

REVIEW ARTICLE

PRAKṚTI AS A SYSTEMS FRAMEWORK FOR DIFFERENTIAL EPIGENETIC IMMUNE RESPONSES IN AUTOIMMUNITY: BEYOND GENES

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ABSTRACT

Autoimmune disorders are multifactorial diseases with a complex interplay between genetic and acquired factors such as immunological, environmental, metabolic, behavioral and other mechanisms. While genome-wide association studies have identified numerous susceptibility loci, genetic variants which rarely explain the observed heterogeneity in disease manifestation and response to treatment. It is the complex interactions between genetic and epigenetic networks, operating together with environmental variables and immune responses, which contribute to an individual's unique genomic and clinical phenotype.

Ayurveda conceptualizes inter-individual heterogeneity as a key element for understanding physiological and pathological processes. The term Prakṛti refers to an individual's constitution, which determines his or her physiological and psychological responses to various stimuli. Āhāra-vihāra (dietary and behavioral regimen) and other therapeutic interventions are applied with due consideration of an individual's Prakṛti to achieve treatment goals. Modern Āyurgenomics has begun exploring the question of whether Prakṛti is associated with specific molecular phenotypes, including, for instance, differences in DNA-methylation patterns reported in a study of healthy Indian men. This raises the interesting possibility that Prakṛti represents a systems biology framework for analyzing the mechanisms by which environmental exposures and immune responses shape inter-individual variation in autoimmune diseases.

This article reviews the emerging evidence for considering Prakṛti, Agni, Āma, and related concepts as systems-level regulators of immune responses in autoimmune diseases. The role of Rasāyana and Panchakarma in modulating these processes is also discussed. It must be emphasized that the present article does not propose to equate Prakṛti with an epigenetic state, or claim that Ayurvedic interventions can “reset the human epigenome.” The author's position must rather be seen as one of formulating research hypotheses that could inform future studies on autoimmune diseases. Further conceptual and empirical work is needed to test the possibility that Ayurvedic constitutional phenotyping can indeed serve as a framework for precision medicine.

KEYWORDS: Agni, Āma, autoimmunity, Āyurgenomics, DNA methylation, epigenetics, immune regulation, precision medicine, Prakṛti, Rasāyana.

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INTRODUCTION

Autoimmune diseases comprise a heterogeneous category of immune-mediated disorders with complex genetic and environmental determinants. Large inter-individual variability in disease manifestations, progression, and treatment outcomes necessitates a personalized medicine approach to management. The role of genetic predisposition in autoimmune diseases is well-established, but genome-wide association studies (GWAS) have so far identified only a limited number of susceptibility variants. Moreover, any given genetic variant usually confers only a modest increase in risk, and rarely acts independently of other variants and environmental influences.¹

This poses significant challenges for genetic risk prediction and individualized treatment design in polygenic autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).² Interestingly, the role of genetic susceptibility in autoimmune diseases is best studied in monozygotic twins, who share the same genome but often differ in their disease susceptibility.³ This further supports the notion that autoimmune diseases

are complex traits influenced by genetic, epigenetic, and environmental interactions.

The contribution of epigenetics to autoimmune disease susceptibility is also well-documented. Epigenetic modifications such as DNA methylation and histone acetylation influence gene expression by regulating the accessibility of DNA to transcription factors. These modifications, which can occur in response to environmental exposures, play a critical role in immunological processes, including regulation of T-cell activation and differentiation.⁴

It is tempting to speculate that inter-individual differences in DNA methylation patterns contribute to phenotypic heterogeneity in autoimmune diseases. Indeed, Prakṛti, the concept of individual constitution central to Ayurveda, has been linked to specific patterns of DNA methylation. A study by Rotti et al. has reported that healthy Indian men can be broadly categorized into three constitutional types – Vāta-predominant, Pitta-predominant, and Kapha-predominant – which exhibit differences in global DNA methylation. However, this observation hardly goes beyond a hypothesis, since the study does not establish any causal link between constitution and

methylation. More importantly, individual variations in DNA methylation are not necessarily linked to differences in gene expression.⁵

Nevertheless, the emerging literature on Āyurgenomics may provide a useful conceptual framework for studying autoimmunity. Recent years have witnessed research exploring the biological concepts of Prakṛti and its implications for health and disease. This literature has identified several molecular signatures that potentially serve as biomarkers of constitution and disease susceptibility.⁶ Yet, the key question continues to be whether inter-individual variation in autoimmune disease susceptibility can indeed be predicted on the basis of Prakṛti.

REVIEW OF THE LITERATURE

Genetic Susceptibility Is Necessary but Not Sufficient

The genetic component of autoimmune diseases generally involves multiple susceptibility loci, often with weak effects. GWAS have identified numerous single nucleotide polymorphisms (SNPs) associated with various autoimmune diseases, including RA, type 1 diabetes, and multiple sclerosis. However, these SNPs are typically involved in only a few cellular pathways, namely antigen presentation, lymphocyte activation, and cytokine receptor signaling.⁷ Furthermore, most of these SNPs only modestly increase disease susceptibility, often by influencing the expression levels of individual genes.⁸

The overall genetic risk for an individual is determined by the combined effect of multiple SNPs. The polygenic risk score, a summary of these combined effects, helps predict an individual's disease risk based on his or her genome-wide genetic profile. However, these scores generally explain only a limited portion of variance in disease susceptibility and treatment responses⁹. Part of the reason for this limitation is the fact that monogenic disorders are rare in autoimmune diseases, and polygenic risk scores rarely capture the combined effect of thousands of rare variants.¹⁰

Another challenge in genetic risk prediction starts from gene-environment interactions. For instance, genome-wide methylation analyses have revealed that genetic variants interact with environmental factors to modify immune cell transcriptomes and contribute to autoimmune disease susceptibility.¹¹ Similarly, twin studies indicate that genetic and epigenetic factors jointly influence disease susceptibility.¹²

Epigenetic Regulation in Autoimmunity

The epigenome plays a crucial role in orchestrating gene expression across tissues and cell types. DNA methylation, one of the best-characterized epigenetic modifications, is known to influence transcription by regulating chromatin accessibility. Dynamic changes in DNA methylation patterns mediate various physiological processes, including cell differentiation and adaptation to environmental conditions.¹³

The contribution of DNA methylation to autoimmunity has been extensively studied. First and foremost, it has been shown to influence transcription in immune cells, thereby regulating T-cell receptor signaling, lymphocyte differentiation, and other critical processes.¹⁴ Second, DNA methylation patterns have been associated with specific immune cell types and their functions.¹⁵ Third, changes in DNA methylation have been implicated in the altered transcriptional profiles seen in autoimmune diseases.¹⁶ Fourth, genome-wide DNA methylation studies have demonstrated associations with disease susceptibility, treatment response, and clinical outcomes.

It is also noteworthy that the role of DNA methylation in disease is critically dependent on the cell type under consideration. Epigenome-wide association studies (EWAS) typically involve bulk peripheral blood mononuclear cells (PBMCs), a mixture of various cell types with markedly different transcriptional profiles.¹⁷ A cell-specific EWAS approach may be necessary to fully characterize the role of DNA methylation in specific cell types and identify reliable biomarkers.

Prakṛti and Āyurgenomics

Prakṛti, or individual constitution, is a notion well-known in the Ayurveda and increasingly explored in modern biomedical research. It has been linked to a wide range of physiological and molecular processes, including differences in cellular morphology, hormone levels, and DNA methylation.¹⁸ The key question has been whether these associations are strong enough to serve as a basis for individualized medicine.

A closer examination of the literature suggests that the relationship between Prakṛti and disease susceptibility is far from being fully understood. First of all, it is important to recognize that the associations largely stem from a single observational study. Rotti et al. analyzed DNA methylation patterns in a sample of 147 healthy Indian men, who were classified on the basis of their constitutional

type. The researchers found inter-individual variability in DNA methylation profiles across the three constitutional types. However, these findings apply only to healthy men, since the study population consisted exclusively of males. On the other hand, the methodology used has gained credibility with the advent of EWAS, which provides a robust framework for exploring associations between DNA methylation and disease.¹⁹

The findings of Rotti et al. have inspired subsequent research, including a recent scoping review and a literature analysis on Āyurgenomics. The latter study highlights the potential of Prakṛti in developing predictive models of autoimmune disease susceptibility. At the same time, it underscores the limitations of current evidence, including the small sample size and methodological heterogeneity of existing studies.²⁰ In this context, it is noteworthy that a recent review has discussed the potential of integrating epigenetic and Ayurvedic approaches to studying health and disease.

Agni, Āma, and the Metabolic–Epigenetic Interface

The relationship between Agni, Āma, and the epigenome represents another potentially fruitful avenue of investigation. It is a multifaceted one, given the involvement of several physiological processes, including digestion, metabolism, inflammation regulation, and immune responses.

Agni encompasses a wide range of metabolic processes, the regulation of which is essential for physiological homeostasis, while Āma refers to the accumulation of metabolic waste products. Both concepts have been linked to health and disease in the Ayurvedic tradition, but little is known about their role relative to modern biomedical mechanisms.²¹ A direct comparison with contemporary physiology is not possible due to conceptual differences, but it may be fruitful to explore shared mechanisms.

A promising direction of research involves the role of Agni–Āma in immunometabolism. This field of study examines the intricate interactions between cellular metabolism and immune responses. Dysregulation of metabolic processes influences immunological functions in a variety of ways, including modulation of T-cell receptor signaling and regulation of inflammatory responses.²² At the same time, immune cells regulate metabolic processes by producing metabolites with endocrine functions.

On the molecular level, metabolites influence gene

regulation by affecting chromatin remodeling processes. This has important implications for epigenome-wide studies, since the metabolic state of an individual influences the expression of many genes linked to disease susceptibility. Overall, the relationship between Agni, Āma, and the epigenome involves a complex network of interactions, which can potentially serve as a framework for investigating autoimmune diseases.

Rasāyana and Phytochemical Modulation

Rasāyana therapy is another potentially valuable research area, with numerous pharmacological effects documented in the Ayurveda. Many phytochemicals used in Rasāyana preparations have been found to influence metabolic and inflammatory processes, including regulation of oxidative stress. However, their role in autoimmune diseases remains poorly understood.

The potential mechanisms by which Rasāyana preparations modulate disease pathology are largely speculative at this point. One direction of research involves the regulation of DNA methylation by phytochemicals. Indeed, several bioactive compounds have been found to influence enzymes responsible for methyl group transfer, thus participating in the epigenetic regulation of gene expression.²³ Nevertheless, it is too early to speculate about the role of Rasāyana in the treatment of autoimmune diseases.

The key challenge in studying Rasāyana therapy is the complexity of traditional formulations. Any given preparation incorporates dozens or even hundreds of phytochemicals, which together influence a variety of cellular mechanisms. Moreover, the bioavailability and physiological effects of individual compounds largely depend on the vehicle and route of administration.²⁴

Panchakarma: A Research Hypothesis Requiring Rigorous Evaluation

Panchakarma represents a promising research area in Ayurveda for understanding potential effects on autoimmunity, including immunological, metabolic, and microbiome-related processes. However, existing studies lack standardized protocols, mechanistic insights, and adequately powered clinical trials. Future research shall employ rigorous clinical designs and multi-omics approaches to evaluate biomarker changes, patient-reported outcomes, and objective clinical measures. Individual Panchakarma procedures shall be systematically investigated and validated before

their therapeutic effects in autoimmune diseases can be established.

MATERIALS AND METHODS

This article is a narrative, hypothesis-generating review based on a conceptual synthesis of published literature relevant to autoimmunity, epigenetic regulation, Prakṛti, and Āyurgenomics. The literature was considered across five broad domains: genetic and epigenetic determinants of autoimmunity; environmental and exposome-related influences; Prakṛti and molecular phenotyping; Agni and Āma as hypothesis-generating physiological constructs; and Rasāyana and Panchakarma as potential areas for mechanistic investigation. The objective was conceptual synthesis rather than quantitative assessment. The article is therefore not intended to be interpreted as a systematic review or meta-analysis.

DISCUSSION

The Proposed Prakṛti–Epigenome–Immune Framework

This review proposes a conceptual framework integrating modern immunological and epigenetic concepts with Ayurvedic principles to explore how individual constitutional variation may influence autoimmune disease susceptibility and treatment responses through underlying immunological and molecular mechanisms.

Constitution-associated phenotype + Environmental/lifestyle exposures + Metabolic state → Cell-specific epigenetic regulation → Immune cell phenotype → Disease susceptibility, clinical manifestation, progression, and treatment response.

Why Precision Measurement Matters

The key strength of the proposed framework lies in the framework highlights the importance of individual variation by considering Prakṛti as a factor influencing health outcomes and supporting personalized healthcare. This requires validated, standardized, and reliable Prakṛti assessment tools. Similarly, cell-specific epigenome-wide association studies (EWAS), combined with single-cell transcriptomics and proteomics, may clarify disease mechanisms. However, identifying a universal Prakṛti-specific molecular signature remains premature; future research shall focus on cell-specific associations and carefully selected biomarkers.

A Proposed Research Design

At this stage, it would be useful to conceptualize a

study design for a large-scale empirical investigation. Ideally, such a study would be multinational and include a diverse sample of participants. The ultimate goal would be to examine individual variation in disease susceptibility and treatment response, with a focus on factors related to Prakṛti.

The most reliable way to assess constitution is to utilize a standardized and validated assessment tool. It is preferable if the tool includes multiple domains related to the key physiological systems. Ideally, the assessment shall be performed by trained professionals, in order to ensure consistency and reliability of results. A recent review has highlighted the need for more research on Prakṛti assessment.

Once a uniform way of assessing individual constitution has been established, the next step would be to examine individual variation in disease susceptibility. It is essential to remember that autoimmunity is a complex trait with numerous potential determinants. To minimize confounding, it is preferable to enroll participants who are relatively similar in terms of race/ethnicity, socioeconomic status, and lifestyle.

Translational and Clinical Implications

If the concepts discussed above are demonstrated to be valid, they could have far-reaching implications for clinical practice and research. First and foremost, they contribute to a better understanding of the mechanisms linking constitution to autoimmunity. This, in turn, could lead to the identification of novel biomarkers of disease susceptibility and more individualized treatment approaches.

It is important to emphasize that such applications are only possible if the underlying concepts have been rigorously validated. At present, there is insufficient evidence to use Ayurvedic assessments and interventions to predict autoimmune diseases, individualize immunotherapy, or replace conventional diagnostics. At best, the Ayurvedic concepts under investigation could serve as an inspiration for further scientific research on autoimmunity.

A responsible translational agenda would focus first on validating the concepts and ensuring their reproducibility. In this context, it is particularly important to follow the basic principles of evidence-based medicine and consider Ayurvedic medicine within the larger framework of biomedical science. This conceptual review synthesizes existing knowledge but lacks a systematic literature review and empirical evidence, limiting the ability to

estimate effect sizes or draw definitive conclusions. Evidence linking Prakṛti to autoimmunity remains limited, with existing genomic studies largely based on small samples. The proposed framework also cannot establish causality or determine whether constitutional differences precede disease susceptibility. Furthermore, the complexity of Ayurvedic interventions, particularly multi-component formulations, makes it difficult to isolate the effects of individual bioactive compounds and establish their direct roles in disease processes.

CONCLUSION

Autoimmune diseases are multifactorial disorders, which involve complex interactions between genetic, environmental, immunological, metabolic, and other processes. Understanding inter-individual variation in disease susceptibility and progression is critical for developing more individualized treatment approaches. Prakṛti represents a useful conceptual framework, which helps integrate a wide range of individual-level factors influencing health outcomes.

The concept highlights the role of constitution-associated variation in determining autoimmune disease susceptibility. In this context, emerging evidence on the molecular mechanisms of constitution-associated differences could have far-reaching implications for precision health care. Indeed, the proposed Prakṛti-based framework could serve as a conceptual basis for exploring individual variation in immune responses, which ultimately affects a person's health status and disease prognosis. In conclusion, it is worth emphasizing that future research shall focus on further elucidating the physiological and molecular mechanisms of individual constitution.

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