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Review

Globin genes transcriptional switching, chromatin structure and linked lessons to epigenetics in cancer: A comparative overview ☆

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Abstract

At the present time research situates differential regulation of gene expression in an increasingly complex scenario based on interplay between genetic and epigenetic information networks, which need to be highly coordinated. Here we describe in a comparative way relevant concepts and models derived from studies on the chicken α- and β-globin group of genes. We discuss models for globin switching and mechanisms for coordinated transcriptional activation. A comparative overview of globin genes chromatin structure, based on their genomic domain organization and epigenetic components is presented. We argue that the results of those studies and their integrative interpretation may contribute to our understanding of epigenetic abnormalities, from β-thalassemias to human cancer. Finally we discuss the interdependency of genetic–epigenetic components and the need of their mutual consideration in order to visualize the regulation of gene expression in a more natural context and consequently better understand cell differentiation, development and cancer.

Keywords: Chromatin; Chromatin domain; Enhancer; Epigenetic; Insulator; Globin genes; Silencer; Transcription

Contents

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1. Introduction

Cell lineage commitment in metazoans is established early during development by specific gene expression networks determining highly specific cell differentiation patterns that are mitotically propagated. For several years we have been interested in the relationship between gene regulation and chromatin structure. Epigenetic processes recently emerged as responsible for temporal- and tissue-specific gene expression, not only during cell differentiation and development but also in cancer.

Over the years, comparative genetics had contributed to the understanding of gene organization and conservation among different species (Kosak and Groudine, 2004; Wasserman and Sanderlin, 2004), leading to visualization of a genetic landscape in different organisms. Today, such a view seems to be limited without considering two critical components: the extended non-coding or intergenic sequences and the genome structured into chromatin, i.e., the epigenome. Consequently, to attain an overview of how cellular processes like DNA replication, recombination, DNA repair and differential gene regulation among others occur inside the cell and particularly into the nucleus, we clearly need an integrative genome–epigenome approach (Cremer and Cremer, 2001; Chakalova et al., 2005). Thus a comparative and multidisciplinary approach is nowadays needed to address different genomic processes that could lead us not only to better understand cell physiology but also to propose novel and more effective biomedical strategies to improve human health.

In the present manuscript we present a comparative overview of the α- and β-globin family of genes, with particular emphasis on the regulation of chicken globin domains, their chromatin organization as well as the epigenetic switching mechanisms occurring during cell differentiation and developmental gene expression. Finally, our knowledge about epigenetic mechanisms of aberrant silencing is linked to tumour suppressor gene promoters in cancer.

2. The α- and β-globin group of genes: generalities

Since their genomic sequence isolation, globin genes have been one of the most studied loci contributing to the generation of a long list of new concepts and revealing regulatory mechanisms, which are now been extrapolated to other genomic loci in diverse organisms. Part of those observations allowed the introduction of the transcriptional active domain concept that was previously anticipated from cytological evidences, in particular the differential chromosomal band staining (Cremer and Cremer, 2001; Razin et al., 2003). For more than 15 years we have been interested in the study of the chicken α- and β-globin group of genes (Farache et al., 1990; Recillas-Targa, 2000; Burgess-Beusse et al., 2002; Rincón-Arano et al., 2005). Those investigations have constantly been busted by the large amount of data generated on human and mouse genomes (Stamatoyannopoulos, 2005; Higgs et al., 2005). Even with such accumulation of data and progress, the chicken α- and β-globin loci remain as an apparent endless source of new information contributing to novel views for differential gene expression and chromatin conformation at the domain scale, allowing constant proposals for new models.

As in other organisms, the chicken α- and β-globin domains differentially and coordinately express their genes, which encode distinct types of hemoglobins with variations of oxygen affinity determining their physiological role during development. Each set of genes is grouped as a cluster, which are located in distinct chromosomes, the minichromosome 14 for the α-globin group of genes and the chromosome 1 for the β-globin domain in the chicken.

3. The chicken α-globin domain and its regulatory components

The chicken α-globin domain is contained in a genomic region of around 40 kilo bases (kb) with an embryonic π gene and two adult α^D and α^A genes that are differentially regulated during erythroid differentiation and development (Fig. 1; Recillas-Targa, 2000; Recillas-Targa and Razin, 2001). A series of erythroid-specific and constitutive DNase I hypersensitive sites (DHS) have been identified all along the domain, including the intergenic DHS and those corresponding to individual regulatory elements like promoters, enhancers and structural chromatin components (Fig. 1). Individual promoters contain the classical set of nuclear factor binding sites present in the great majority of other globin genes (Stamatoyannopoulos, 2005; Dean, 2006). Interestingly, a recent publication demonstrated that Sox6 is involved specifically in the ε-globin gene silencing in definitive erythropoiesis at the mouse β-globin locus (Yi et al., 2006). We hypothesize that Sox6 may contribute, through chromatin remodeling, to the autonomous silencing of the embryonic π gene when adult genes are needed to

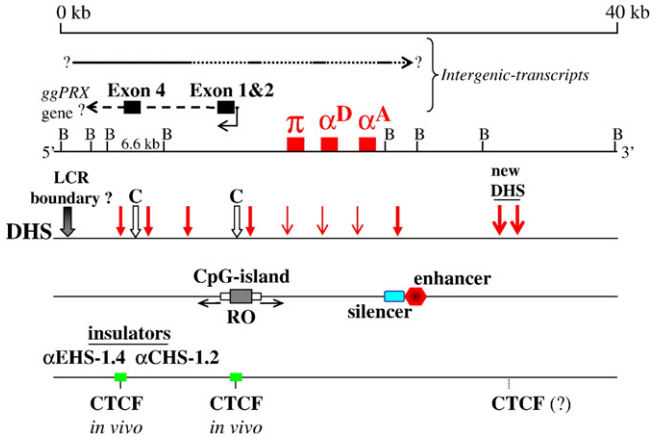

Fig. 1. The chicken α-globin domain regulatory and chromatin structure elements. The embryonic π gene, and adult α^D and α^A genes are shown. *Bam*HI restriction enzyme recognition sites are indicated (B). Intergenic transcripts are presented, although their starting and ending points are not clearly known. Part to the *ggPRX* gene transcript I represented. Distribution of DNase I hypersensitive sites (DHS) is indicated by vertical arrows, with alternate presence of two constitutive (C) sites on the domain 5′-side. Regulatory elements upstream and downstream of the α-globin genes are shown. The two newly defined insulators are located at the domain 5′-side (αEHS-1.4 and αCHS-1.2) and the *in vivo* CTCF binding is indicated.