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Genomic DNA in eukaryotic cells is compressed and packaged with histone and non-histone proteins. This compressed state is often inaccessible for transcription and opening up of these structures is required before transcription can occur. Thus, change of chromatin structure is a crucial step in the regulation of gene expression. There are many players in the regulation game and most act through post-translational modifications of histones and chromatin associated non-histone proteins. It is natural that malfunction of such a highly important central process in the biology of the cell will lead to a diseased state. However, the role of chromatin modifications in many disease processes is only beginning to be understood.

During embryonic development in humans, a totipotent single cell differentiates into more than 200 types of functionally specialized cells. This differentiation programme can be regarded as the one establishing many types of genomic packaging leading to the corresponding epigenome defined by a unique set and level of expressed genes and features of the chromatin across the genome. Once the cell type-specific expression state is established, its maintenance – referred to as the epigenetic cellular memory, is also critical for the appropriate functioning of the cell throughout the life of any organism. Two groups of genes, *Polycomb* group (*PcG*) and *trithorax* group (*trxG*), maintain the active and repressed expression state. Mechanisms of maintenance of expression state involve recognition of the expression state of chromatin by the *PcG*/*trxG* members, appropriate epigenetic modification of the associated histones and, finally, recruitment of a number of other factors that recognize such a mark to maintain the expression state[1]. For example, *Polycomb* repressive complex 2 (PRC2) interprets the repressed state and puts the H3K27Me3 mark, which is recognized by the chromodomain of *Polycomb*, a core member of the PRC1 complex. Active state modification is H3K9Ac that is recognized by bromodomain of *Brahma*, a member of the trxG complex that maintains the active state. Since *PcG* and *trxG* genes maintain the expression state of chromatin, it is obvious that malfunction of this class of proteins could contribute to disease conditions. Weakening of this epigenetic cellular memory may cause mis-regulation of a number of genes – a situation similar to that of aging and diseases like cancer, where a large degree of mis-regulation of genes takes place. While a number of examples are known where *PcG*/*trxG* genes have been found to be linked to a disease like cancer[2], a linkage of changes in the epigenetic state of genome packaging caused by the alteration of activity/expression state of PcG/trxG proteins to the process of aging is beginning to emerge.

A number of studies point to a major role of PcG and trxG proteins in cancer. The mixed lineage leukaemia gene, *MLL1*, was found to be associated with 11q23 translocations that are linked to a variety of haematopoietic malignancies. *MLL1* (also known as *HRX* or *ALL1*) is human homologue of the *trithorax* (*trx*) gene of *Drosophila*. This finding established direct connection between cancer and a trxG protein involved in the maintenance of active chromatin state[3]. Involvement of *PcG* genes in cancer has also been established in a number of cases. For example, over-expression of BMI-1 and EZH2 has been linked to breast and prostate cancers[4]. BMI-1 is over-expressed in several other cases – non–small-cell lung cancer, colorectal cancer, nasopharyngeal carcinoma, and oral cancer[5].

One of the early studies that linked chromatin to disease was on Retinoblastoma protein (Rb), a tumour suppressor that controls gene expression by modulating chromatin architecture. One of the major mechanisms of Rb action is through the recruitment of histone deacetylase HDAC1 and bringing it to the E2F bound to promoters of cell-cycle progression genes, including cyclin E. This explains why many cancer cells have to work their way past the Rb protein. The repression brought about by these interactions is released by oncoproteins or mutations in Rb. Viral oncogenes have been shown to bind to Rb and hence, release it form the HDAC1–Rb–E2F complex, which allows transcription to occur from the E2F-bound promoters[6].

Since the discovery of the role of Rb action in cancer development, many other signalling pathways that play a role in tumourigenesis have been discovered. Many of these pathways regulate gene expression through modification of the chromatin and are dysregulated in cancer[7]. One of the most important transcription factors which is at the heart of tumour development that regulates gene expression through recruitment of chromatin modifying complexes, is p53. This transcription factor controls many regulatory pathways that regulate cell division. A large number of genes are either activated or repressed by p53, mostly through binding in the upstream region and recruitment of histone-modifying complexes. The protein itself is mutated and inactivated in 50% of the cancers and its associated proteins are inactivated in the rest. The intimate role of tumour development and signalling pathways that regulate cell proliferation and apoptosis through chromatin modification, has been known for last several years. It was mostly seen as a consequence of mutations that happen during tumour development to escape from the regulation of growth under normal conditions. Recent studies have revealed extensive changes

in the epigenome of cancer cells[8]. A recent hypothesis suggests that epigenetic changes may even be early events that make it easier for cancer cells to accumulate mutations and escape regulation[9].

Histone acetyl transferases (HATs) and histone deacetylases (HDACs) play counterbalancing roles in keeping the genome in silenced or active states, as required. Many of the signalling pathways ultimately target HATs or HDACs. Although there are several types of HATs, p300 and its close relative CBP, are perhaps the most well known. Perturbation and deletion of HATs are well known in many diseases, including Rubinstein–Tyabi syndrome, cardiac hypertrophy, diabetes, asthma and cancer. However, their critical role in many systemic diseases, such as cancer, is only being appreciated now. Another newly discovered link of acetylation and deacetylation (ultimately acting through chromatin modification) and disease is in the field of Chronic Obstructive Pulmonary Disease (COPD)[10]. Recent evidence points to down-regulation of HDAC activity in COPD and enhanced HAT activity in asthma. Either of these probably leads to up-regulation of many pro-inflammatory genes. Corticosteroids are the first line treatment of asthma. It appears that a major role of corticosteroids is to switch-off the inflammatory genes. A fraction of asthma patients and most COPD patients are resistant to corticosteroids, and newer therapeutic approaches are needed. Restoration of HDAC activity or inhibition of HAT activity may be a new therapeutic target in this disease field. In the case of viral diseases, establishment of retroviral pathogenesis (e.g. AIDS), depends on HAT and HDAC activity. HDAC inhibitors break the HIV latency. A combination of HATi and HDACi may be considered as a future therapeutic strategy.

Progress in linking chromatin and epigenetic link to disease has been rapid and a number of genes have now been implicated in a variety of cancers and other diseases. It is therefore not surprising that a number of new drugs against cancer are designed to target chromatin features – epigenetic modifications like DNA methylation and histone modifications to achieve inactivation of tumour suppressor or corrective reactivation of genes switched-off in disease state.

This is a field that is expected to blossom in the near future. However, little secondary literature is available to students and research scholars. In this volume, the editors have assembled an impressive array of articles on chromatin structure and its relationship with several human diseases. In part I, the first five articles deal with structural organization of chromatin and how they are modified by different chemical modifications, such as PARP-1. The last three articles in this section deal with the role of chromatin-associated proteins in disease, particularly the role of histone chaperones.

Part II is a short section in which the role of acetylation of non-histone proteins has been described by one of the editors. It also contains a brief article on the role of matrix attachment regions and proteins that bind to it, in human diseases. Part III contains eight articles, most of which deal with the role of chromatin modifications in the disease process as well as some newly discovered inhibitors of chromatin modifications that have the potential for therapeutics. Many of the important modifications have been covered including acetylation, phosphorylation and methylation. We enjoyed reading the articles and found them illuminating. We are sure that this volume would be useful to graduate students and starting investigators in this important area of biology.

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