The International Journal of Biochemistry & Cell Biology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Review

Genomic imprinting: A missing piece of the Multiple Sclerosis puzzle?☆

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ARTICLE INFO

Article history:
Received 24 February 2015
Received in revised form 10 May 2015
Accepted 11 May 2015
Available online xxx

Keywords:
Parent-of-origin
Genomic imprinting
Multiple Sclerosis (MS)
Experimental autoimmune
encephalomyelitis (EAE)
Epigenetic
Inflammation
Complex disease

ABSTRACT

Evidence for parent-of-origin effects in complex diseases such as Multiple Sclerosis (MS) strongly suggests a role for epigenetic mechanisms in their pathogenesis. In this review, we describe the importance of accounting for parent-of-origin when identifying new risk variants for complex diseases and discuss how genomic imprinting, one of the best-characterized epigenetic mechanisms causing parent-of-origin effects, may impact etiology of complex diseases. While the role of imprinted genes in growth and development is well established, the contribution and molecular mechanisms underlying the impact of genomic imprinting in immune functions and inflammatory diseases are still largely unknown. Here we discuss emerging roles of imprinted genes in the regulation of inflammatory responses with a particular focus on the *Dlk1* cluster that has been implicated in etiology of experimental MS-like disease and Type 1 Diabetes. Moreover, we speculate on the potential wider impact of imprinting via the action of imprinted microRNAs, which are abundantly present in the *Dlk1* locus and predicted to fine-tune important immune functions. Finally, we reflect on how unrelated imprinted genes or imprinted genes together with non-imprinted genes can interact in so-called imprinted gene networks (IGN) and suggest that IGNs could partly explain observed parent-of-origin effects in complex diseases. Unveiling the mechanisms of parent-of-origin effects is therefore likely to teach us not only about the etiology of complex diseases but also about the unknown roles of this fascinating phenomenon underlying uneven genetic contribution from our parents.

This article is part of a Directed Issue entitled: Epigenetics dynamics in development and disease.

Contents

Abbreviations: MS, Multiple Sclerosis; QTLs, quantitative trait loci; EAE, experimental autoimmune encephalomyelitis; IGN, imprinted gene networks; T1D, Type 1 Diabetes; RA, Rheumatoid Arthritis; SLE, Systemic Lupus Erythematosus; HLA, Human Leukocyte Antigen; GWAS, genome-wide association studies; DMR, differentially methylated region; ICR, imprinting control region; SNP, single nucleotide polymorphism; nt, nucleotide; lncRNA, long non-coding RNA; miRNA, microRNA.

☆ This article is part of a Directed Issue entitled: Epigenetics dynamics in development and disease.

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http://dx.doi.org/10.1016/j.biocel.2015.05.010
1357-2725/

Please cite this article in press as: Ruhrmann, S., et al., Genomic imprinting: A missing piece of the Multiple Sclerosis puzzle? Int J Biochem Cell Biol (2015), http://dx.doi.org/10.1016/j.biocel.2015.05.010

1. Introduction

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Complex diseases, also known as multifactorial diseases, are conditions that arise from an intricate interplay between multiple genes in combination with environmental and lifestyle factors. The majority of diseases falls in this category and includes a large group of inflammatory disorders that underlie a variety of human diseases such as allergy and autoimmune diseases but also atherosclerosis and cancer. With the initial optimism of solving disease etiology by identifying the catalog of genes predisposing for each disease, a lot of effort has been placed in genetic studies. However, decades of genetic epidemiology research suggest that the complexity is even greater than originally anticipated, and many of the contributing factors have yet to be identified. Moreover, complex diseases cannot be described merely by the sum of genetic and environmental effects. One phenomenon observed in several complex diseases is an uneven genetic contribution from the parents, also known as parent-of-origin effects. Genomic imprinting, whereby a gene is expressed only from the maternally or paternally inherited chromosome, is one of the causes underlying such parent-of-origin effects. The expression of one allele is achieved by epigenetic mechanisms that refer to modifications of the DNA (e.g. methylation) resulting in altered gene expression without a change in the actual DNA sequence.

Inflammation is a response of body tissues to potentially harmful stimuli and while inflammation has a protective role failure to tightly regulate inflammatory response can lead to inflammatory diseases. This failure is often associated with abnormalities in the immune system, which is the body's defense against infectious agents and other invaders. Chronic inflammatory diseases such as Multiple Sclerosis (MS), Type 1 Diabetes (T1D), Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) among others show typical features of complex genetic diseases. They present with clinical, etiological and genetic heterogeneity and involve many factors, none of which are essential or sufficient to cause disease on their own. MS, which is one of the leading causes of neurological disability in young adults, is characterized by autoimmune destruction of myelin and neurons in the central nervous system. Although T cells are considered as key mediators nearly every cell type of the innate and adaptive immune system has been implicated in immunopathology of MS as recently reviewed (Hartung et al., 2014; Kutzelnigg and Lassmann, 2014; Naegele and Martin, 2014). While the cause of MS remains unknown, epidemiological studies clearly establish MS as a heritable disease (Ebers et al., 1986; O'Gorman et al., 2013; Sadovnick et al., 1988; Westerlind et al., 2014). The first genetic risk factor was established in the 1970s and it mapped to the Human Leukocyte Antigen (HLA) complex region (Jersild et al., 1975; Jersild et al., 1972). The HLA region contains over 200 genes, many of which are involved in immune system development and functions, and alleles at different loci are often inherited together in established haplotypes. The original association was later refined to the extended haplotype *HLA-DRB5*0101–HLA-DRB1*1501–HLA-DQA1*0102–HLA-DQB1*0602* (Fogdell et al., 1995) encoding key molecules that present antigens to T lymphocytes and conferring a threefold increase in risk to develop MS. Since then, more than 100 genetic variants have been identified to predispose for MS (Australia and New Zealand Multiple Sclerosis Genetics Consortium, 2009; Beecham et al., 2013; Sawcer et al., 2011), including multiple variants and alleles within the HLA locus (Patsopoulos et al., 2013). Jointly, the 110 non-HLA and the HLA effects explain 20% of the sibling recurrence risk (Beecham et al., 2013). A recent meta-analysis estimated genetic heritability of MS to be 54% and a model of inheritance that is consistent with one locus of moderate effect and many loci of modest effects (O'Gorman et al., 2013). The difference between estimated and explained heritability begs the question of where the 'hidden heritability' resides.

Increasing incidence of MS during the last several decades (Melcon et al., 2014) is speculated to result from changes in the environment and gene–environment interactions. Among the best established environmental factors are infection with Epstein–Barr virus, low vitamin D and sun exposure, high BMI and smoking (Ascherio, 2013). Recently, an interaction between smoking and the *HLA-DRB1*15* and *HLA-A*02* genes was reported to modulate risk to develop MS (Hedstrom et al., 2011). It is tempting to speculate that epigenetic mechanisms can mediate some of the impact of the environmental factors. For example, both current smoking and prenatal exposure to smoking induce DNA methylation changes (Lee and Pausova, 2013). Those changes, which can be passed on through cell divisions, might provide an explanation for the fact that the increased risk of MS in smokers persists at least five years after cessation (Hedstrom et al., 2013).

Taken together, there is emerging evidence for complex interactions of genetic, environmental and epigenetic mechanisms underlying the pathogenesis of MS. To understand complex diseases and MS in particular we need to extend our quest beyond risk variants and environmental triggers to encompass parent-of-origin effects such as genomic imprinting and epigenetic mechanisms in general.

2. Parent-of-origin effects and genomic imprinting

2.1. Parent-of-origin effects in complex diseases

The Mendel's laws of inheritance describe the way genetic traits are transmitted from one generation to another. One of the assumptions of Mendelian inheritance is that genes originating from maternal and paternal genomes are equally expressed in the offspring. The term parent-of-origin effect refers to the phenomenon in which the phenotype depends on the parental origin of the associated allele, i.e. on whether the allele was inherited from the mother or father, causing non-Mendelian inheritance. In other words, the allele influences the trait only if it is inherited from a particular parent. Parent-of-origin effects comprise a range of genetic and epigenetic mechanisms, and combinations thereof. Genomic imprinting, where one parental allele is expressed while the other remains silent, is one of the best-characterized epigenetic mechanisms that cause parent-of-origin effects. Additional mechanisms involve the sex chromosomes, mitochondria, gender transmission bias, and trans-generational effects (including maternal intrauterine effects and maternal-offspring interactions) (Guilmatre and Sharp, 2012).

The extent to which parent-of-origin effects contribute to the heritability of complex diseases is not yet known. Moreover, parent-of-origin effects, in particular epigenetic silencing of one allele, could mask the effect of genetic variation since only the expressed allele would be informative in the studied population. This could be one of many explanations for 'hidden heritability', i.e. why all the identified risk variants together explain only a fraction of heritability to complex diseases (Lander, 2011).

Despite a number of studies that implicate parent-of-origin effects in the etiology of MS, the exact mechanisms are difficult to establish and study, often due to the lack of detailed information regarding the degree of relatedness between studied individuals. Moreover, parent-of-origin effects can easily be confounded by environmental and in utero effects. In a large Canadian cohort, half-siblings and avuncular pairs have been studied to assess parent-of-origin effects in MS. The maternal route was favored in disease transmission, with maternal half-siblings of MS-affected persons having a significantly higher risk for developing MS compared to paternal half siblings (Ebers et al., 2004; Herrera et al., 2008). Similarly, significantly more MS-affected

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