Laboratory of Genome Structure and Function

Graduate School of Science

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The ability of cells to store, retrieve, and translate genetic information is essential for the development and sustaining of living organisms. The genetic information of mammalian cells is preserved in the nucleus, in which DNA together with proteins and RNA form a complex called chromatin. Different types of cells in our body are originated from one cell, fertilized egg. Thus, such different types of cells still possess the same genetic information, but their cellular identities are determined by each cell-type-specific gene expression. This cell-type-specific gene expression pattern is controlled by epigenetic information including DNA methylation, histone post-translational modifications, and chromatin structure. This epigenetic information or epigenomes can be changed during differentiation or by environmental factors, but are also maintained and inherited by the next generation if cellular identity is fixed. We are interested in genetic and epigenetic mechanisms to inherit genetic information and utilize it properly. In addition, we want to understand how cell-type-specific epigenome can be switched or maintained through cell division at the molecular level. We employ omics approaches using mass spectrometry and next-generation sequencer, as well as molecular biological and genetical, biochemical, and cell biological approaches, to elucidate these issues.

How epigenome is inherited to and overwritten by the next generation.

In these years, the functional expression of genes in response to cell differentiation and stimuli has come to be thought to be regulated by marks on chromatin such as chemical modifications of histones and DNA, the so-called epigenome. These marks can be inherited or overwritten by the next generation without changing the genome DNA sequence. A single cell, the fertilized egg, proliferates and is into a terminally differentiated cell through various cell fates. During this process, the genetic information in the genome DNA is accurately preserved over the cell division, while the epigenome, which directs gene expression pattern for differentiation, is continually being overwritten. On the other hand, to maintain the terminally differentiated state, the epigenome must be accurately inherited to the next generation over the cell division. We are elucidating these mechanisms through analysis of uncharacterized chromatin proteins that we have originally discovered in human cells by a proteomic approach.

How epigenome is converted into higher-order chromatin structures

Chemical modifications of histones and DNA regulate gene expression by converting them into higher-order chromatin structures. For example, in heterochromatin, condensed chromatin structure prevents accession of transcription factors to DNA to inhibit transcription. We are trying to elucidate mechanisms of how epigenomic marks are converted into chromatin structures. For example, the inactive X chromosome in females has a condensed chromatin structure and represses almost all genes on it. We clarified that proteins we identified specifically bind an epigenomic mark to form condensed chromatin structure in cooperation with noncoding RNA, XIST.

Diseases caused by a catastrophe in the mechanisms of the epigenome

A catastrophe of the mechanisms in the epigenome can lead to a variety of diseases. For example, the dysfunction of proteins involved in the condensation of inactive X chromosomes we discovered, has been shown to cause certain types of muscular dystrophies. Our understanding of the epigenome mechanism is expected to lead to a better understanding of the molecular basis of the causes and pathophysiology of diseases, which subsequently will contribute to the diagnosis and treatment of these diseases.

Omics-based Research on the Epigenome

In our laboratory, we use comprehensive analytical methods that utilize genome sequence information. For example, using mass spectrometer, we can identify the name of even a very small amount of a protein. Using this technology, we are discovering uncharacterized proteins that are involved in the epigenome mechanism successively. In addition, the next-generation sequencer is a powerful device; we can find out where on the chromatin the protein we have identified is located and what function it performs.

The regulation of the epigenome is involved in various life events. This mechanism is still full of mysteries. Let's try to solve the mystery together!

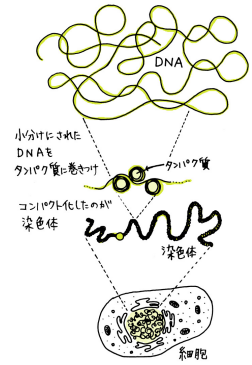

Fig. 1 DNA, accompanied by proteins such as histones and RNA, forms chromatin and is stored in the nucleus.

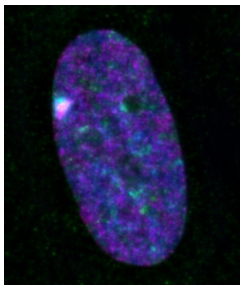

Figure 2 The nucleus of a female cell. Specific chemical modifications of the histones (green, red) are enriched in the condensed inactive X chromosome.

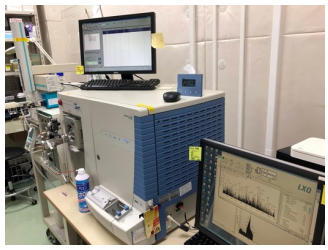

Figure 3 Mass spectrometer; for identification of trace amounts of proteins.

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