Imprinted Genes and Multiple Sclerosis

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Multiple sclerosis (MS) is a chronic autoimmune neurodegenerative disease of the central nervous system that arises from interplay between non-genetic and genetic risk factors. The epigenetics - the study of heritable changes in gene expression that do not involve changes in the primary DNA sequence or genotype - functions as a link between these factors, affecting gene expression in response to external influence. Among others, the epigenetic mechanisms underlie the establishment of parent-of-origin effects that appear as phenotypic differences depending on whether the allele was inherited from the mother or father. The most well described manifestation of parent-of-origin effects is genomic imprinting that causes monoallelic gene expression. It becomes more obvious that disturbances in imprinted genes affecting their expression do occur in MS and may be involved in its pathogenesis.

Keywords: multiple sclerosis ; parent-of-origin effect ; genomic imprinting ; DLK1-DIO3 locus ; miRNA

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disease of the central nervous system (CNS) in which inflammation, demyelination, and axonal degeneration lead to a fast progression of neurological disability in young adults [1]. MS is a relatively common disease affecting about 1 in 1000 individuals in Europe and North America [2]. In the last few decades, its prevalence has increased substantially due to not only improved diagnostics and survival of patients, but also the rise of MS incidence [3], which contributes to the high social and economic importance of the disease. Demographic studies have shown that MS, like many other autoimmune diseases, is about 2 times more common in women than in men. Moreover, women are diagnosed with MS 1–2 years earlier than men, but men are more likely to develop a more severe MS course.

The clinical course of MS is highly heterogeneous. Most patients have relapsing-remitting MS (RRMS), which is characterized by recurrent acute exacerbations followed by partial or complete recovery, and, with time, they develop secondary progressive MS (SPMS), specified by gradual accumulation of irreversible impairment. Ten to fifteen percent of patients have so-called primary progressive MS (PPMS) with a steady increase of the irreversible neurological dysfunction from onset [4]. To date, RRMS is the most well studied MS course due to its highest prevalence.

MS is a complex disease that arises from interplay between non-genetic and genetic risk factors. Lifestyle and environmental factors, such as Epstein-Barr infection, vitamin D deficiency, smoking, as well as changes in sex hormone profiles are among the best-established non-genetic risk factors of MS [5][6]. The *HLA* locus on chromosome 6 is known as the main marker of genetic susceptibility to the disease; beyond it, more than 200 other loci affecting MS risk are currently identified. At the same time, their cumulative contribution cannot explain more than 48% of MS heritability [7].

Epigenetic changes affecting gene expression in response to external influence represent the link between non-genetic and genetic risk factors, which should be extensively studied to improve the knowledge of MS molecular mechanisms. Epigenetic mechanisms are involved in the establishment of parent-of-origin effects (POEs) that appear as phenotypic differences depending on whether the allele was inherited from the mother or father [8]. The parental transmission of alleles is accomplished by mechanisms other than classical Mendelian segregation of nuclear genes [9].

2. Parent-Of-Origin Effects in MS Development

POEs could be determined as effects that arise (1) from the epigenetic regulation of gene expression (such as genomic imprinting, GI—one of the best characterized POE); (2) from the effects of the maternal intrauterine environment on the developing fetus; and (3) from genetic variation in the maternally inherited mitochondrial genome. POEs were until recently almost exclusively discussed in the context of classical diseases of GI, but they are now receiving recognition in a wider range of complex diseases, including MS. Studying POEs in MS is tricky since the establishment of its impact on

the disease is influenced by environmental and in utero effects and requires a large population of phenotyped individuals of varying degrees of relatedness, whose genotypes are assigned with parental origin. However it is believed that POEs hold the potential to explain “hidden” heritability to MS.

The increased risk for MS in children of affected mothers was described [10]. A number of studies demonstrated POE for *HLA* locus, where a significant over transmission of *HLA-DRB1**15 from mothers was observed [11][12].

A reciprocal backcross study in rats with experimental autoimmune encephalomyelitis (EAE), the widely-accepted animal model of MS, demonstrated that 37–54% of EAE susceptibility loci depended on parental transmission; these loci overlapped with experimentally confirmed or predicted imprinted genes [13]. Similarly, a study in mice showed that several loci were predisposed for EAE in a parent-of-origin-dependent manner [14].

3. The Genomic Basis of Imprinting

GI is epigenetically regulated POE in placental mammals that cause monoallelic gene expression. Most of the known imprinted genes are characterized by monoallelic expression in all tissues, but about 28% exhibit monoallelic expression in only one or several tissues, i.e., are imprinted in a tissue-specific manner [15][16][17]. The genes are imprinted depending on the stage of ontogenesis, i.e., imprinted in a stage-specific manner, being biallelically expressed early in development and undergoing only monoallelic expression at later embryonic stages, or vice versa [18][19][20]. For a few imprinted genes a reversal imprinting was demonstrated: The gene is expressed from the maternal allele in some tissues or developmental stages, and from the paternal allele in others [21][22][23].

Many imprinted genes tend to group into extended clusters from hundreds to thousands of bp in length, the so-called imprinted loci, within which there is a coordinated regulation of gene expression [24]. The imprinted loci may include paternal and maternal expressed genes. The structure of the imprinted loci always includes protein coding genes, long noncoding RNA genes, and, commonly, small noncoding RNA genes: MicroRNA (miRNA) and small nucleolar RNA [25]. It is known that genes of non-coding RNA (both long and small) are involved in regulatory processes. Thus, long non-coding RNAs are important regulators of gene expression, organizing nuclear architecture and regulating transcription; they also modulate mRNA stability and translation, and are involved in the process of posttranscriptional modifications in the cytoplasm [26]. MiRNAs, single-stranded short non-coding RNAs, are involved in posttranscriptional regulation of gene expression due to complete or partially complete sequence complementarity between miRNA and target mRNA, which leads to mRNA degradation or inhibition of its translation [27]. Small nucleolar RNAs are mainly involved in posttranscriptional modifications and maturation of rRNA, tRNA, and small nuclear RNAs, as well as in the regulation of alternative splicing [28].

The monoallelic gene expression at the imprinted loci is controlled by independent imprinting control regions (ICRs). ICRs are characterized by the presence of germline differentially methylated regions (DMRs)—CpG-rich sequences, the methylation of which is carried out on one of the parental chromosomes at the stage of gametogenesis [29]. These DMRs direct alternative splicing, regulate the rate of transcription elongation, or select alternative polyadenylation sites, leading to the synthesis of various allele-specific isoforms of transcripts [30][31]. To date, 35 such germline DMRs have been identified in the human genome [32]. In humans most of them are methylated in female gametes, and only three DMRs (in *H19/IGF2*, *MEG3/DLK1* and *ZDBF2/GPR1-AS* imprinted loci) are known to be methylated in male gametes. In addition to these “primary” germline DMRs in the ICRs, imprinted loci can also contain so-called “somatic”, or “secondary” DMRs in which parent-specific methylation is established after fertilization. These “secondary” DMRs are found in the promoters of some imprinted genes or transcription factors’ binding sites [30]. Methylation status of “secondary” DMRs is usually guided by “primary” DMRs.

Long non-coding RNAs [33], insulator proteins [34], and also histone modification [35] take part in the regulation of imprinting together with DNA methylation. Moreover, the products of imprinted genes interact with each other, forming networks, and, thus, participate in a finer tuning of imprinting regulation; it is known that a dysfunction of one imprinted gene can affect other genes expressed from the maternal or paternal alleles [36][37]. The existence of such a network may partially explain the fact that all hereditary GI disorders are characterized by common clinical features, affecting development, growth, behavior, and metabolism [38][39].

By today, disturbances in imprinted genes are found in the pathogenesis of complex diseases, among which cancer is the most studied [40]. Such disturbances may also be involved in the development of several autoimmune and neurodegenerative disorders [41][42][43], including MS [13][44][45]. MS is not a “classic” GI disorder. Nevertheless, it becomes

more obvious that disturbances in imprinted genes at the least affecting their expression do occur in MS, as well as in other polygenic diseases, and may be involved in its pathogenesis. Therefore, a promising way of studying MS development may be the search for disturbances in known imprinted genes.

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