ISSN: 2322-0066

Research and Reviews: Research Journal of Biology

Epigenetics a Promising Therapy for Future Disease Cure

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Review Article

Received: 28/07/2016
Accepted: 19/08/2016
Published: 23/08/2016

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Keywords: Immune, Cytokines, Polygenicity, Endophenotypes.

ABSTRACT

Studies indicate that epigenetic modification promotes susceptibility among human due to altered gene expressions. The epigenetic mechanisms used by the cells to control the transposable elements are well comprehended in the studies. Silencing mechanism of gene throughout the course of evolution is a key aspect of gene regulation and chromosome biology. The study of these epigenetic regulations has provided new possibilities for diagnostics, prognostics and therapy of many diseases including cancer, ageing and many other genetic diseases. This mini-review provides an in-sight into the advancements of the therapy to treat few genetic aberrations due to epigenetic modification.

INTRODUCTION

The heritable change in phenotype without any alteration in DNA sequence is called epigenetics. These changes may be natural and essentials for organism function and survival; an improper change can lead to adverse effects [1-4]. Epigenetics changes are commonly influenced by some factors such as age, lifestyle, environment and disease. Methylation, phosphorylation, acetylation etc. have been identified as epigenetic process [5,6]. In the past few years there have been several cutting-edge studies in the field of epigenetics. Understanding these phenotypic changes distributed genome wide has shed light on topics of genetics such as stem cell, evolution, cloning and agriculture. While epigenetic variations naturally occur for a normal development and health, mammalian development and stable inheritance of epigenetic settings is essential for the maintenance of tissue- and cell-type-specific functions. An alteration in the inheritance can also be responsible for some disease states [7-11].

Epigenetic modifications in autoimmune disease

Autoimmune disease is an abnormal response of the immune system of the body to tissues (or) substances that are present in a human body [12,13]. Studies have shed a new light to the AID, genomics and epigenetics in the pathophysiology of AID. HLA associations and polymorphisms in cytokine genes have been reported in growing numbers of AID. Molecular and genomic studies of polymorphism of cytokines expressed in cell have resulted in the study of epigenetic marks for a health and diseased cell [14].

Epigenetics in developmental disorder

Attention-deficit/hyperactivity disorder (ADHD) is well-known by numerous heterogenous aspects. It is due to the interactive neurobiological and environmental factors functioning in a highly complex manner

[15]. The significances of these multiple gene interactions with environment and with each other through complex mechanisms, such as genetic heterogeneity or polygenicity, with phenotypic variability has contributed to marked individual differences in the manifestation, severity and comorbidity of symptoms in neuropsychiatric and developmental disorders [16].

ADHD involves in a multiple aspect of complex environmental factors, genotypic variations along with gene structure expression leading to endophenotypes [17,18]. Development disorders are also known to be an eventual response to the therapeutic interventions such as methylphenidate. Particularly impulsive behaviors have been observed are due to epigenetic factors have occupied both dopamine and serotonin in ADHD symptoms [19,20]. The genome wide association studies carried out on ADHD population samples have failed to identify replicable associations that explain plausibly the heritable variation, but twin studies have provided sufficient instruments in the development of endophenotypes, defined as alternative, more highly heritable traits that act at earlier stages of the pathway from genes to behavior [21].

Alzheimer's disease is a central nervous system (CNS) disorders. It is said that the environment and also epigenetic modification results in the phenotypic expression of the disease [22-24]. It has been observed that the genes associated with Alzheimer's disease tend to exhibit epigenetic changes signifying that this epigenetics might contribute to the pathogenesis of neurogenerative disorder. These changes may be due to DNA methylation which in turn influences the phenotype of the gene, such as susceptibility to pathogens and genetic disorders, drug resistance and xenobiotic agents [25-30].

Epigenetic modification are said to be reversible and thus act as a potential target for dietary interventions and pharmacological. DNA methyltransferase inhibitors, histone deacetylase inhibitors have possible effects against major problems of health [31]. There are many studies that indicate that the pathogenesis of genetic disorders/medical conditions to the drug resistance is due to the epigenetic modification. Implementation of pharmacoepigenetic studies may prove proper efficacy and safe use of dru development and clinical trials for central nervous system (CNS) disorders and many more [32].

Epigenetic marker and anticancer drug interaction

Epigenetic markers have developed as one of the most studies therapeutic agents for diseases, histone deacetylase inhibitors and DNA methyl-transferase inhibitors which are commonly used molecules in clinical and pre-clinical anticancer studies [33]. These epigenetic markers have the ability to regulate gene expression and increase the effect of pharmaceutical drugs due to which the HDI, DNMT inhibitors are single agents and also combined therapy. Pharmacophore modeling may therefore serve the purpose to optimize pre-clinical research and to develop more efficient and targeted therapies incorporating epigenetic regulators [34].

Effect of androgen-bound AR on epigenetic regulation

Androgen receptor takes place in the epigenetic regulation of genes expression. Conserved and diversified sequences in the 5'-flanking region of Androgen receptor can be utilized for the epigenetic setting [35,36].

Androgen is an important aspect for cell physiology but also a species specific which includes sexual behavior. The epigenetic setting of Androgen receptor is primarily driven by genetic differences in the regulatory region. DNA methylation and histone modification regulate the epigenetic modification of AR transcription thus acting as cis-elements with the ability to turn on and/or off the epigenetic switches in cell, tissue (or) species specific [37-40].

Epigenetics and cancer

Epigenetic changes can switch genes on or off and regulate the proteins to be transcribed. The first human disease to be linked to epigenetics was cancer, in 1983 [41].

Researcher found that diseased tissue from patients with cancer has low methylated DNA than the normal tissue from the same person. Methylated genes are generally turned-off by body mechanism. Thus hypermethylation of CpG islands at tumour suppressor genes switches off these genes, whereas global hypomethylation leads to genome instability and inappropriate activation of oncogenes and transposable elements. Over-expression of DNMTs is linked to cancer in humans, and their deletion from animals is lethal [42-46].

It is vital to note that there is an immediate connection between DNA methylation and histone alteration. Various proteins required in DNA methylation (e.g. DNMTs and MBDs) specifically interface with histone altering compounds, for example, histone methyltransferases (HMTs) and histone deacetylases (HDACs) [47,48]. Truth be told, it is trusted that DNA methylation and histone methylation are entwined in a strengthening loop where one modification depends on the other. Aberration in this relationship will more likely than not have serious results on the epigenome and chromatin association. Subsequently most, if not all, variables that influence DNA methylation levels will likewise influence histone alterations [49-55]. Case in point, it appears that H3K9 methylation and DNA methylation are connected. In addition, in growth cells, interruption of DNA methylation is connected to loss of H4K20 methylation [56,57].

The FDA has approved the following epigenetic therapies for cancer treatment Azacitidine (Vidaza), Decitabine (Dacogen), Vorinostat (Zolinza), Romidepsin (Istodax) [58].

SUMMARY

As the studies revealed that epigenetic changes involve histone and DNA modifications, resulting in drastic phenotypic changes that are particularly interesting because these epigenetic events are inherently reversible [59-63]. In response to circumstantial and environmental changes, epigenetic

modifications can proceed forward or backward, even removing the modification completely and reverting the substrate back to its original state. Current studies indicate that histone modifications are linked to CpG nucleotide methylation in DNA [64-70], thus connecting multiple forms of epigenetic modifications and regulations. This link poses a new scenario where an "epigenetic code" could dictate the expression of a particular set of genes, in essence serving as an "on/off" switch for many cellular events [71-75]. As epigenetic drugs continue to be developed and increased sensitivity and specificity are obtained, greater control over this epigenetic switch is possible. Once the correct combinations of treatments are developed, it may be possible to utilize the switch to reverse the disease phenotype, particularly if drugs are administered during early disease progression [76-80]. For example, it has been proposed that epigenetic drugs may prevent the formation of cancer progenitor cells while also killing drug-resistant cancer cells. As described in this review, there are many more examples of diseases for which epigenetic treatment holds great promise. Future studies will demonstrate how much exploitation of epigenetic events could be useful for preventing and treating different diseases [81-100].

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