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Review

A systems biology approach to developmental toxicology☆

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Abstract

Recent advances in developmental biology have yielded detailed models of gene regulatory networks (GRNs) involved in cell specification and other processes in embryonic differentiation. Such networks form the bedrock on which a systems biology approach to developmental toxicology can be built. In this review, an introduction to GRNs in general is followed by a description of specific networks involved in sea urchin and Drosophila development. A hypothesis is presented regarding the role of GRN analysis in the determination of mechanisms of chemical toxicity during embryonic development. Potential for future directions and research approaches in this area is discussed.

Keywords: System biology; Gene regulatory network; Developmental toxicology

Contents

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1. Gene regulatory networks

1.1. Introduction

Embryonic development involves precise regulation of DNA transcription such that cell fates are specified appropriately leading to formation of germ layers and later tissues and

organs. Gene expression patterns, their regulation, and their translation to proteins determine the structure and ultimate function of the cells and tissues of the developing individual. Transcription factors are the proximate means by which changes in gene expression are ultimately produced, and embryonic development is determined by the interconnections among the transcription factors, the *cis*-regulatory elements, and genes. These complex interactions make up the genetic systems known as gene regulatory networks (GRNs). Recent reports using a number of species including sea urchin [1], Drosophila [2], and *C. elegans* [3] have described details of GRNs associated with particular genes, important for development, at specific points in time and space and have described methodological approaches for investigating developmental gene regulation. Our goal in this paper is to review the role of GRNs in embryonic development and to present support for the proposal that induction of birth defects by some xenobiotics may be the result of altered transcriptional regulation and could be best understood in terms of gene regulatory network theory and systems biology.

1.2. Basics of GRNs

Britten and Davidson [4] posited the concept that "A given state of differentiation tends to require the integrated activation of a very large number of noncontiguous genes". This theory of gene regulation stands as a basis for current work that seeks to delineate the molecular mechanisms that govern cellular development and differentiation. Important to the progress made in this field has been the development of a multitude of experimental methods, such as gene knock-outs, reporter molecules, microarrays, proteomics, and computational methods, that are needed to develop models of gene networks. One of the goals of systems biology and computational modeling is to understand the coordination of the expression of interrelated genes across time and under various physiological conditions.

A fundamental unit of a genomic network is the *cis*-regulatory element, a DNA sequence that is usually found in regions of the DNA flanking a gene; the binding of regulatory proteins to a *cis*-regulatory element directs the transcription of genes [5]. Regulatory modules consist of multiple *cis*-regulatory elements all of which play a role in the modulation of the expression of that gene. A group of genes under the control of similar regulatory modules is a gene battery, and a single *cis*-regulatory element can appear in a large number of distinct genes. One may think of a gene regulatory network as a structural gene in association with (although not necessarily contiguous to) a number of DNA sequences which either code for transcription factors (TFs) or serve as recipients of the activating or repressive action of the factors themselves. The process becomes more complex as one considers that the regulators of the gene regulatory factors are themselves regulated by regulators, seemingly ad infinitum. Information is integrated within a module based on the occupancy of the *cis*-regulatory sites by the cognate regulatory factors to positively or negatively control the timing, location, and or amplitude of expression of nearby genes [5]. Fig. 1 shows a model of some of the basic components of a gene regulatory network, incorporating *cis*-regulatory elements, regulatory factors, the genes encoding the regulatory factors, genes being regulated, and a gene battery consisting of a number of co-regulated genes [6,7].

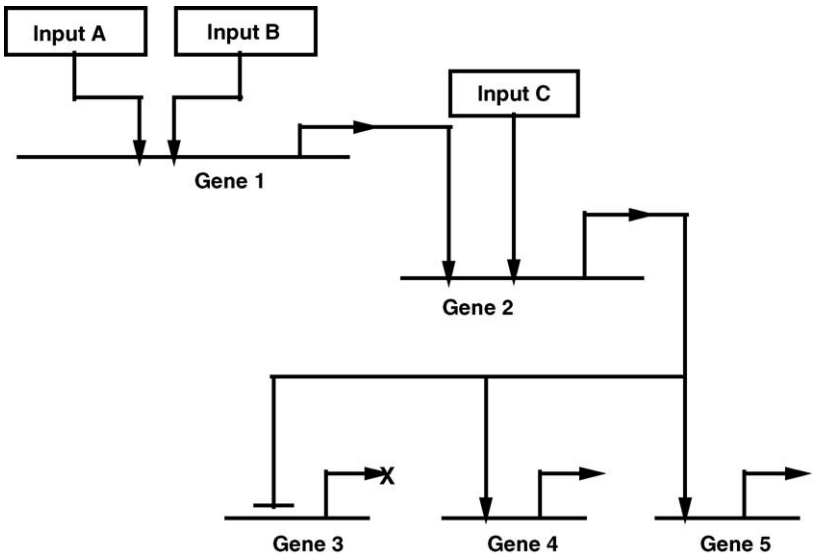

Fig. 1. Representation of basic subunits of gene regulatory networks (GRNs). Genes 1 and 2 code for regulatory factors, and Genes 3–5 represent structural genes. The regulatory region of gene 1 receives input from sources A and B, and, in this case, both A and B are required to activate the gene. The product of this activation plus input from another source, C, permits activation of Gene 2 and transcription of the corresponding transcription factor. Transcription factor 2 activates Genes 4 and 5 but inhibits the activation of Gene 3, a gene additionally regulated by other transcription factors not shown. Downward arrows represent activation, and horizontal bars represent repression. Adapted with permission from Bolouri and Davidson [7].