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Epigenetics of psoriatic disease: A systematic review and critical appraisal

Remy A. Pollock [a, b], Fatima Abji [a, b], Dafna D. Gladman [a, b, *]

[a] University of Toronto Psoriatic Arthritis Program, Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital, 1-412 East Wing, 399 Bathurst Street, Toronto, ON, M5T 2S8, Canada
[b] Krembil Research Institute, University Health Network, 5KD-405, 60 Leonard Avenue, Toronto, ON, M5T 2S8, Canada

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ABSTRACT

Psoriasis is an inflammatory disease of the skin that is sometimes accompanied by an auto-inflammatory arthritis called psoriatic arthritis (PsA). Psoriasis and PsA are multifactorial diseases that result from complex interactions of environmental and genetic risk factors. Epigenetic marks, which are labile chemical marks with diverse functions, form a layer of biological information that sits at the interface of genetics and the environment. Aberrant epigenetic regulation has been previously implicated in other rheumatological disorders. The purpose of this review is to summarize and critically evaluate the nascent literature on epigenetics in psoriasis and PsA. A systematic review yielded 52 primary articles after applying inclusion and exclusion criteria. Data were extracted using a standardized template and study quality assessed using a methodological quality checklist. Studies reflect a broad range of epigenetic sub-disciplines, the most common being DNA methylation, followed by the parent of origin effect or genomic imprinting, expression or activity of epigenetic modifying enzymes, and histone modifications. Epidemiological studies demonstrating excessive paternal transmission provided the earliest evidence of epigenetic deregulation in psoriatic disease, however few studies have examined its molecular mechanisms. Methylation studies evolved rapidly from low resolution global to targeted analyses of known psoriatic disease susceptibility loci such as *HLA-C*0602*. The recent explosion of epigenome-wide association studies has provided us with novel insights into psoriasis pathogenesis, and the mechanism of action of UVB, methotrexate, and anti-TNF therapies, as well as molecular signatures of psoriasis that may have clinical relevance. Finally, recent studies of pharmacological inhibitors of epigenetic modifier enzymes demonstrate their potential applicability as novel treatment modalities for psoriasis. Challenges of epigenetics research in psoriasis and PsA were identified and future perspectives are discussed herein.

1. Introduction

Psoriasis is a common, chronic, immune-mediated skin condition that affects 1–3% of Caucasians. In approximately 30% of cases, psoriasis is accompanied by a potentially destructive and disabling inflammatory arthritis called psoriatic arthritis (PsA) [1]. Psoriasis and PsA, collectively known as psoriatic disease, are associated with several comorbidities including obesity, metabolic syndrome, arthrosclerosis, inflammatory bowel disease, uveitis, and depression. Psoriatic disease can lead to a reduced quality of life, increased morbidity and mortality, and presents a considerable economic burden [2].

In the past few decades, several advances have been made in our understanding of the multifactorial etiology of psoriatic disease. As a common, complex condition, it is currently thought to result from the interaction of numerous genetic risk loci and environmental exposures, several of which have been characterized and replicated. At the interface of genes and environment, there sits another layer of biological information called epigenetics. Recent discoveries in various cancers [3] and autoimmune conditions such as rheumatoid arthritis [4], and systemic lupus erythematosus [5], have underscored the importance of epigenetic deregulation in disease pathogenesis, raising the possibility that it may also play a key role in psoriatic disease.

* Corresponding author. University of Toronto Psoriatic Arthritis Program, Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital, 1E-410B East Wing, 399 Bathurst Street, Toronto, ON, M5T 2S8, Canada.
E-mail addresses: rpollock@uhnresearch.ca (R.A. Pollock), fabji@uhnresearch.ca (F. Abji), dafna.gladman@utoronto.ca (D.D. Gladman).

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Epigenetics refers to the molecular mechanisms that regulate gene expression but are extrinsic to the DNA sequence. The two major epigenetic mechanisms are the covalent modification of the DNA sequence and histone proteins. Both types of epigenetic marks are transmitted stably through mitosis and act in concert to affect gene expression levels. Considerable variation in DNA and histone modifications occurs across loci, cells, and tissues within an organism. Despite their stability, epigenetic marks also display a degree of plasticity, reversibility, and environmental responsiveness that allows them to act as an interface between genes and environment [6]. There is increasing recognition of the importance of epigenetics in the differentiation and functioning of immune cells, including those implicated in autoinflammatory disorders [7]. These features make epigenetics of considerable interest in psoriatic disease as they can offer explanations for intriguing epidemiological and clinical observations, such as disease discordance in genetically identical monozygotic (MZ) twins with psoriasis and PsA [8], a fluctuating disease course characterized by periods of remission and flares [1], and a parent-of-origin effect [9–12].

This work aims to systematically review the nascent primary literature, assess the evidence for the involvement of epigenetic mechanisms in the etiology of psoriatic disease, identify methodological limitations, discuss challenges in epigenetic research in psoriatic disease, and offer recommendations for the design of future studies.

2. Methods

2.1. Definition of subjects and outcome measures

The systematic review was limited *a priori* to studies of human subjects with psoriatic disease (psoriasis without arthritis and/or PsA) or studies of primary tissues derived from human subjects with psoriatic disease. Outcome measures included the search terms psoriasis and epigenetics, epigenomics, DNA methylation, and histone. miRNA studies were not included as they have been extensively reviewed in the recent literature [13–21].

2.2. Literature searches and data extraction

Electronic literature searches were performed in the Medline, Embase, Scopus, Cochrane Library, Cochrane Central Register of Controlled Trials, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases (searches up to date as of November 5, 2016). References were imported into EndNote X6 and abstracts were screened to remove duplicates, secondary sources (reviews, editorials, and commentaries), and articles not published in English. Full-text articles were then screened independently by two authors (R.A.P. and F.A.) for the following inclusion criteria: experimental studies characterizing epigenetic differences between subjects with psoriatic disease and a control group, experimental studies measuring the activity or expression of a component of the epigenetic machinery in subjects with psoriatic disease, or epidemiological studies related to epigenetic phenomena. Studies focused on computational or *in silico* analysis, animal models, xenotransplanted human tissues, clinical reports, non-epigenetic marks, and non-psoriatic skin diseases were excluded.

2.3. Data extraction and quality assessment

Data were extracted using a standardized template. Following extraction, methodological limitations were identified using a checklist that consists of a series of yes/no questions pertaining to study design [22]. Extraction template and checklist can be found in the Supplementary Information. The checklist encompassed various measures of methodological quality such as clear definitions of objectives and outcomes, a sample that is representative of its population, statistical rigor (such as adjustment for confounding and correction for multiple testing where applicable), adequate power, validation and replication of results; and additional measures of methodological quality specific to epigenetic studies such as tissue homogeneity [23,24].

3. Results

3.1. Summary of literature searches

After screening and applying the inclusion and exclusion criteria, 52 papers or abstracts were included in the review (Fig. 1). Among these, four different types of studies were identified: studies related to the parent-of-origin effect and genomic imprinting in psoriatic disease (17), and studies examining DNA methylation (22), histone modifications (2), and expression or activity of epigenetic modifying enzymes (11) (Fig. 1A). Notably, the majority of published studies (29) focus on psoriasis but do not specify whether patients were assessed for concomitant PsA, therefore these patients may be better described collectively as 'psoriatic disease'. Few studies explicitly indicate the inclusion (15) or exclusion (8) of PsA patients (Fig. 1B).

3.2. Parent-of-origin effect and genomic imprinting

Parent-of-origin effects refer to the differential risk or pathogenicity of a disease that depends on the sex of the disease-transmitting parent. A greater tendency for psoriasis to be inherited from affected males compared to females has been replicated in large, cohorts of patients from the United States [25–29], Denmark [30,31], Germany [32] and Britain [33], as analyzed and summarized by Theeuwes [29]. More recent studies in cohorts from the Faroe Islands [10], Scotland [11], and Canada (Table 1) [9,12] show consistent results. However, other studies in Italian, Newfoundland (Canada), Australian, cohorts have found no significant paternal transmission effect [29,34–36]. A meta-analysis which included several of these studies showed a significant ($p = 0.0014$) excess of paternal transmissions overall [29]. Moreover, some studies [12,34] have found no differences in age of psoriasis onset in paternal compared to maternal transmissions, while one study showed that psoriasis probands reporting an affected father have a significantly greater intergenerational reduction in age of onset compared to probands reporting an affected mother (24.1 vs. 10.9 year reduction, $p = 0.009$), suggesting that paternal transmission is accompanied by genetic anticipation [11].

Investigations of the parent-of-origin effect in PsA patients have shown conflicting results. In the Scottish study, no evidence of a parent-of-origin effect was found among 900 PsA probands [11]. This contrasts findings from a smaller Canadian cohort of 95 PsA probands, in which 65% reported an affected father and 35% reported an affected mother ($p = 0.001$) [9]. A recent follow-up study in the same Canadian cohort replicated these findings. By incorporating additional data on disease severity in their affected mothers and fathers (*i.e.* presence of psoriasis or PsA), this study also provided evidence of genetic anticipation manifesting as a greater tendency for psoriatic disease to increase in severity (parental psoriasis - > proband PsA) during paternal transmissions [12].

Genomic imprinting, an epigenetic phenomenon mediated by DNA and histone methylation, is one molecular mechanism hypothesized to explain parent-of-origin effects. Imprinting involves differential epigenetic marking of alleles in the oocyte and sperm, and these marks are maintained in the next generation, resulting in