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SPLITTING HARES AND TORTOISES: A CLASSIFICATION OF NEURONAL IMMEDIATE EARLY GENE TRANSCRIPTION BASED ON POISED RNA POLYMERASE II☆

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Abstract—Immediate early transcription is an integral part of the neuronal response to environmental stimulation and serves many brain processes including development, learning, triggers of programmed cell death, and reaction to injury and drugs. Following a stimulus, neurons express a select few genes within a short period of time without undergoing de novo protein translation. Referred to as the 'gateway to genetic response', these immediate early genes (IEGs) are either expressed within a few minutes of stimulation or later within the hour. In neuronal IEGs that are expressed rapidly, productive elongation in response to neuronal activity is jump-started by constitutive transcription initiation together with RNA polymerase II stalling in the vicinity of the promoter. IEGs expressed later in the hour do not depend on this mechanism. On the basis of this Polymerase II poising, we propose that the immediate early genes can be grouped in two distinct classes: the rapid and the delayed IEGs. The possible biological relevance of these classes in neurons is discussed. Published by Elsevier Ltd. on behalf of IBRO.

Key words: RNA polymerase II, transcription, immediate early genes, neuronal activity, arc, plasticity.

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INTRODUCTION

The phrase 'immediate early genes' was initially coined by virologists and was used exclusively to describe viral regulatory factors transcribed de novo by host cells immediately within 2 min after viral integration (Jayaraman, 1972). Any subsequent transcription was, at that time, termed *delayed*-early transcription and referred to downstream genes on the circular viral plasmid. Decades later, the threshold of 2 min faded as the phrase 'immediate-early' was adopted widely by cell biologists (Cochran et al., 1983). This alteration in meaning was based on the recognition that many of the genes induced by viral integration were also induced immediately by extracellular signals such as growth factors (Greenberg and Ziff, 1984; Mulcahy et al., 1985). The mRNAs of most of these genes were detected at their peaks between 30 min and an hour (Curran et al., 1985). This observation led to incorporation of the first hour into the general definition of IEGs, which are usually defined as genes that can be expressed without de novo protein synthesis. Henceforth, most IEG studies in neurons were largely restricted to the hour-long timeframe.

As the molecular mechanisms underlying long-term memory were becoming known to neurobiologists, one important realization was that long-lasting synaptic changes such as long-term potentiation (LTP) relied on mechanisms distinct from the shorter lasting forms (Bliss and Collingridge, 1993). Depending on persistence, LTP has been classified as LTP1, LTP2 or LTP3 (Raymond, 2007). The fast decaying LTP1, also known as the early- or E-LTP, is protein and mRNA-synthesis independent. LTP2, the intermediary phase, is protein synthesis-dependent but independent of gene transcription. Presumably, LTP2 could be supported from existing pools of mRNA and protein in the cell, but LTP3, the longest lasting form of LTP, seemed to require de novo mRNA synthesis followed by their translation within a very short 'critical window' of time (Montarolo et al., 1986; Nguyen et al., 1994; Frey et al., 1996); if gene

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Abbreviations: CREB, cAMP response element-binding protein; CRTC, CREB-regulated transcription coactivator 1; GTF, general transcription factor; IEG, immediate early genes; LTP, long-term potentiation; MMTV, mouse mammary tumor viruses; NELF, negative elongation factor; NMDA, *N*-methyl-D-aspartic acid.

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transcription was blocked outside of this window, consolidation of L-LTP was unaffected. Thus the immediate induction of genes was proposed to be an integral step in the consolidation of LTP. Identification of these immediate early genes, therefore, was widely considered to be a priority for understanding how synaptic changes could last for extended periods (Curran and Morgan, 1985; Greenberg et al., 1985; Morgan and Curran, 1986; Morgan et al., 1987). Consistent with the idea that immediate transcription can occur in neurons, several IEGs such as *cfos* were found to be strongly induced within a matter of minutes by such diverse stimuli as seizure activity, electrical stimulation and injury (Dragunow and Robertson, 1987a,b; Morgan et al., 1987; Saffen et al., 1988). Due to their reliable temporal signature, IEG expression is now commonly used to track neuronal activity in specific areas of the brain in response to specific behaviors. For example, IEGs can be induced in the visual cortex by exposing dark-reared animals to light and in hippocampal neurons in response to an animal exploring a novel environment (Worley et al., 1990; Guzowski et al., 1999). Thus, it appears that IEG expression is a major early step in the neuronal genetic response to many different physiological processes.

Given the likely relevance of IEGs to neuron function, therefore, identification of every neuronal IEG was soon attempted using subtractive hybridization and differential cDNA cloning (Nedivi et al., 1993; Qian et al., 1993; Yamagata et al., 1993). Based on these screens, the number of neuronal activity-induced IEGs was initially estimated to be around 500–1000 (Nedivi et al., 1993). Subsequently however, the number of activity-induced IEGs was found to be closer to 30–40 (Lanahan and Worley, 1998). A substantial number of these IEGs were transcription factors and, as such, are expected to regulate expression of downstream gene products. Additionally though, neurons express a small number of unique IEGs that are not transcription factors. These neuronal IEGs, often referred to as 'effector IEGs', perform a range of functions outside the nucleus and many localize to synaptic sites and regulate synaptic function (Leslie and Nedivi, 2011). Because IEGs have such an important role in neuronal physiology, understanding the mechanisms leading to their induction could lead to important insights into neuronal contexts in which different genes are induced.

MANY ROUTES TO NEURONAL IEG INDUCTION

Under physiological conditions, neurons perceive environmental signals in the form of both electrical activity through synapses and neuromodulatory signals through the release of compounds such as growth factors. In the case of excitatory synapses in the brain, binding of glutamate to ligand-gated ion channels leads to Ca^{2+} influx through *N*-methyl-D-aspartic acid (NMDA)-type glutamate receptors. In addition, glutamate also binds to and opens AMPA-type glutamate receptors, which generate a post-synaptic potential that depolarizes the membrane, allowing further influx of Ca^{2+} through voltage-gated ion channels. Calcium, a strong inducer of neuronal and non-neuronal IEGs (Greenberg et al., 1986), is thought to be sensed locally near the membrane and the signal then relayed to the nucleus via signaling cascades that require post-synaptic second messengers and cAMP- and calcium-dependent protein kinases (Greer and Greenberg, 2008; Kandel, 2012). Phosphorylation of constitutively expressed transcription factors could then bind to specific regulatory elements in a gene promoter or enhancer and initiate gene transcription by recruiting RNA Polymerase II (Pol II) (Greer and Greenberg, 2008; West and Greenberg, 2011). This 'synapse-to-nucleus' signaling model is built on two lines of evidence. Firstly, activity-induced gene transcription is typically sensitive to antagonists of NMDA receptors, a major source of synaptic Ca^{2+} influx in neurons. Secondly, and more recently, signaling molecules have now been imaged en route to the nucleus in response to synaptic activity. These molecules include widely studied MAP and CaM kinases and more recently AIDA-1 and CRTC1 (Martin et al., 1997; Deisseroth et al., 1998; Jordan et al., 2007; Ch'ng et al., 2012). Such spatial translocation of signaling molecules is well characterized in non-neuronal cells where the nucleus is not far from the membrane signaling events and thus the mechanism is well suited to mediate immediate cellular response. However, neuronal nuclei are often located several hundred microns away from distal synapses and signaling molecules may not translocate to the nucleus fast enough to explain very fast IEG induction in response to neuronal activity or behavior: several studies have reported behavioral task-induced IEG products in 2 min (Guzowski et al., 1999, 2001).

To explain signal transduction suitable for the fastest IEG expression, we have previously proposed that the signal for LTP-related gene transcription may be relayed to the nucleus via action potentials through calcium (Adams and Dudek, 2005; Saha and Dudek, 2008). Integrated post-synaptic potentials create trains of action potentials that depolarize the membrane to allow Ca^{2+} influx through NMDA receptors and voltage-gated channels. Because the synaptic depolarization travels along the membrane in a flash, Ca^{2+} influx can occur throughout the neurons and at somatic membranes in proximity of the nucleus, thus requiring very little time for the signal to travel from distal synapses. At that point, Ca^{2+} can either act at plasma membrane microdomains associated with L-type Ca^{2+} channels, or else diffuse into the somatic cytosol to trigger signaling cascades such as the Ca^{2+}–calmodulin and MAP kinase pathways (Hardingham et al., 2001; Wheeler et al., 2008). Alternatively, incoming Ca^{2+} can act directly in the nucleus where it can potentially signal gene transcription (Zhang et al., 2009). Along these lines, several studies have shown that action potentials can trigger important signaling cascades, induce gene transcription and rescue long-term potentiation from

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