Impact of epigenetics on human health and possible tool for remediation

Somnath Paul¹

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Abstract

Epigenetics is a colossal subject and beyond the scope of being covered in a single issue. It provides a constructive regulatory regime over the information possessed within the genome. Alterations lead to various diseased outcome. In this special thematic issue “Epigenetics and Chromatin Dynamics: Role in health and disease”, we have emphasized some of the aspects that will help our understanding about how epigenetic regulation drives various molecular functions with special emphasis on disease development (initiation, progression and outcomes). A collection of twelve review articles discusses on covalent modification of the genome, molecular interactome of the epigenetic species, epi-mutagenesis to epi-therapeutics.

Keywords Epigenetic regulation · Human health · Epitherapeutics

Overview of epigenetic regulation

The Central Dogma prevails the basic functioning of all living organisms, whereby the regulation of cell cycle integrates the molecular link between the DNA, RNA and proteins. In the simplest version, a conglomerated co-operation between these three, lead to the phenotypic fate of a cell, but epigenetic regulation in turn generates degree complexity in organisms. Epigenetic alterations include various type of modifications like methylation, acetylation, phosphorylation of the nucleic and amino acids, as well as crosstalk between molecules to regulate downstream activities like replication, DNA damage/repair responses, etc. These alterations can start as early in the embryonic development and well into adult livelihood [20, 52]. They are time dependent as well as on the trajectory of an individual's lifestyle where diet, substance abuse to addictions and environmental exposures like occupational hazards [1, 4, 35, 39, 48]. Alterations in the epigenetic network can spatially induct definitive changes and establish as well as dictate the outcome of several diseases. In the present thematic issue of ‘*The Nucleus*’ entitled “Epigenetics and Chromatin Dynamics: Role in health and disease” we tried to compile some of the

interesting aspects of epigenetic network and their relevance to health, outcome of diseases as well as potential foci for epi-therapeutic intervention.

Covalent modifications of the chromatin lead to epigenetically regulated expression profile

As discussed in this issue, the chromatin organization is not simple [41]. It has several layers of architectural niches that cause the DNA to super coil and compact the genomic material into the nucleus. The two main components of the chromosome are the DNA and the histones. There are five types of histones (H1, H2A, H2B, H3 and H4). Except for H1, all the other types are found within the nucleosomal core. The amino acids of the histones as well as the nucleotides within the DNA can be covalently modified raising the chance to alter the gene expression activity within the cells. Historically, methylation of the cytosine is heavily researched in the field of epigenetics. Several attributes to this covalent modification landscape include regulation of transcription, accessibility of the DNA template, DNA repair signaling, etc. A fine balance maintains the normal profile of the cell and an imbalance can be associated with development of diseased states including cancer, neuronal disorder, impaired DNA repair, exposure associated disorders [6, 27, 42, 51]. In the present issue, Dhar et al.[12] and Banerjee et al.[2]

✉ Somnath Paul
somnath4you@gmail.com; SPaul2@mdanderson.org

¹ Department of Epigenetics and Molecular Carcinogenesis,
UT MD Anderson Cancer Center, Houston, TX, USA

outlines some of the major aspects of DNA methylation and how it affects gene expression and development of neuronal disorder like autism. In both the articles, issues relating to genomic imprinting have been discussed along with how understanding epigenetic alterations can help in countering these disorders in humans, clinically. Moreover, the present issue cover many new avenues where epigenetic modifications can be associated like migraine pain and possible remediation strategies that may be adopted in future to counter such ailments [26].

In addition to the above-mentioned DNA modifications, histone post translational modifications (PTMs) play an important role in maintaining the structural as well as functional integrity of the chromatin. Several variations existing within the five major histones. Their PTMs, considered as “epigenetic signatures”, have shown significant association with various molecular functions like transcription, DNA damage/repair, etc. [49]. Dysregulation of these epigenetic signatures can provide tell-tale signs for diseased state [38]. Taking all types of cells into account, histone PTMs can help in encounter microenvironmental demands like regulation of cell cycle, dormancy to active states of pathogens / microbes, develop tolerance to drugs, etc. [15, 17–19, 30, 45]. Besides the known post-translational modifications of the histones and DNA methylation, structural features like the histone acidic patch within the nucleosomes affect the interaction of these protein complexes, as reviewed in this issue [41].

Molecular interactome and it's role in epigenetic regulation

Epigenetic regulation is not exclusively associated with DNA and histone modifications. Rather, it relays to the overall chromatin architecture that allows other additional aspects like active promoters, enhancers as well as chromatin interacting proteins such as ATP dependent chromatin remodelers that interact with the genome and play an important role in epigenetic regulation [16, 31]. In short, they can alter the fate of gene expression and subsequently drive the phenotypic characteristics of the cell. ATP dependent chromatin remodelers act on the nucleosomes by altering their positions on the chromatin landscape, thereby resulting in gain or loss of accessibility to the chromatin. This impact several functions of the chromatin interacting factors like polymerases, transcription factors, etc., as they need adequate access to the DNA template for their downstream activities [24, 29, 43]. One such pertinent functional aspect have been covered in the present issue by Ngubo et al. [36], where the author have discussed the intricate association of ageing to these ATP dependent remodeling activities.

RNA is the central mediator between DNA and translated proteins. Nevertheless, several different classes of RNA are present like microRNA (miRNA), long non-coding RNA (lncRNA), messenger RNA (mRNA), etc., each having own characteristics and functional features [22]. They provide an additional layer of gene regulation, befitting epigenetic regulation [24]. As covered in the present issue as well as by other groups, miRNA regulates several genes by interacting with the transcripts at 3' untranslated regions, thereby repressing translation of the target proteins [32]. This impacts development of diseased states like cancer, allergy, inflammation, neurological disorders, maintenance of cellular homeostasis by autophagy, etc. [3, 7, 9, 10, 37]. In the present collection, Ghosh Roy has discussed about how wide range of diseases like cardiovascular, renal and gastrointestinal disorders to cancers like glioblastoma and neurodegenerative diseases; related to autophagy can be understood in the light of miRNA [47]. Similarly, lncRNA have been implicated in maintaining key chromatin architectural features, leading to regulation of chromatin dynamics including aspects like dosage compensation as in X chromosome inactivation, pluripotency, heterochromatin maintenance [5, 14, 15, 18, 40]. In this present issue, Heyt et al. [21] have highlighted these aspects with special emphasis and comparison of research findings in various model systems.

Epimutagenesis

Unlike genetic mutations which leads to change in the sequence of the DNA. Mutations in the genomic sequence can encompass deletion or addition of a stretch of nucleotide sequence or just a single base pair change, the latter being known as Single Nucleotide Polymorphism (SNP). Technically, if the change in a single nucleotide base is observed in > 1% of the study population, it is termed as SNP or else, mutation (29). Without doubt, such changes in the exonic region can result in formation of abnormal proteins, leading to deviation in their functions. Epimutagenesis refers to the dysregulation in the normal epigenetic profile due to changes in the epigenetic signatures [23, 28, 40, 44]. This may be an active or a passive mechanism. Aberration in the epigenetic profile, specifically with such mutated genes, can alter the abundance of abnormal proteins. In the present collection of articles, Chowdhury et al. talks about the importance of cytochrome P450 (CYP) and emphasized how it's polymorphic variants can affect the metabolism of nonsteroidal anti-inflammatory drugs (NSAIDs). In the context of epimutagenic mechanisms discussed in this review like regulatory role of miRNA(s) in CYP expression; it was interesting to learn how H3K27ac modulates the binding of mediator complex subunit 25 (MED-25), thereby regulating the expression of CYP variant (2C9) in humans [11].

Progeny is important for continuation of any species. Hormonal regulation play one of the major roles in maintaining the physiological homeostasis of gametes during the reproductive phase of any organism. Gonadotropin releasing hormones (GnRH) from the pituitary oversees the signaling cascade responsible in gametogenesis. With age, the reproductive phase peaks and gradually fades out. In this edition, Chandra et al. presents elaborately on the physiological importance of GnRH genes, age associated changes in their expression and how epigenetic guardians [12] like DNA methyl transferases (DNMTs), ten-eleven translocases (TETs), play crucial role in fine tuning the expression of these genes [8].

Epitherapeutics: the future perspective of epigenetic studies

Inhibitor (*i*) type drugs like DNMT*i*, HDAC*i*, HAT*i* and SIRT*i*, have been found efficient in re-establishing the normal epigenetic profile of a system upon administration [33, 34]. Although most of the drugs under development target diagnosis of cancer, but given the prospects of epigenetic regulation, several other diseases like HIV, hypertension are under consideration by various research groups [46]. Throughout this special thematic issue of ‘*The Nucleus*’, the authors have tried to review the available literature in their respective fields and develop a consensus about the importance of exploring epigenetic regulation. Some have even tried to correlate the known signatures and their potency to act as therapeutic targets. For example, Ghosh et al. points that although some HDAC inhibitors used to treat HIV are being considered as diagnostic tool for parasitic infection; they may be of concern in some infection mechanisms HDAC is naturally suppressed so as to increase parasitic proliferation in the host [17]. Interestingly, HDAC*i* mediated therapies have suggested in treatment of several neurological disorders like Alzheimer’s and as suggested by Jasrotia *et al.*, may be considered for relieving individuals from migraine [26].

Unlike immune check point blockade therapies, where you can develop specific antibodies against mutated epitopes displayed by cancerous cells [13, 25, 50]; epimutagenesis has a wider spectrum. Thus, caution should be maintained while controlling the rogue mechanisms so as not to harm the co-existing normal profile within the system.

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