A major challenge in neuroscience is to define the molecular mechanisms and signalling pathways modulating changes in synaptic communication between neurons. These changes are believed to underlie cognitive processes that include memory acquisition and consolidation, reward and reinforcement as well as fear conditioning. It is well-established that synaptic communication strength is linked to neural activity and can be modulated pre-synaptically (by changing the probability of neurotransmitter release) or post-synaptically (by changing the number of receptors at synapses). In the last few decades significant progress has been made to address mechanisms linking network activity with changes in synaptic communication and many of the critical molecules involved were identified. One such molecule is the 50 kDa activity-regulated cytoskeleton associated protein (Arc), also known as Arg3.1. Arc was discovered in a study designed to screen for molecules upregulated during seizure activity. Subsequently Arc has proven to be of great interest to neuroscientists because increases in its expression specifically weakens synapses through the endocytosis of synaptic AMPA receptor subunits and causes structural changes in dendritic spines. Furthermore, Arc expression kinetics are highly dynamic, it can be switched on and off rapidly in response to changes in activity, and Arc function is compromised in a number of neurological diseases leading to deficits in cognition.

In this special issue of *Seminars in Cell and Developmental Biology* a collection of reviews have been assembled to reflect the latest findings that outline the role of Arc as a key coordinator of synaptic plasticity and cognition; highlighting some of the outstanding questions remaining in the field.

A series of articles discuss the properties of Arc expression and how they are controlled during several forms of synaptic plasticity. Specifically Ruth Carmichael and Jeremy Henley provide an engaging overview on the pathways causing alterations in Arc at the transcriptional and post-translational level in response to changes in neural activity. Unlike the processes regulating Arc expression and its abundance at synapses, not much is known about its loss. The processes regulating ubiquitin-dependent degradation of Arc protein and its implications in AMPA receptor endocytosis is covered by Angela Mabb and Michael Ehlers. In this exciting review, the authors discuss how disrupting the precise temporal removal of Arc limits the range of Arc-mediated endocytosis of AMPA receptors causing abnormal synaptic plasticity. Mark Wall and Sonia Correa considered how Arc interaction with components of the clathrin-mediated endocytosis machinery facilitates endocytosis of AMPA receptors. They also discuss the contentious issue of whether Arc preferentially internalises calcium permeable AMPA receptor subunits. Thomas Newpher, Scott Soderling and collaborators highlighted important findings showing how Arc coordinates AMPA receptor trafficking and cytoskeleton alterations at dendritic spines.

Arc is involved in several divergent forms of synaptic plasticity including long-term potentiation, long-term depression and synaptic scaling, demonstrating how adaptable this molecule is. Clive Bramham and colleagues provided an excellent and comprehensive review showing that Arc is a master regulator of synaptic strength due to its flexibility in selecting and coordinating its binding partners. In a complementary review Haruhiko Bito and colleagues describe the surprising observation that Arc is involved in long-term potentiation. This mechanism, termed inverse synaptic tagging, is when Arc is targeted to weak non-potentiated synapses to supress transmission at these synapses which consequently improves the signal-to-noise ratio for information transfer at strongly potentiated synapses.

In order to achieve a desired behaviour, the amount of synaptic potentiation and depression must be finely tuned. For example block of synaptic potentiation can interfere with memory formation. Kimberley Huber and colleagues elegantly consider how experience-driven activity induces Arc transcription and trafficking of Arc mRNA to spines, where it can be translated by activation of group I metabotropic glutamate receptors (mGluR). Activation of mGluR induces a form of long-term depression involved in cognitive flexibility. Irina Epstein and Steven Finkbeiner provided an exciting and extensive account of Arc trajectory from its transcription in the nucleus to Arc protein expression underlying synaptic plasticity and cognitive function.

Finally Jason Shepherd raises an intriguing possibility of how Arc has originated and highlights exciting recent studies providing evidence that mammalian Arc is evolved from a vertebrate lineage of Ty3/gypsy retrotransposons, which are also ancestral to retroviruses.

Arc is a very unique molecule mainly because it is specifically expressed in neurons and its temporal and dynamic expression is dependent on changes in neural activity in specific brain regions associated with learning and memory formation. These properties place Arc as a potential drug target. The authors considered how defects in the properties regulating Arc expression, interaction and removal impact on behaviour, cognitive function and neurodegenerative disease.

I am very grateful to the authors (and reviewers) for their contributions towards this issue and I hope that the readers will find the articles to be exciting and informative.

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