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Gene regulation in the immediate-early response process

Shahram Bahrami [a, b], Finn Drabløs [a, *]

[a] Department of Cancer Research and Molecular Medicine, NTNU - Norwegian University of Science and Technology, NO-7491 Trondheim, Norway
[b] St. Olavs Hospital, Trondheim University Hospital, NO-7006 Trondheim, Norway

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ABSTRACT

Immediate-early genes (IEGs) can be activated and transcribed within minutes after stimulation, without the need for *de novo* protein synthesis, and they are stimulated in response to both cell-extrinsic and cell-intrinsic signals. Extracellular signals are transduced from the cell surface, through receptors activating a chain of proteins in the cell, in particular extracellular-signal-regulated kinases (ERKs), mitogen-activated protein kinases (MAPKs) and members of the RhoA-actin pathway. These communicate through a signaling cascade by adding phosphate groups to neighboring proteins, and this will eventually activate and translocate TFs to the nucleus and thereby induce gene expression. The gene activation also involves proximal and distal enhancers that interact with promoters to simulate gene expression. The immediate-early genes have essential biological roles, in particular in stress response, like the immune system, and in differentiation. Therefore they also have important roles in various diseases, including cancer development. In this paper we summarize some recent advances on key aspects of the activation and regulation of immediate-early genes.

Contents

Abbreviations: IER, immediate-early response; IEG, immediate-early gene; PRG, primary response gene; SRG, secondary response genes; PDGF, platelet-derived growth factor; EGF, epidermal growth factor; SRF, serum-response factor; NF-kB, nuclear factor-kB; CREB, cyclic AMP response element-binding protein; AP-1, activator protein-1; TCF, ternary complex factor; ERK, extracellular signal-regulated kinase; MAPK, Mitogen-activated protein kinases; ELK1, E26-like kinase; MRTF, myocardin related transcription factor; NF1, nuclear factor 1; PARP1, Poly (ADP-ribose) polymerase 1; RSK, p90 ribosomal S6 kinase; JNK, c-Jun N- terminal kinase; ERK5, extracellular signal regulated kinase-5; BMK1, Big MAP kinase-1; MSK, Mitogen/stress activated protein kinase; RNA Pol II, RNA polymerase II; GO, Gene Ontology; TBP, TATA binding protein; TSS, Transcription Start Site; HAT, histone acetyl transferase; IRF3, interferon regulatory factor 3; TLR, Toll-like receptor; NGF, nerve growth factor; G protein, guanine nucleotide binding protein; TF, Transcription Factor; MKL, megakaryoblastic leukemia; ESC, embryonic stem cells; DSIF, DRB sensitivity-inducing factor; NELF, negative elongation factor; P-TEFb, positive transcription elongation factor; CTD, C-terminal domain; eRNA, enhancer RNA.

* Corresponding author. Department of Cancer Research and Molecular Medicine, NTNU - Norwegian University of Science and Technology, P.O. Box 8905, NO-7491 Trondheim, Norway.
E-mail addresses: shahram.bahrami@ntnu.no (S. Bahrami), finn.drablos@ntnu.no (F. Drabløs).

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1. Introduction

Regulation of gene transcription is one of the main mechanisms that are used by cells to increase or decrease the concentration of specific gene products (RNA and protein) (Lewin, 2004). Gene transcription is controlled through many layers of regulation, where the choice of specific pathways affects the timing of induced gene expression as a response to an external signal. A specific group of genes seems to be able to respond very quickly to regulatory signals, for example in immune responses or cellular stress. Such processes are often known as immediate-early response (IER) processes, and the genes involved are therefore known as immediate-early genes (IEGs).

There are many relevant questions regarding IEGs. For example, how are IEGs activated, since they are able to respond very rapidly to external signals? What are the key aspects of their promoters? Do they interact with enhancers? How important is the epigenetic profile of the IEGs? This paper tries to summarize and provide updated information on some of these questions.

2. Early gene responses

2.1. Primary responses

Several genes respond rapidly to cellular signals, and such signal-responsive primary response genes (PRGs) are expressed following a wide range of different stimuli, linked to diverse signaling pathways. They can be divided into two main classes; the immediate-early response genes, and the delayed primary response genes.

2.1.1. Immediate-early response genes

The mRNA for IEGs may appear in cells within minutes after stimulation. Even more important, cells can transcribe mRNA for IEGs in the presence of protein synthesis inhibitors, indicating that the proteins required for their synthesis (including e.g. the transcription factors) are already available in the cell, and not synthesized as part of the activation process (Herschman, 1991; Morgan and Curran, 1991). These genes respond to a wide variety of extrinsic stimuli and in multiple cell types (Fowler et al., 2011), indicating a very general response mechanism. There are probably a few hundred genes in this group. These genes were first identified in cells exposed to mitogens, and have an important role in the regulation of the cell cycle (Greenberg and Ziff, 1984). Many IEGs are proto-oncogenes and their sustained expression can have profound effects on cellular growth.

2.1.2. Delayed primary response genes

Many of the primary response genes encode transcription factors, which again regulate secondary response genes (Winkles, 1998) (see subsection Secondary responses). However, it has been shown that some of the delayed inductions do not require protein synthesis, and therefore represent delayed induction of primary response genes rather than induction of secondary response genes. This group of genes is called delayed primary response genes, and they are different from IEGs both in function and in genomic architecture (Tullai et al., 2007).