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A REVIEW ON THE EXPRESSION, REGULATION AND FUNCTIONING OF THE *ARC* GENE COMPLEX IN CONEXT OF MEMORY FORMATION AND SYNAPTIC PLASTICITY

Genetics

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ABSTRACT

The Arc (activity regulated cytoskeleton associated) gene , located on chromosome 15 in mouse , chromosome 7 in rat and chromosome 8 in human genome , is conserved across vertebrate species and has low sequence homology to Spectrin. Arc encodes proteinaceous extracellular vesicles that pinch off from one neuron to another allowing them to communicate that may be key to long term memory formation and other neurological functions, and Arc knockout mice were observed having problems in long term memory formation. Arc is localised in the hippocampal region of the brain in higher vertebrates and plays a part in helping neurons form and break connections over time as an animal's nervous system adapts to a new environment . Changes in Arc mRNA or protein are connected with a number of behavorial changes including fear conditioning, contextual fear conditioning and inhibitory avoidance and has also been observed as a notable contributor in several neuro - degenerative diseases .

KEYWORDS

Arc , memory , plasticity

INTRODUCTION

The brain extracts information about the world that shapes our behaviour and ultimately influences our personality . The immense capacity and specificity of memory storage in the mammalian CNS is thought to depend on the plasticity of synaptic connections . Key to current thinking is the requirement for new gene expression and protein synthesis in the development of enduring synaptic modification and long term changes in behaviour , probably involving orchestrated synthesis and degradation , of hundreds of proteins [1] [2] [3] . Recent research has zeroed in on the functional relevance of the immediate early gene (IEG) Arc / Arg 3.1 . Arc mRNA is induced by synaptic activity and trafficked rapidly to dendrites where the RNA accumulates at sites of synaptic activity and undergoes local translation [4] . The Arc transcript is dependent upon the activation of MAP kinase pathway and various growth factors like EGF , NGF , BDNF acting at NMDA receptors contribute to the proper expression of Arc gene .

Arc gene in synaptic memory

Glutametargic synapses are capable of expressing diverse forms of plasticity in response to synaptic inputs , including several mechanistically distinct kinds of synaptic strengthening (potentiation) , weakening (depression) and homeostatic synaptic scaling .

The dendritic tree of a typical projection neuron in the adult mammalian brain contains some 10,000 dendritic spines onto each of which a single excitatory , glutametargic synapse is formed . Dendritic spines offer a necessary degree of synaptic autonomy for information processing and storage . Through activity-dependant local synthesis and degradation of proteins , synaptic inputs may directly remodel the protein composition and thereby the functional state of individual dendritic spines or spine neighbourhood.

Arc mRNA is induced by synaptic activity and trafficked rapidly to dendrites where the RNA accumulates at sites of synaptic activity and undergoes local translation [5] .

Arc interacts with components of the clathrin-mediated endocystosis machinery endophilin-3 (Endo 3) and dynamin 2 (Dnm 2) to promote post-synaptic internalization of AMPA-type glutamate receptors and recruitment to recycling endosomes . Arc interacts with scaffold proteins PSD-95 and GKAP along with actin binding proteins to mediate LTP or LTD [6] .

Transcription of Arc

Arc mRNA is rapidly expressed in principle neurons of rodent forebrain following seizures , learning experience and following LTP induction by HFS or BDNF [7] . Activation of N-methyl-D-aspertate receptor (NMDAR) type glutamate receptors and extracellular signalling regulated kinase (ERK) are necessary for Arc transcription following LTP induction [8] and in response to neuronal activity in primary hippocampal or cortical neuronal cultures [9] . Arc is also induced pharmacologically in hippocampal neurons by BDNF and by application of group 1 mGluR against dihydroxyphenyl glycine (DHPG) or activation of adenylate cyclase by Forskolin [10]. Interestingly , AMPA-type glutamate receptors downregulate Arc gene expression in hippocampal neurons and organotypic hippocampal slice cultures through pertussis toxin sensitive G- protein , suggesting that active neuronal networks are subject to negative feedback at the level of Arc transcription .

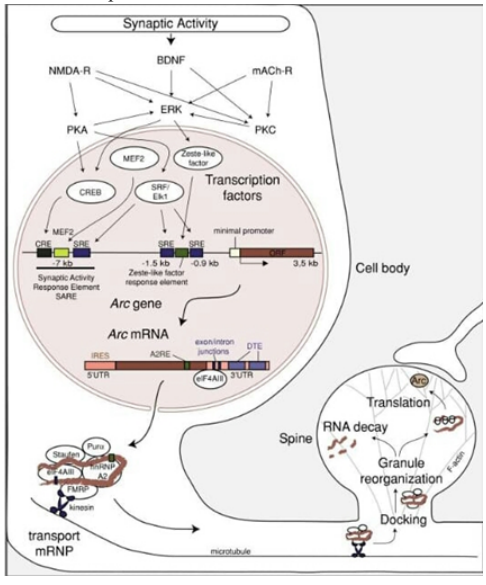

Fig - 1 : Synaptic activity dependent transcription of Arc gene through ERK pathways. [5]

Translation control and local Arc synthesis

One important feature of Arc regulation is translation dependant RNA decay . Arc is a physiological target for a process known as nonsense-meditated RNA decay (NMD) [11] . NMD serves as a quality contol surveillance mechanism for the rapid elimination of mRNAs with stop codons situated upstream of a splice site . During pre-mRNA splicing in the nucleus , exon-junction complex (EJC) proteins consisting of an RNA binding telomeric core (eIF4AIII , MLN51 , Y14 , MAGOH) are deposited on the RNA and subsequently removed by the ribosome during the first round of translation , allowing bulk rounds of translation to proceed . Recruitment of a key NMD factor UPF-1 , leads to degradation of RNA after a single round of translation .

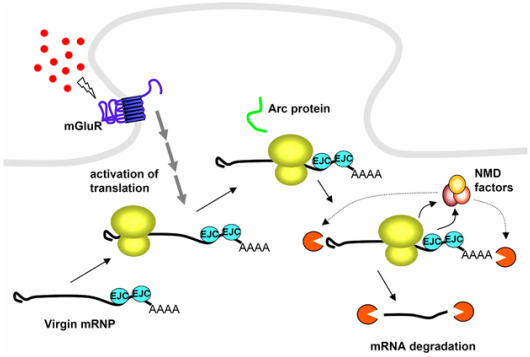

Fig 2 : Nonsense mediated RNA decay of Arc mRNA through EJCs regulating the translation process [5]

Arc and human cognition

1. Mutations in Arc signalling complexes :

Genetic variations and loss of function mutations related to glutametargic transmission are implicated in schizophrenia (SCZ) risk and syndromic autism . In large scale genome wide Association studies (GWAS) , the Arc related gene set was widely enriched for small de-novo mutations , copy number variants and more variants in SCZ as well as autism spectrum disorders . Remarkably , several of the genes associated SCZ risk encodes protein binding to Arc N-lobe , which in vitro is abrogated by the antipsychotic drug thioridazine . Cognitive functions are highly heritable and polygenic . A recent study examined genetic association of Arc complex with general intellectual function in children from the Avon Longitudinal Study of Parents And Children (ALSPAC) . The curated Arc complex is associated with both verbal and total intelligence quotient in children . The data collectively suggests that genetic variation in Arc protein interaction network contributes to cognitive performance as well as risk of cognitive disorders .

2. Aberrant Arc expression :

Several disorders of human cognition are associated with aberrant Arc expression . In Fragile X-syndrome , the leading cause of syndromic autism , loss of translational repressor , FMRP , results in exaggerated Arc synthesis . In Gordon Holmes syndrome , which is characterized by cognitive decline and dementia , missense mutations in Triad 3 prevent binding of E3 ligase with Arc , thus disrupting Arc ubiquitination and degradation . In Angelman syndrome , loss of Ube3A is similarly coupled to accumulation of Arc protein and defects in ubiquitination and plasticity . In AD , both increased and decreased Arc expression are reported which reflects the stage of the disorder and proximity of neurons to plaque deposits . Activity induced Arc enhances APP processing and amyloid - beta formation which may contribute to AD pathogenesis.

Arc-NMDA receptor synergy for LTM formation

Inhibition of NMDA receptors is known to hinder activity-dependent Arc mRNA expression , localization at activated dendritic sites and degradation [12] . Contextual fear conditioning is known to involve NMDA receptors - dependent plasticity mechanisms in the hippocampus and showed an increase in Arc protein accumulation in the hippocampus at one hour after acquisition that was blocked by NMDA receptor antagonist APV . Furthermore , pre-training infusions of Arc asODNs impaired consolidation but spared acquisition of contextual fear conditioning tasks .[13] . These results clearly point to a role of NMDA receptors-dependent Arc synthesis in the hippocampus in the formation of a long term contextual fear memory . Moreover , NMDA receptors activity upon retrieval proved to be essential for contextual memory maintenance as the increased locomotion upon subsequent context exposure was attenuated in rats treated with NMDA receptors antagonist APV [14] . These findings bring to light further support for the idea that retrieval memories , even well-consolidated ones , place the involved circuits in a labile state that require further NMDA receptors-dependent Arc protein synthesis for their stabilization .

Role of Arc in Alzheimer's

Alzheimer's disease (AD) is the most common form of dementia . The deposition of beta - amyloid plaques in the brain was considered one of the main neuropathological hallmarks of AD . As the loss of synapses is characteristic of AD progression , AD has been gradually regarded as a "synaptopathy" .As Arc has active roles in synaptic plasticity , learning , memory , it was recently identified as a key factor for AD . A two stage case central study of 1471 Han Chinese showed that variant rs 10097505 in the 3'UTR of Arc was significantly associated with AD . Whole exon of Arc screening in 99 AD patients with a high heritability (familial / early onset) identified a missense variant (c 20G > A , p . T71) that was absent in the control from general populations . Both rs 10097505 and c 20G > A were predicted to be potentially pathogenic. Further assay , data mining and integrative analysis revealed that the AD-risk genotype AA of rs 10097505 was associated with an increased Arc mRNA expression and an elevated level [15] .

The results indicates that Arc gene would confer AD susceptibility to Han Chinese , through protein misfoldings or overexpression of Arc in brain tissues leading to pathogenesis and development of AD .

DISCUSSION

Activity regulated cytoskeleton associated genes or Arc belong to the group of immediate early genes which are a group of genes that are activated transiently and rapidly in response to a wide variety of cellular stimuli .

Arc is an unique gene in terms of its expression and propagation which indicates it's viral ancestry . Arc has multifaceted role starting from neuronal growth , dendritic expansion , long term memory formation and cognition in humans as well as other higher vertebrate animals . Owing to its role in synaptic plasticity modulations in terms of LTP and LTD , it can regulate various aspects of our day to day life and survival. Overproduction of Arc gene products and their consequent accumulation facilitated beta-amyloid plaque formation in the amygdala region which paves the way for neuro - degenerative diseases like Alzheimer's . Under-expression of Arc genes causes severe memory impairment and hinders long term memory formation as evident in patients undergoing ECT for treatment of depression.

CONCLUSION

Activity regulated cytoskeleton associated gene (Arc) has a very deep impact on our nervous system and daily activities . From all the aspects of this immediate early gene it can be inferred that the expression and activity of this gene is not fully understood and needs vigorous research activities to understand its mode of action . The Arc gene is associated with cytoskeletal elements and aids in dendritic expansion and synaptic modulation . This activity can be put to therapeutic use for treatment of nerve damage and neuronal re - modelling . People lacking normal levels of Arc protein can be subjected to Gene Augmentation Therapy (GAT) for Arc gene and NMDA receptors to restore normal long term memory formation in the affected individuals . Patients with mutations in 3' - UTR of Arc mRNA has shown increased succeptibility to amyloid - beta plaque formation which leads to AD . So Arc gene can be used as an early indicator for a possible onset of AD . Mutated Arc gene can be silenced through epigenetic modification and other genetic counselling procedures to cure this menacing neuro - degenerative disease affecting millions world wide .

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