Regulatory Domains and Their Mechanisms

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The concept of gene regulation is being refined as our understanding of the role of enhancer elements grows. Although described more than 30 years ago, the mechanisms through which these *cis*-regulating elements operate remain under debate. With the recognition that most of the human genetic variation contributing to common disease risk lies outside of genes and probably in enhancers, unraveling these mechanisms becomes ever more important. Originally, a popular view was to consider regulatory elements as an entry site for the transcription machinery that could scan the intervening chromatin until the cognate core promoter was located. Now, the most prominent model for distal enhancer–promoter interaction involves direct enhancer/promoter contacts with a looping out of intervening chromatin. However, a rising awareness of the importance of chromatin architecture and organization forces us to consider enhancer–promoter communication in light of the polymer folding properties of chromatin. Here, we discuss how three-dimensional chromatin folding, topological domains, and the constrained motion, plasticity, and accessibility of chromatin could offer a structural basis for regulatory domains that greatly enhances the probability of enhancer–promoter and transcription factor–promoter interactions and gene activation.

The definition of a gene has evolved significantly over the past 35 years. In metazoans, and particularly in mammals, the functional genetic unit now goes far beyond the genomic region that encodes an mRNA. 5' elements adjacent to the transcription start site encompass the core promoter and serve as the docking site for the RNA polymerase II preinitiation complex (PIC). However, additional layers of complexity have emerged, including multiple alternative promoters, alternative exons, and *cis*-regulatory sequences positioned upstream, downstream, or even within an intron of the transcription unit.

Although the core promoter determines where transcription begins, the *cis*-regulatory sequences—or enhancers—stimulate promoters in a time and tissue-specific manner and increase the efficiency of transcription in a position- and orientation-independent manner. However, both enhancer and gene activation are associated with similar events—that is, recruitment of transcription factors, coactivators, and RNA polymerase II and production of RNA (albeit short and unstable at enhancers) (Koch et al. 2011). Therefore, enhancers have long been seen as simple extensions of promoters as both lead to assembly of an active transcription complex and are often bound by the same components (Andersson et al. 2015).

The first enhancer described was the 72-bp tandem repeat of SV40 DNA, which was identified as a sequence located ~100 nt upstream of the core early viral promoter (Fig. 1) and whose deletion reduced gene expression and abolished virus viability (Benoit and Chambon 1981; Gruss et al. 1981). Later, the SV40 enhancer was found to comprise three main segments, each of which provides

cell type specificity (Schirm et al. 1987). In parallel, it was discovered that the SV40 enhancer could work when associated with other diverse promoters. Surprisingly, it could also act over considerable distances (>10 kb) and its activity appeared to rely on the sequence of the intervening chromatin rather than the distance (Banerji et al. 1981; Mellon et al. 1981; Moreau et al. 1981).

Other sequences with equivalent function in mammalian cells were soon identified (Conrad and Botchan 1982; Banerji et al. 1983), including locus control regions (LCRs)—which define regulatory domains that are groups of enhancers. The first LCR element identified 25-kb upstream of the human ϵ -, γ -, δ -, and β -globin genes (Fig. 1) shared characteristics of the SV40 enhancer including clustered DNase I hypersensitive sites (DHSs) (Grosveld et al. 1987; for review, see Li et al. 2002).

Now, human and mouse Mendelian genetics have revealed enhancers located up to 1 million base pairs (megabase/Mb) 5' or 3' of target genes (Fig. 1), often with other intervening genes located in-between, or embedded within the introns of nearby genes (Noonan and McCallion 2010). Thus, the functional unit of gene regulation in the mammalian genome, for coding regions that are themselves often <10 kb in size, can be of the order of 2 Mb in size.

Since they were first described, many of the molecular characteristics of enhancers have been established including transcription factor binding, coactivator recruitment, DHS, distinctive histone marks, and eRNA production. Here, we specifically consider the regulatory domains in which enhancers operate and how these domains may be

Figure 1. Different scales of enhancer and promoter distances. (Top) Proximal enhancers can be located a few tens of bp from their target promoter. An example of this is the SV40 early promoter. (Middle) Enhancers such as the β -globin locus control region (LCR) are located tens of kilobases from their target promoters. (Bottom) Some developmental enhancers can be located hundreds or even 1000 kb from their target gene, often with other, unrelated genes, in between. The *Shh* limb enhancer (ZRS) is an example of this.

integrated in specific chromatin conformations that influence enhancer–promoter communication.

cis-ACTING ELEMENTS

For the most part, enhancers function in *cis*. Exceptions include the ability of enhancers to work between homologous chromosomes in *Drosophila* cells that show somatic pairing (Schoborg et al. 2013) and the infrequent interaction of multiple enhancers—located on different chromosomes—with murine olfactory receptor genes, as the basis for stochastic choice in olfactory receptor gene expression in olfactory neurons (Markenscoff-Papadimitriou et al. 2014).

The requirement for a target gene and its enhancer to be located in *cis*, in order for gene activation to be robust, is evidenced by the Mendelian genetic disorders that arise when translocations separate enhancer and promoter onto different chromosomes (Kleinjan and van Heyningen 2005; Benko et al. 2009; Lango Allen et al. 2014; Rainger et al. 2014).

Genetic evidence indicates that enhancers can act over 1 Mb of intervening chromatin. However, their range may not be much greater than this. Chromosomal inversions that increase the genomic distance between an enhancer and its target gene can, in some cases, abrogate enhancer function (Lettice et al. 2011).

Chromosome structural rearrangements have set the likely limits of enhancer function in the human genome and indicate that correct enhancer function usually depends on the enhancer being present within a range of ~ 1 Mb in *cis* with its target gene. However, it is important to remember that enhancers are not constrained to have to work at a distance. Both enhancer reporter assays (Bhatia et al. 2015) and localized transposon hopping (Anderson et al. 2014; Symmons et al. 2014) show that endogenous mammalian enhancers that act at long range in their normal chromosomal context are quite capable of also acting

at short range. It is within this framework that we now consider possible mechanisms of enhancer function in the context of three-dimensional chromatin conformation.

SPREADING OF A SIGNAL: LINKING AND TRACKING MODELS

The original view of regulatory element action was that it provided a precise docking site for RNA polymerase II or other components of the transcriptional machinery, followed by tracking of these factors on the chromatin fiber until they met the cognate core promoter and activated it in a time- and position-dependent manner.

Exploration of tracking-like mechanisms at several loci, such as β -globin, has reported the unidirectional spreading of histone H3 and H4 acetylation, the CBP/p300 histone acetyltransferases, P/CAF, subunits of the SWI/SNF chromatin remodeling complex, or RNA polymerase II and TBP with accompanying synthesis of short, polyadenylated, intergenic RNAs (Gribnau et al. 2000; Hatzis and Talianidis 2002; Spicuglia et al. 2002; Masternak et al. 2003; Kim and Dean 2004; Zhao and Dean 2004; Wang et al. 2005; Zhu et al. 2007). These studies implicate tracking as the primary step for enhancer–promoter interaction and speculate that a stable enhancer–promoter loop is only formed when the tracking is complete (Fig. 2A). However, the formation of stable enhancer–promoter complexes has not always been convincingly shown. The linking hypothesis differs from the tracking mechanism, as the proteins involved do not scan all of the intervening chromatin but instead oligomerize to spread the signal (Fig. 2B).

In these examples of enhancer–promoter communication, the genomic distance separating the two elements is modest (generally < 20 kb) and, from both kinetic and spatial perspectives, it is hard to imagine how one-dimensional tracking or linking mechanisms could operate over much larger (e.g., 1-Mb) distances and over intervening genes.

Figure 2. Enhancer and promoter communication mechanisms. Activating signals, such as transcription factors, bind enhancers recruiting other proteins, such as coactivators, that may track along the chromatin fiber until they meet their cognate promoter (*A*: tracking model) or oligomerize and form a protein bridge to meet their cognate promoter (*B*: linking model). Enhancer elements may be brought to the vicinity of their cognate promoter by direct interaction and looping out of the intervening chromatin region (*C*: looping model), or enhancers may just be constrained within the same nuclear domain as their target genes with protein and chromatin constrained diffusion then being sufficient to activate gene expression (*D*: nuclear domain model).

BRIDGING THE DIVIDE: THE CHROMOSOME LOOPING MODEL

The current favored model for long-range enhancer–promoter communication involves direct homotypic or heterotypic interactions between enhancer- and promoter-bound proteins to form a chromatin loop that juxtaposes enhancer and promoter at the loop base and that loops out the intervening chromatin (Fig. 2C; Su et al. 1991).

Elegant chromosome engineering experiments at the β -globin locus have shown that forcing a chromosome loop between an enhancer and its target promoter is sufficient to trigger gene expression in erythroid cells, in which some other key transcription factors required for β -globin expression are already bound (Deng et al. 2012, Deng et al. 2014). However, the extent to which endogenous enhancers and promoters form relatively stable chromatin loops is currently unclear.

Much of the evidence for enhancer–promoter loops comes from the detection of enhancer–promoter ligation products in the chromosome conformation capture (3C) technique and its derivatives (4C, 5C, Hi-C, etc.) (Tolhuis et al. 2002; Palstra et al. 2003; Montavon et al. 2011; Jin et al. 2013). However, such assays do not have the ability to determine the frequency at which such interactions take place, to determine the molecular nature of such interactions, or to determine whether the interactions are the cause or consequence of enhancer-driven gene activation.

In some instances fluorescence in situ hybridization (FISH) has shown the spatial juxtaposition of distant

enhancers and promoters at frequencies high enough (30% or more of alleles) to be interpreted as the base of a chromosome loop (Williamson et al. 2012; Lettice et al. 2014). However in other cases, visual assays do not provide evidence for relatively stable chromosome loops (Williamson et al. 2012). This does not exclude the existence of very transient enhancer–promoter contacts, but we would argue that such infrequent contacts should not be described as chromatin loops.

How enhancers and promoters find each other in nuclear space is not known, but it seems most likely that it occurs as a consequence of the rapid, but constrained, diffusion (diffusion coefficient of $\sim 1 \times 10^{-4} \mu\text{m}^2/\text{sec}$) that characterizes chromatin motion in living human cells (Chubb et al. 2002). This implies that enhancers and their cognate promoters must both be located within a small enough nuclear volume to be compatible with the radius of constraint for chromatin motion. For the genomic loci measured to date, this constraint ($< 0.5 \mu\text{m}$) could encompass loci that are up to ~ 1 Mb from each other (Fig. 3A,B).

The formation of a stable chromatin loop has an entropic cost to polymer dynamics as it would need to overcome inherent diffusion. It would be interesting to investigate the strength of binding energies between enhancer- and promoter-bound proteins that would be required to stabilize chromatin loops of various sizes. This may be even more of an issue for enhancers located close to promoters, where the persistence length of the chroma-

Figure 3. Chromatin compaction and constrained motion and its influence on transcription factor diffusion. (A) FISH image illustrating a highly compact chromatin conformation of an inactive enhancer (red) and its cognate promoter (green), despite their being separated by several hundred kilobases, in the cell nucleus of a nonexpressing cell type. Scale bar, 5 μm. (B) Schematic representation of constrained chromatin motion (0.5 μm average range) where chromatin can only sample a small proportion of the nuclear volume or indeed of the chromosome territory (pale blue). Enhancers and their cognate promoters must be close enough to each other in nuclear space to be able to encounter each other through constrained diffusion. Scale bar, 5 μm. (Chubb and Bickmore 2003.) (C) Compact chromatin domains, such as topologically associated domains (TADs), and their viscoelastic properties, can affect the dimensionality of transcription factor diffusion and create compact volumes that can locally concentrate transcription factors, RNA polymerase, and coactivators.

tin polymer may be a further energetic barrier to loop formation.

KEEPING IT CONCENTRATED: REGULATION WITHIN NUCLEAR DOMAINS

The activation of gene expression requires the formation of protein–protein and protein–DNA complexes, the efficiency of which will be dependent on the laws of mass action and so will be very sensitive to local concentration of both proteins and DNA. Chromatin packaging may

therefore be an important determinant of regulatory domains. In vivo analysis of the binding regimes of transcription factors shows that some use facilitated diffusion (i.e., 3D diffusion interspersed with local 1D sliding along the chromatin fiber). This greatly reduces their search space to give an efficient means of finding their specific binding sites (Chen et al. 2014; Izeddin et al. 2014; Woringer et al. 2014; Normanno et al. 2015). A transcription factor bound at an enhancer might then rather efficiently, by oversampling the local volume, be able to find a promoter-proximal binding site located

within the same chromatin domain, obviating any need for a specific enhancer–promoter chromatin loop (Figs. 2D, 3C).

A second mode by which chromatin packing might affect enhancer function is by reducing the volume in which proteins involved in transcription (e.g., coactivators, components of the PIC) are free to diffuse and to form complexes with each other (excluded volume effect) (Woringer et al. 2014). Interestingly, ~1 Mb chromatin domains containing genes subject to complex developmental regulation that is driven by suites of enhancers appear to have a very compact chromatin structure, even in nonexpressing tissues (Fig. 3A; Williamson et al. 2012; Lettice et al. 2014). This suggests that they may have evolved to facilitate both excluded volume and facilitated diffusion effects. Because of the viscoelastic properties of the nuclear environment, compact chromatin domains have been shown to affect chromatin motion and to dramatically reduce the first encounter time for distant genomic regions (Lucas et al. 2014).

A domain model for enhancer function may help to explain how primary and shadow enhancers, by both being contained in the same compact nuclear domain, could provide robustness to gene regulation during development, particularly when key molecules required for specific gene activation are limiting in the nucleus (Bothma et al. 2015; Lam et al. 2015). It also provides a plastic environment within which new enhancers can evolve to drive new patterns of gene regulation, or within which existing enhancers can relocate (Villar et al. 2015), without having to disrupt and rewire preexisting defined chromatin loops mediated by other enhancers in the same domain.

How such chromatin domains remain compact is unclear. It has been suggested that closed DNA domains could be formed by supercoiling with architectural proteins bound at the ends of these domains hindering the axial rotation that would relieve supercoiling (Duncan et al. 1994; Ner et al. 1994; Yang et al. 1995; Gilbert and Allan 2014). Indeed several studies have shown that enhancers and their target promoters tend to be located within the same topologically associated domains (TADs)—as defined from HiC data (Jin et al. 2013). In addition, reporter assays show that the influence of an enhancer declines sharply beyond the TAD domain boundary (Anderson et al. 2014; Symmons et al. 2014). Conversely, disrupting TAD boundaries can rewire enhancer and promoter communication leading to inappropriate gene activation (Lupiáñez et al. 2015).

What forms TAD boundaries is not completely clear, but convergently oriented CTCF sites, which also recruit cohesin, have been shown to be one important factor (Guo et al. 2015). The mechanistic basis for this is unclear, but it suggests the propagation of a directional signal from the boundary CTCF site in toward the TAD. Conceptually, this has some similarity to linking/tracking models of enhancer–promoter communication. However, the nature of that signal is unknown and it is likely that not all boundaries are the same.

CONCLUSION

Characterization of mammalian genomes using chromosome conformational capture techniques and microscopic imaging strongly support a model in which three-dimensional chromatin structures are organized into domains within which DNA–DNA and protein–DNA interactions are facilitated. It is within this framework that possible mechanisms of enhancer activation must be considered. Therefore, it becomes imperative that methods are developed that will allow the biophysical properties of chromatin domains and of transcription factor and chromatin motion to be quantified and manipulated in physiologically relevant systems.

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