

Genome Organization Inside the Nucleus

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Summary

The mammalian cell nucleus is organized in a highly-ordered manner. Within nucleus, the genetic loci occupy preferential location [1-4]. For instance, some gene loci are present at nuclear periphery; some other gene loci interact with nuclear bodies such as nucleoli, nuclear speckles, Cajal bodies, etc. [5]. This preferential localization of gene loci varies depending on cell type or physiological conditions.

Discussion and Conclusion

Increasing evidence suggests a role of spatial localization of genetic material in influencing genome function. Several developmentally regulated genes are present at the nuclear periphery when they are inactive but reposition to the nuclear interior when they are active [6,7]. For example, immunoglobulin heavy chain (IgH) locus is located at the nuclear periphery when it is inactive, during the developmental stage. Whereas, when IgH gene is active, it is present in the nuclear interior [6]. There are also examples of gene loci changing their association with other nuclear bodies correlating with changes in transcription, e.g. heat shock genes associated with nuclear speckles upon activation by heat shock [8,9]. In addition, there are several descriptions where co-regulated genes cluster within the nuclear space, e.g. co-expressed erythroid genes were shown to cluster around nuclear speckles [10].

The molecular mechanism that governs the organization of genome is an active area of research. Some of the recent findings show that chromatin modifiers or epigenetic marks are responsible for the specific localization of a few genetic loci, e.g. histone H3K9 di and trimethylation by histone methyltransferase are required to localize some gene loci to nuclear periphery [11-14].

The disruption in the spatial organization of the genome has been identified in multiple human diseases. Chromosomal translocations, which are common in various cancers, are proposed to preferentially occur between chromosomes occupying nearby space in the nucleus [15]. In a variety of diseases, there are examples where individual genes, larger genomic segments or whole chromosomes change their localization [16,17]. Additionally, several proteins involved in the higher order organization of the genome are also implicated in diseases [18-20]. The most prominent are laminopathies, which are a group of diseases caused by mutations in nuclear envelope (NE) proteins. For example, mutations in lamin A/C causes Emery-Dreifuss muscular dystrophy (EDMD) and premature aging disease Hutchison-Gilford progeria syndrome (HGPS) [20-22].

With the help of advanced approaches like Chromosome conformation capture techniques (also known as 3C based techniques), DNA adenine methyltransferase identification (DamID), and microscopy; nuclear organization of genome is mapped at a greater depth [23-27]. Mapping of the genome organization across different cell types, development stages, and various physiological conditions will help us to better understand the role genome organization in genome function. In depth knowledge of genome organization along with genome editing tools can help towards better diagnosis and treatment of diseases.

Over the years, spatial organization of genetic material inside nucleus

has been shown to be critical for genomic functions and its disruption has been linked to diseases. Although poorly understood, the recent advancement of technologies holds a promising future towards mapping the genome organization to a greater detail and understanding the underlying molecular mechanisms.

The mammalian cell nucleus is organized in a highly-ordered manner. It is compartmentalized into chromosome territories along with many distinct nuclear bodies such as speckles, nucleoli, Cajal bodies among others [1-5]. Within nucleus, the genetic loci occupy preferential location. For instance, some gene loci are present at nuclear periphery; some other gene loci interact with nuclear bodies [6]. This preferential localization of gene loci varies depending on cell type or physiological conditions [7,8].

Increasing evidence suggests a role of spatial localization of genetic material in influencing its function. Several genes that change their nuclear location during cellular development also change their expression status [9,10]. For example, during lymphocyte development, immunoglobulin heavy chain (IgH) locus is located at the nuclear periphery when it is inactive. Whereas, when IgH gene is active, it is present in the nuclear interior [9]. There are also examples of gene loci changing their association with other nuclear bodies correlating with changes in transcription, such as heat shock genes associate with nuclear speckles upon activation by heat shock [11,12]. In addition, there are several descriptions where co-regulated genes cluster within the nuclear space, for instance coexpressed erythroid genes have been shown to cluster around nuclear speckles [13].

The molecular mechanism that governs the organization of genome is an active area of research. Some of the recent findings show that chromatin modifiers or epigenetic marks are responsible for the specific localization of a few genetic loci. For example, histone H3K9 di and trimethylation by histone methyltransferase are required to localize some gene loci to nuclear periphery [14-17].

Disruption in the spatial organization of genome has been identified in multiple human diseases. Chromosomal translocations, which are common in various cancers, are proposed to preferentially occur between chromosomes occupying nearby space in the nucleus [18]. For example, chromosomes 12 and 16 that are frequently translocated in liposarcoma patients are also found in close proximity in differentiated adipocytes [19]. In a variety of diseases, there are examples where individual genes, larger genomic segments or whole chromosomes change their localization [20,21]. Additionally, several proteins involved

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in the higher order organization of the genome are also implicated in diseases [22-24]. The most prominent of these are laminopathies, which are a group of diseases caused by mutations in nuclear envelope (NE) proteins. For example, mutations in lamin A/C cause Emery-Dreifuss muscular dystrophy (EDMD) and premature aging disease Hutchinson-Gilford progeria syndrome (HGPS) [25-27].

With the help of advanced approaches like Chromosome conformation capture techniques (also known as 3C based techniques), DNA adenine methyltransferase identification (DamID), and microscopy; nuclear organization of genome is mapped at a greater depth [28-33]. Mapping of the genome organization across different cell types, development stages, and various physiological conditions will help us to better understand the role genome organization in genome function. In depth knowledge of genome organization along with genome editing tools can help towards better diagnosis and treatment of diseases.

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