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Restraining the enhancers from straying

Among the regulatory elements that control transcription of genes, especially in higher eukaryotes, enhancers are the most dramatic and often seemingly defy simple interpretations/expectations. An enhancer can drive gene expression in the most precise and regulated manner, so much so that among billions and trillions of cells, only a few cells may be expressing a gene by its enhancer. It may be a particular neuron, a particular cell type or even at a specific time in a cell time. Enhancers can act from a distance that is surprising at first sight, sometimes several hundred kilobases away in *cis* or even in *trans* from another chromosome, although much less often. They can be upstream of the gene, downstream of the gene or in the middle of the gene within introns, and all these combinations have same accuracy and precision.

In the context of these observations, it becomes important to know how enhancers achieve such extreme degree of specificity (Pennacchio *et al*. 2013). How does an enhancer lock in to the promoter of only the target gene and not to any other promoter even if there were one present at a shorter distance? To add to the surprises, it turns out that enhancers actually do not have promoter specificity or even great degree of promoter preference. When brought in the context by genetic manipulations, any enhancer will pretty much drive the expression of any gene. The functional test of the enhancer is, in fact, based on this feature, as a test fragment put along with the reporter gene inserted in the genome to see when and in which cell type expression of the reporter gene is seen by the putative enhancer test fragment.

It is now emerging that enhancer specificity is largely due to chromatin elements that prevent enhancers from straying and leaving them no option but to drive the correct target promoter (figure 1). The chromatin environment is locally defined for restricted access of enhancers is set by the chromatin domain boundary elements, a.k.a. insulators, barriers or enhancer blockers, depending on the experimental assay used to characterize such elements (Mishra and Karch 1999). For example, if inserted between enhancer and promoter, a boundary element will prevent the interaction between the two (Kellum and Schedl 1992). Boundary elements identified in species can function on evolutionarily distant species (Chung *et al*. 1993), suggesting that they are part of the very basic feature of genome organization and gene expression that evolved early on before the expansion of eukaryotes.

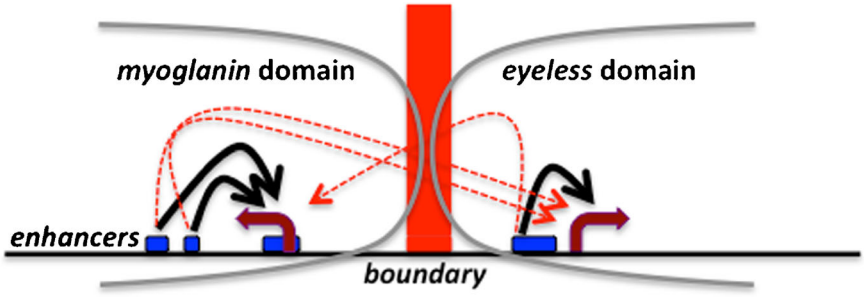

Figure 1. Cartoon showing regulatory two domains separated by boundary element (red bar). The two domains, containing *myoglanin* and *eyeless* genes have distinct pattern of expression different from each other although the two genes are closely spaced. The boundary element separating the two domains prevents inappropriate enhancer–promoter interactions, shown as broken red arrows, and restricts enhancers to act on appropriate promoters, shown as solid black arrows.

Keywords. Boundary element; chromatin; enhancer; gene regulation; promoter

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Recent technical advances have made it possible to predict or map boundary elements across the genome using specific tools or by utilizing the high throughput data available on mapping of histone modifications, accessibility and binding of specific proteins that may define functional domains of the genomes bordered by chromatin domain boundary elements (ENCODE Project Consortium 2012; Srinivasan and Mishra 2012). It turns out that the genome is packaged in a very precise and regulated manner where domains of differential transcriptional potential are established by elements like chromatin domain boundaries and regulatory elements appropriate to a gene are made accessible or inaccessible as per the requirement (Sultana *et al*. 2011). Luckily this time, enhancers follow this rule! An enhancer will drive expression of the gene within the domain defined by the boundary and not stray across the boundary!

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Rakesh K Mishra
Centre for Cellular and Molecular Biology
Uppal Road, Hyderabad 500 007, India
(Email, mishra@ccmb.res.in)