs, achieving translational inhibition. In the second proposed mechanism the RNAs bind to Poly

“A” binding protein (PABP) to inhibit translation initiation. In the third mechanism, BC1 binds to eif4a, a prototypical member of the Dead box RNA helicase family of proteins. Eif4a comprises two globular domains, the ATPase domain, and the helicase domain, and is required for translation of a certain subset of mRNAs that harbor significant secondary structure in their 5' UTRs. Tiedge and colleagues have shown that BC1 disrupts a mechanical coupling between these two domains, thereby depriving the helicase domain of the free energy of ATP cleavage.

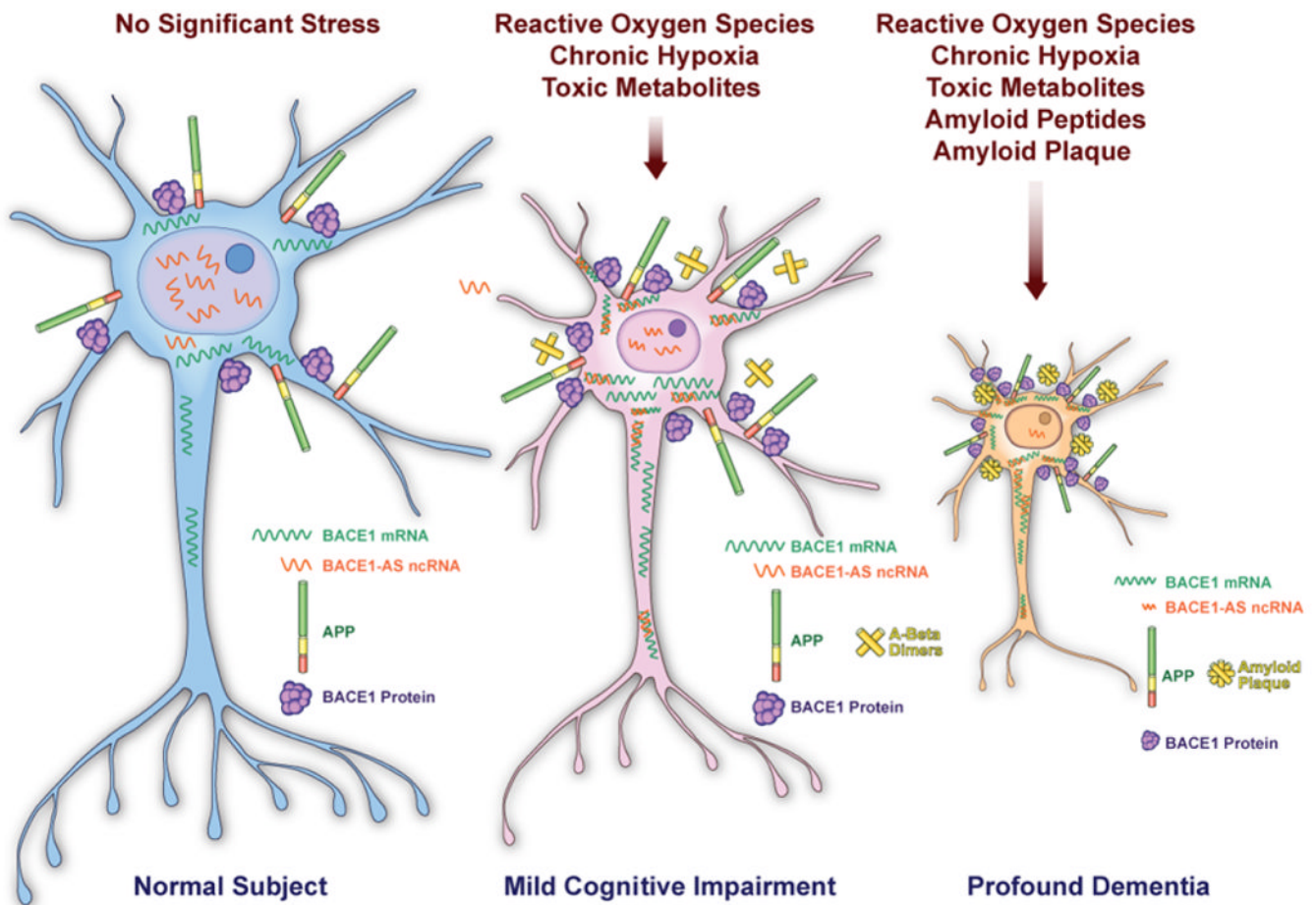


Figure-2. Elevated antisense RNA up-regulates β -secretase-1 in Alzheimer's disease

BACE1-AS is a non-protein-coding antisense RNA that regulates β -secretase-1 (*BACE1*). *BACE1*, a β -site amyloid precursor protein (APP)-cleaving enzyme, has been implicated in the pathogenesis of Alzheimer disease. *BACE1* is involved in the production of the amyloid β ($A\beta$) peptides that form plaques in the brains of individuals with Alzheimer disease. (a) *BACE1-AS* is enriched in the nucleus in the physiologic conditions, when neurons producing basal levels of *BACE1* mRNA and protein. (b) Exposure of the neuronal cells to various cell stressors, such as reactive oxygen species, chronic hypoxia and toxic metabolites, may cause cytosolic translocation of *BACE1-AS* transcripts. *BACE1-AS* can possibly form a duplex RNA with the *BACE1* mRNA, leading to stabilization of this transcript and up-regulation of *BACE1* protein. *BACE1* protein up-regulation, in turn can produce more $A\beta$ peptides and drive the generation of amyloid plaques. (c) Amyloid peptides and plaques are known cellular stressors and could provoke more stress to neuronal cells and lead to over-expression and release of *BACE1-AS*. This later event possibly drives a feed-forward mechanism resulting in neuronal cells loss. The expression of *BACE1-AS* is elevated in Alzheimer's disease and induces feed-forward regulation of *BACE1*⁶. It has also been shown that *BACE1-AS* induces production of $A\beta$ peptides, which leads to increased expression of *BACE1*, which in turn further amplifies $A\beta$ production⁶. Subsequently, increasing $A\beta$ levels can further boost that *BACE1-AS* expression, thereby accelerating the onset of Alzheimer's disease. We suggest that therapeutic targeting of *BACE1-AS* could mediate the transition between the essential physiological functions of *BACE1* and its pathological malfunction in early Alzheimer's disease⁶.