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Review article

Genomic imprinting in psoriasis and atopic dermatitis: A review

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ABSTRACT

Genomic imprinting is a genetic process where only one allele of a particular gene is expressed in a parent-of-origin dependent manner. Epigenetic changes in the DNA, such as methylation or acetylation of histones, are primarily thought to be responsible for silencing of the imprinted allele. Recently, global CpG methylation changes have been identified in psoriatic skin in comparison to normal skin, particularly near genes known to be upregulated in psoriasis such as *KYNU*,*OAS2*, and *SERPINB3*. Furthermore, imprinting has been associated with multi-chromosomal human disease, including diabetes and multiple sclerosis. This paper is the first to review the clinical and genetic evidence that exists in the literature for the association between imprinting and general skin disorders, including atopic dermatitis and psoriatic disease. Atopy was found to have evidence of imprinting on chromosomes 6, 11, 14, and 13. The β subunit of the IgE receptor on chromosome 11q12-13 may be imprinted. Psoriatic disease may be related to imprinting effects on chromosome 6 for psoriasis and 16 for psoriatic arthritis.

Contents

1. Introduction

Genomic imprinting occurs when only one allele of a particular gene is expressed in a parent-of-origin dependent manner [1] (Fig. 1). The "imprinted" allele refers to the allele that has been silenced, either the maternal allele or paternal allele. In mammals, imprinting affects only a small fraction of the total number of genes. In humans, it is estimated that there are at least 79 imprinted genes, although some studies suggest the number may be higher up to 300 genes [2]. However, imprinting of certain human genes is a required and normal part of embryologic development.

Imprinting is largely thought to occur through the epigenetic mechanisms of DNA and histone methylation, where epigenetics refers to chemical modifications (e.g., methylation) of DNA or DNA-

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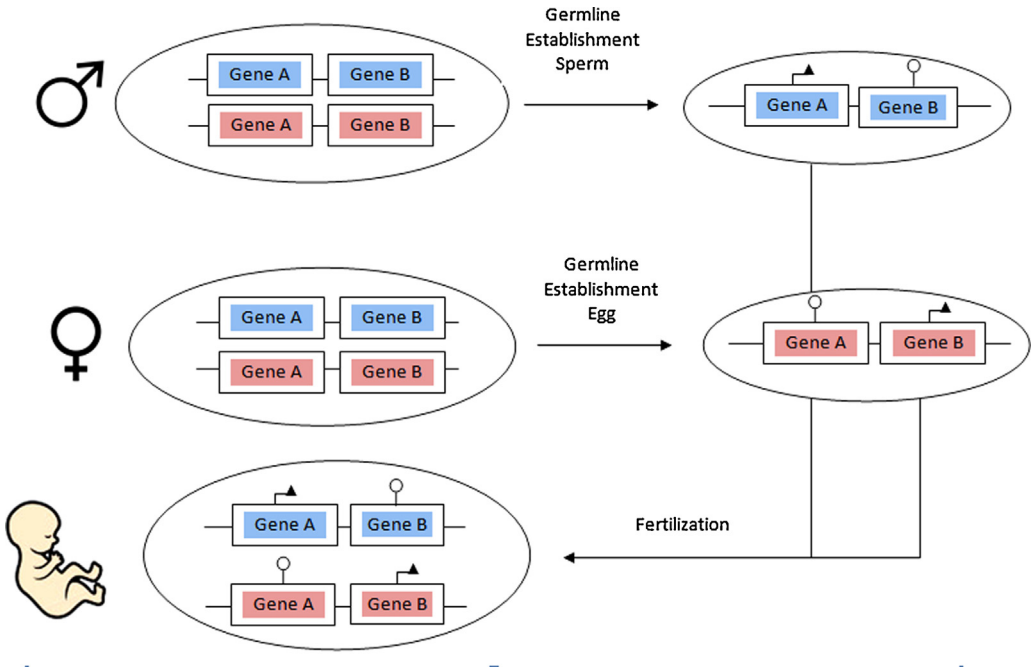

Fig. 1. Schematic for Genomic Imprinting. Imprinting occurs when there is preferential parental expression of a chromosome or gene. Gene A (e.g., psoriasis gene such as *HLA* or *CARD14*) is depicted here to have preferential paternal expression, denoted with an arrow, and maternal silencing denoted with a circle. Gene B (e.g., atopic dermatitis gene such as filaggrin) is depicted here to have preferential maternal expression.

associated proteins that alter gene expression without a change in the genetic code [3]. In imprinting these epigenetic marks are made in the paternal sperm or maternal egg cells and are maintained through mitotic cell divisions in the somatic cells of an organism. The DNA sequences affected by these epigenetic modifications are known as "differentially methylated regions," or DMR [4].

Genomic imprinting can be considered a specific subset of the more general phenomenon of allele-specific expression (ASE). ASE occurs when two alleles of the same gene have different levels of expression, ranging from slight differences in expression to one allele expressed while the other is completely silenced. The most common form of ASE is the first situation, in which both alleles of a gene are expressed, but one allele moreso than another. In this case the differential gene expression typically results from either genetic or epigenetic changes specific for a particular allele, and expression levels are unrelated to the parental origin of the allele. In contrast, imprinting occurs in the second situation of all-or-none expression and is dependent only on the parental origin of the allele, not on its allelic DNA sequence.

Imprinting is important because of its association with human disease. Both single chromosome and multi-chromosome diseases have been implicated in imprinting. Examples of single chromosome diseases affected by imprinting include Beckwith–Wiedmann, Prader-Willi, and Angelman syndrome [5]. Moreover, imprinting has been explored for complex diseases involving multiple chromosomes, such as diabetes and multiple sclerosis. Similar to psoriasis, multiple sclerosis susceptibility is associated with genetic polymorphism with the human leukocyte antigen (HLA) region on chromosome 6 [6]. Through HLA genotyping, it was found that the major susceptibility haplotype *HLA-DRB1* had a maternal preference of inheritance [6]. Similarly, a genome-wide association (GWA) study has suggested a paternal bias in inheritance for risk of type of diabetes, related to the imprinting effects of the gene *DLK1* [7]. Recently, epigenetics has been explored in the realm of common skin disorders, such as atopic dermatitis (AD) and psoriatic disease, which are known to have a genetic basis. Global CpG methylation changes have been identified in psoriatic skin in comparison to normal skin, particularly near genes known to be upregulated in psoriasis such as *KYNU*, *OAS2*, and *SERPINB3* [8].

This article is the first to review the literature on genomic imprinting in psoriatic disease and AD. We aim to explore whether imprinting may play a role in the pathogenesis of psoriatic disease and AD, possibly leading to new avenues for future research.

2. Methods

A Pubmed search using the terms ("imprinting" AND ("psoriasis" OR "eczema" OR "atopic dermatitis" OR "psoriatic arthritis")) was conducted on February 2015. Results included 17 articles. The abstract of each article was reviewed for relevance. References of selected articles were also reviewed. In addition, a Pubmed search using the terms ("imprinting" AND "atopy") was conducted due to the inclusion of atopic dermatitis in the definition of general atopy. Results included 13 articles, which were screened for relevance via their abstracts.

3. Results

3.1. Atopy in relation to atopic dermatitis

3.1.1. Clinical evidence

A number of studies have supported a possible role for imprinting in atopic disease by examining whether the presence of maternal or paternal atopy affects risk of atopy development in children. In 2012, Folsgaard et al. collected the upper airway mucosal lining fluid and quantified levels of 18 cytokine and chemokine mediators of atopy, including IFN-gamma, IL-2, and TNF-α, from 309 asymptomatic neonates [9]. Among them, 241 neonates had either a mother or father with history of atopy, which included atopic dermatitis, asthma, and hay fever. Neonates of atopic mothers and non-atopic fathers had lower levels of mediators in the blood when compared neonates of atopic fathers

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