

Epigenetics in Rare Diseases **Khue Vu Nguyen**

Abstract

The role of epigenetics in rare diseases is a key issue in molecular physiology and medicine because the understanding about the mechanisms that explain the influences of epigenetic regulation in rare diseases will provide useful principles for other common and complex disorders. Here, I discuss current knowledge about this matter and future directions in the field.

Keywords: Rare diseases; Epigenetics; Epistasis; Lesch-Nyhan disease; Amyloid precursor protein; Alzheimer's disease

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Introduction

By definition, a rare disease is any condition that affects a small percentage of the population. However, the cutoff number for which a disease is considered as rare varies with different regions. In the United States, the cutoff was fewer than 200,000 people [1] and while in Japan, it was fewer than 50,000 [2]. For Europe, rare diseases are life-threatening or chronically debilitating ones in which are of such low prevalence that special combined efforts are needed to address them and found to be 1 in 2,000 people [3]. As a consequence of low prevalence of rare diseases, there is a relative low interest to engage in academic and pharmaceutical research that would attempt to offer a therapeutic solution. Such rare diseases are also called orphan diseases. In any case, the rare diseases are usually genetic [4] and the symptoms can occur at any time. The present mini-review provides an overview about our current knowledge regarding the influences of epigenetic regulation in rare diseases and concludes with some future perspectives.

Epigenetic Regulation in Rare Diseases

Some rare diseases have an epigenetic component or involve epigenetically regulated genes [5]. While genetic mutations are very rare, epigenetic changes are common and occur through our lifetimes. Therefore, when discussing the etiologic factors in some rare diseases, the interplay between genetics and epigenetics should be considered. The current definition of epigenetics is "the study of heritable changes in gene expression that occur independent of changes in the primary DNA sequence" [6]. At the molecular level: DNA methylation, histone modification, and RNA-associated silencing are currently defined as the three main inter-related mechanism of epigenetic inheritance [6]. Disruption of one or other of these interacting systems caused by genetic, environmental factors as well as stress, diet, lifestyle,

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and aging can lead to inappropriate expression or silencing of genes, resulting in "epigenetic diseases" [6]. In particular, the nervous system represents an immensely complex structure and makes it especially sensitive to these epigenetic changes, and consequently, many mental disorders are caused by mutations in the epigenetic machinery [7]. For examples, genetic mutations of genes related to DNA methylation found in Rett syndrome (RTT) (due to mutations in the methyl-binding domain protein MeCP2) [8], and in immunodeficiency centromere instability facial syndrome 1 (ICF1) (due to mutations in the DNA methyltransferase DNMT3) [9,10] or to histone modifiers found in Rubinstein-Tabi syndrome (RTS) (due to mutations in the histone acetyltransferase p300/CBP) [11], and in Sotos syndrome (associated with mutations in the histone methyltransferase NSD1) [12]. As new members of the epigenetic machinery are described, the number of human syndromes associated with epigenetic alterations increases [13].

Epigenetic Therapy

Epigenetic changes are dynamic and unlike genetic mutations, they can be reversed for therapeutic purposes by targeting enzymes or other factors that control or maintain them [14,15]. The approval of epigenetic drugs for cancer treatment has opened the door for the development of epigenetic drugs for other disorders including neurodegenerative diseases. In particular, the methyl donors and histone deacetylase (HDAC) inhibitors have been investigated for possible therapeutic effects to rescue memory and cognitive

decline found in such disorders. This has been further boosted by the recent US Food and Drug Administration (FDA) approvals for the potent HDAC inhibitors such as suberoylanilide hydroxamic acid (SAHA, trade name Vorinostat) and romidepsin (trade name Istodax) in the treatment of hematological malignancies. Indeed, a large body of preclinical work has suggested that HDAC inhibitors could have therapeutic potential in a wide range of neurological conditions. These include acute brain injury and stroke paradigms, various neurodegenerative conditions such as Parkinson's and Alzheimer's disease (AD) [16,17] and depression and other psychiatric illnesses [18,19]. But it is still unclear whether HDAC inhibitors would benefit the patients affected by any of these conditions. Several inhibitors of DNA methylation, including the cytidine analogs 5-azacytidine and zebularine and nucleoside analogs that sequester the DNA methyltransferase enzymes after being incorporated into DNA [20], have also been well characterized and are approved or are in preclinical and clinical trials for the treatment of cancer [20]. Despite the promise of epigenetic therapy, there are several concerns regarding the clinical applications of these agents. These relate mainly to the nonspecific activation of genes and transposable elements in normal cells, and also to potential mutagenicity and carcinogenicity [21].

Perspective

Epigenetics is one of the fastest growing fields of sciences; illuminating studies on human diseases by looking beyond genetic make-up and acknowledging that outside factors play a role in gene expression. Our knowledge about epigenetics is still limited, and some mechanisms have been studied more thoroughly like histone acetylation and DNA methylation, yet much remains to be revealed. Until now, we had identified genetic mutations that could change the epigenetic patterns; but we still do not understand which are the altered putative downstream genes (epigenetically regulated) that result in specific clinical phenotypes. Most importantly, we are still in the infancy of the understanding of how such epigenetic defects (potentially reversible) could provide a target for therapeutic intervention. Recently, a discovery of epigenetic regulation in amyloid precursor protein (APP) and the Lesch-Nyhan disease (LND) (a rare X-linked inherited neurogenetic disorder of purine metabolism affecting 1 in 380,000 people, and caused by deficiency of the enzyme hypoxanthine

phosphoribosyltransferase, HGprt, EC. 2.4.2.8; MIM 300800 [22-24]) has been reported [25-27]. Results of quantification of various APP-mRNA isoforms indicated an epistasis (gene-gene interactions) between mutated Hypoxanthine Phosphoribosyl Transferase 1 (HPRT1) and APP genes. APP-mRNA isoform of 624 bp, with deletion starting after 49 bp of the 5' end of exon 3 followed by a complete deletion of exons 4-15, mutations in exon 1: c.22C>T, p.L18F, and exon 3: c.269A>G, p.Q90R encoding APP₂₀₇ isoform, was the most abundant one in most of the LND patients and would be responsible for the neurobehavioral syndrome in these patients [28]. Interestingly, this APP₂₀₇ isoform was also the most abundant one found in a neurodevelopmental disorder resulting from a nonsense mutation in the Ox-2 antigen domain of the APP gene [29]. This finding underlined the role of the epigenetic regulation in the expression of APP gene. Up to present, there are only suggestions about the influences of epigenetic modifications, and epistasis in susceptibility to diseases and the concept of epigenetics in pathophysiology of diseases but no real experimental results. Here, for the first time, the real profile of APP-mRNA isoforms accounted for epigenetic changes in the regulation of alternative APP pre-mRNA splicing and having an impact on the neurodevelopment has been shown. APP, a house keeping gene [30] and endogenous ligand (<http://www.genenames.org/genefamilies/ENDOLIG>), is an important molecular hub at the center of interacting pathways and acts as a permissive factor for various neurodevelopmental and neural circuit processes [31], altered APP processing may affect brain function through a host of altered cellular and molecular events. My findings may provide new directions not only for investigating the role of APP in neuropathology associated with LND but also for the research in neurodevelopmental and neurodegenerative disorders in which the APP gene is involved in the pathogenesis of diseases such as autism [32], fragile X syndrome [33], amyotrophic lateral sclerosis [34], and AD [33,35], and may pave the way for new strategies applicable to rational antisense drugs design [36].

In sum, the understanding of the contribution of epigenetic changes to rare diseases provides useful principles for other common and complex disorders such as cancer, cardiovascular, type 2 diabetes, obesity, and neurological diseases and will hopefully provide us with better molecular tools for an improved diagnosis, prognosis and therapy for the patients in the future.

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