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The Synergy of Immunology and Precision Medicine in Therapeutic Revolution of Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is an autoimmune disease with prevalent of clinical expressions on the joints of the body especially in the inflammation of synovial membrane, degeneration of cartilage and bone and multi-organ involvement. The current review is an integrative framework synthesising the view of RA immunopathogenesis, biomarkers development, precision medicine, and novel ways of treating RA. Pathogenesis is the result of an interaction of genetic risk alleles such as HLA-DRB1, environmental exposures, and dysregulated immune pathways which converge around Th1/Th17 cells, B lymphocytes and fibroblast-like synoviocytes. The inflammatory condition in the complex rheumatic disease is a clinico-pathological convergence sampling that is based on epigenomic reprogramming and metabolic adaptations. Recent serological and multi-omics assay developments, anti-citrullinated protein antibodies (ACPAs), 14-3-3eta, microRNAs, and exosomes have made early diagnostic sensitivity, longitudinal pattern of disease, and therapeutic accuracy possible. The emergence of precision medicine as defined by pharmacogenomic testing and synovial testing assists in the support of personalised approaches to treatment. Artificial intelligence is more and more being used in order to normalise heterogeneous data on biomarkers in order to facilitate dynamic risk evaluation. The therapeutic front has advanced as usual beyond traditional disease modifying antirheumatic medicines (DMARDs) to biologics medicines, JAK / BTK blockers, and experimental avenues like tolerazine vaccines, stem cell-based medicine, and nanomedicine. Despite of recent advances in therapeutic practice, patients with malignant neoplasms still pose complications in terms of symptom control, namely pain, fatigue and comorbidities. Further, it has increasingly become more and

more common with acquired treatment resistance. Therefore, it is imperative to engage a multidisciplinary patient centred paradigm to facilitate the long term remission and foster long term clinical outcomes.

Keywords: rheumatoid arthritis; pharmacogenomics; biomarkers; immunopathogenesis; regenerative therapies

Introduction

Rheumatoid Arthritis is a chronic, autoimmune, systemic disorder that poses the enormous global impact. Rhumatoid Arthritis is characterized by continuous synovial inflammation, progressive destruction of cartilage and bone and extra synovial manifestation that can afflict the lungs, cardiovascular system and other organs, its global prevalence is estimated to be 0.51% and 1.0 in the adult population [1, 2]. Heterogeneity has a clinical aspect; different people present, progress through the disease, and respond to various treatments, thus not only is clinical heterogeneity difficult to diagnose but also to manage. Pathogenesis of RA is multifactorial in nature arising due to a complex interrelation between genetic predisposition, environmental influences and dysregulation of the immune responses [3]. HLA presented antigens, which are subject to genetic determinants, mainly the human leukocyte antigen (HLA) region in the case of shared epitope HLA-DRB1 alleles, which enhance autoreactive activation. Among non-HLA genes PTPN22, STAT4, and TRAF1/C5 are modulators of immune tolerance and inflammatory reactions. At the same time, environmental factors, such as smoking cigarettes, workplace silica, gum infections, especially Porphyromonas gingivalis, and intestinal microbiome disproportion, overlap with genetic inclination to disturb immune balance and start autoimmunity [4, 5].

Recently JAK or JAK inhibitors and BTK or BTK inhibitors have been found as promising orals being effective in multiple inflammatory pathways. At the same time, a host of investigational mechanisms is being explored, such as tolerogenic immunotherapies and regenerative therapies using mesenchymal stem cells (MSCs) and engineering breakthroughs using nanotechnology applications to deliver therapeutic agents that may achieve sustained remission and repair. Nonetheless, there are still existing gaps in spite of these improvements. Some patients manifest treatment refractoriness, frequent flares, irreversible joint destruction and extra-articular complications. Moreover, the disease burden of RA is increased by the comorbidities that are related to it, including cardiovascular disease, osteoporosis, and depression which require the application of holistic, interdisciplinary approaches to care [6-8].

The current review attempts to provide a combined evaluation of immunopathogenic, biomarker development, precision-medicine strategies, and using emerging therapeutic innovations in rheumatoid arthritis (RA). Based on a synthesis of recent developments in areas of research, transformational opportunities of personalization of care, improved patient outcomes, and collecting remission of disease in RA are outlined.

Immunopathogenesis of Rheumatoid Arthritis

Genetic and Environmental Determinants

Rheumatoid arthritis is polygenic, despite the fact that the major genetic factor relates to the shared epitope allele of human leukocyte antigen DRB1 (HLA-DRB1). These alleles affect the presentation of antigens in a form that aids in the activation of autoimmune. In addition to HLA-DRB1, there are at least 100 non-HLA genes that impact susceptibility to the disease by affecting immune signalling e.g., the PTPN22, STAT4 and TRAF1/C5 genes [9, 10]. The Table.1 shows the immunopathogenesis of Rheumatoid arthritis. Environmental factors, including exposure to smoking, silica dust, due to its presence in periodontal infections especially those caused by periodontal pathogens, particularly Porphyromonas gingivalis, induce post-translational proteinst changes, in particular, they induce citrullination hence breaking immune tolerance [11-13]. Co-occurring alteration in the gut microbiota distorts mucosal immunity and enhance systemic inflammation. All these genetic-environmental interactions lead to the generation of rheumatoid factors and anti-cyclic citrullinated protein antibodies, which is an indication of the development of pre-clinical autoimmunity [14].

Factor Type	*Examples*	*Mechanism/Implication*
Genetic	HLA DRB1 shared epitope alleles	Increases susceptibility through altered antigen
	PTPN22, STAT4, TRAF1C5	Associated with immune cell signaling and autoimmunity
Environmental	Smoking	Promotes citrullination, leading to ACPA production
	Periodontal disease	Induces protein citrullination and local inflammation (e.g., Porphyromonas gingivalis)
	Occupational silica exposure	Enhances systemic inflammation
	Gut microbiome dysbiosis	Alters immune regulation, affects mucosal immunity

Table 1: Factors influencing the Immunopathogenesis of Rheumatoid Arthritis.

Innate and Adaptive Immune Responses

Rheumatoid arthritis represents a persistent inflammatory disease where the synovial microenvironment can be defined as an impaired immune milieu. The innate and adaptive elements of the immune system work together in order to maintain chronic inflammation and bone destruction. Dendritic cells and macrophages release TNF-a, IL-1b and IL-6, which attract neutrophils and stimulate osteoclasts and hence speed up bone erosion [15-17]. T helper cells, especially Th1 and Th17 cells, coordinate pro-inflammatory action and T regulatory cells (Tregs) have a defective inhibition. B cells secrete autoantibodies (including RF and ACPAs), as well as deliver antigens, thus increasing synovial inflammation. The fibroblast-like synoviocytes (FLS) develop the hyperplasia with invasion ability secreting matrix metalloproteinases (MMPs) and chemokines that extend the destruction of joints and the development of synovial pannus [18, 19].

Epigenetic and Metabolic Mechanisms

Epigenetic changes namely DNA methylation, histone remodeling, and disturbed non-coding RNAs, are extra levels of genomic control in immune cells and synovial cells thus manipulating the expression of the genes, and resulting in rheumatoid arthritis (RA) heterogeneity. Such changes affect immune cells differentiation, cytokine production and resistance to apoptosis. Simultaneous metabolic programs of RA cells which were characterized by a high rate of glycolysis (Warburg effect), a change in the balance of lipid metabolism, mitochondrial dysfunction contribute to hyperproliferation and cellular persistence of inflammation. Oxidative stress and reactive oxygen species (ROS) convince the severity of tissue damage, and at the same time, inadequate energy metabolism provokes the cell activation of fibroblast-like synoviocytes (FLS). All of these epigenetic and metabolic changes are converged with immunological abnormalities to promote the occurrence of chronic synovitis and joint destruction [20, 21].

Biomarker Development in Rheumatoid Arthritis

Classic and Emerging Serological Biomarkers

Rheumatic factor (RF) and anti-citrullinated protein antibodies (ACPAs) especially anti-cyclic citrullinated peptide (CCP) antibodies have been the prime biomarkers that have been used in clinical diagnosis of RA. ACPAs, particularly the anti-CCP antibodies act with great specificity and are effective predictors of erosive disease and response to treatment; their absence in seronegative people shows that new markers are necessary. New players like 14-3-3, calprotectin and MMP-3 candidates have proved useful as assessors of early inflammation, disease activity, and predictive of radiographic progression [22, 23]. They are biomarkers with an improved level of diagnostic specificity, before and atypical manifestations. The question is that their use in usual practice will entail sound validation and standardization in a variety of clinical environments and patient groups.

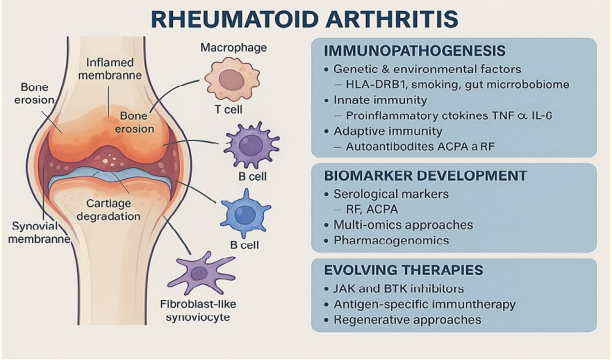

Figure 1: Overview of Rheumatoid Arthritis.

Multi-Omics and Pharmacogenomic Approaches

Molecular stratification of rheumatoid arthritis (RA) has been accomplished using multi-omics platforms (genomics, transcriptomics, and proteomics, and metabolomics) that identify discrete phenotypes of RA as defined by unique pathogenic mechanisms and clinical progression patterns. Biomarker discovery using such comprehensive data can be used in diseases in a diagnostic, prognostic and therapeutic-monitoring way [24, 25]. Genetic variations have been identified through pharmacogenomic studies, e.g. MTHFR during methotrexate metabolism and HLA-DRB1 and biologic responsiveness, that can alter the efficacy and toxicity of a drug. Combination of these profiles can offer precise-guided choice of therapy and follow up dose tailoring. However, transfer into normal clinical care has its limitation due to prohibitive cost, limited access, and the need to harmonize regulations and conduct extensive validation [26].

Toward Personalized, Predictive Biomarkers

The emerging personalized medicine has revised research prospects in eliminating invasive interventions and real-time biomarkers have the potential to predict disease activity and therapeutic outcomes. Extracellular vesicles (especially exosomes) and microRNAs, are becoming regarded as possible diagnostic and prognostic elements since they play important roles in regulating the solitary immune reaction and inflammation [27, 28]. These biomarkers are easily identified in blood and in the synovial fluid and could indicate the fluidity in disease states. In addition, artificial intelligence and machine learning algorithms are being implemented to analyse the large sophisticated biomarker data, thus helping to stratify an individual in treatment. The clinical application of these biomarkers is conditional in terms of multicenter validation and integration to develop a method based on these biomarkers into the current diagnostic framework [29, 30].

Precision Medicine in Rheumatoid Arthritis

Patient Stratification and Individualized Care

Patient stratification in precision care of rheumatoid arthritis (RA) takes center state enabling clinicians to divide patients based on serological, genetic, phenotype and histopathological factors in the synovium. As empirical evidence suggests, seropositive RA is rather likely to be characterized by a more rapid and severe disease course and can prove to be better responsive to certain biologic drugs. Synovial biopsy with high-dimensional omics has also served to disclose molecular signatures predict toxic outcome [31-33]. This stratification forms the basis of early therapy choices, avoiding over and under treatment at the same time. The resulting treatment plans, including drug selections and dosing levels, are, therefore, constructed using these biomarkers in addition to clinical profiles, and thus resulting in a more specific and efficient approach of management [34, 35].

Pharmacogenomics and Treatment Optimization

In pharmacogenomics, rheumatoid arthritis (RA) research is focused on how genetic polymorphisms affect individual sensitivity to the disease-modifying antirheumatic drugs (DMARDs) ranging to both conventional and biologic drugs. The polymorphisms of MTHFR, ABCB1, and some cytokines-related loci have an influence on the drug metabolism, efficacy, and toxicity pattern. The ability to identify such variations helps in the selection of the best drug/dose so that the trial-and-error cycles are minimized and hence the adverse response. Initial evidence has shown that genotype-directed treatment can be a strong predictive indicator to therapeutic success and chances of remission [36, 37]. Clinical utility There is an increasing body of evidence about its clinical utility; however, wider application would also demand cost-effective genotyping platforms, easy translation into routine clinical processes, and amenable payer reimbursement policies.

Integration of Artificial Intelligence and Multi-Omics Data

The fields of artificial intelligence (AI), and machine learning are transforming the treatment of rheumatoid arthritis (RA) by scrutinizing imaging scans, numerous omics profiles, and clinical summaries to identify trends linked to treatment outcomes and disease progression. The predictive algorithms can stratify patients, predict the flares, and recommend dynamic treatments. A typical example, predictive signatures of biologic non-response can be revealed by the combination of transcriptomic and electronic health record (EHR) data. Besides, the AI technology enhances the clinical trial design and biomarker validation. Still, existing barriers such as data heterogeneity, privacy issues, and interoperability remains existent. Ethical implementation, exhaustive training of the clinicians, and effective regulatory systems are essential conditions of successful introduction of AI-powered precision medicine into RA [38].

Evolving Therapeutic Paradigms

Conventional and Targeted Therapies

At present, classic synthetic, disease-modifying antirheumatic drugs (cDMARDs methotrexate, sulfasalazine, and leflunomide) make the foundation of rheumatoid arthritis treatment due to their overall immunosuppressive effect and positive cost-effectiveness. However, their moderate delay in onset of action and non-homogenous therapeutic outcome has led to the formation of biologic disease-modifying antirheumatic drugs (bDMARDs) which act against TNF-a, IL-6 and CD20. Recently, targeted synovial DMARDs (tsDMARDs) especially the JAK inhibitors have included oral agents with acute onset and block of multiple pathways. Table.2 shows detailed therapies currently followed in the market. The introduction of biosimilars has broadened accessibility to the world and enables earlier and more vigorous disease management, sluggish the disease advancement, and enhances patient performance [39, 40]. The individual choices of treatment must be based on disease activity, the serostatus, comorbidities, and the history of the treatment that must be considered during clinical practice.

Therapy Class	*Examples*	*Mechanism of Action*	*Status*
csDMARDs	Methotrexate, Sulfasalazine	Broad immunosuppression	First-line
bDMARDs	Adalimumab, Tocilizumab	Target TNF-α, IL-6 receptor, etc.	Approved
tsDMARDs	Tofacitinib, Baricitinib	JAK inhibitors	Approved
BTK inhibitors	Fenebrutinib, Evobrutinib	Inhibit B-cell signaling	In trials
Tolerogenic therapies	Peptide-based vaccines, cell therapies	Induce immune tolerance	Investigational
Regenerative medicine	MSC therapy, gene editing	Tissue repair and immune modulation	Investigational

Table 2: Various therapies in treating Rheumatoid Arthritis.

Novel Therapeutic Targets and Modalities

New immunological and tissue-remodeling pathways which form the basis of rheumatoid arthritis (RA) have been discovered through contemporary research, and the therapeutic interventions which are based on these discoveries are now under development. Bruton tyrosine kinase (BTK) inhibitors have since come up and are currently under trial as a mode of regulating the B-cell signaling. Tolerogenic therapies on the other hand, e.g. peptide-based vaccines and regulatory cell infusions, aim to restore immune homeostasis with minimum systemic immunosuppression. Regenerative measures such as mesenchymal stem-cell treatment, means of applying gene-editing technicalities would be used to repair tips of the joint [41-43]. At the same time, studies of the neuroimmunological axis are examining therapies including the use of vagus nerve stimulation and more sophisticated drug-delivery systems, which are projected to be both more locally effective and less systematically toxic. All these methods are revolutionary measures and can promise remission or curative measures to patients that resist mainstream therapies.

Addressing Unmet Needs and Comorbidities

Despite the steady improvement in therapeutic procedures, a large number of RA patients still get subjected to unrelenting pain, exhaustion, and incapacity to perform. The role of mainly non-inflammatory pain processing, especially central sensitization, has not been appropriately recognized and treated because of it [44]. The associated less-considered conditions which are comorbid to the uppermost diagnosis such as cardiovascular disease, osteoporosis, interstitial lung disease and depression are outstanding factors influencing morbidity and mortality. This increases the need to screen them regularly, adopt risk-reducing measures and provide inter specialty cooperation. Pharmacological regimens should be combined with lifestyle adjustments, psychological care as well as other non-pharmacological care [45-47]. These unmet clinical needs are essential in improving functional outcomes, adherence, and overall aspects of life in RA patients and therefore infiltrating the need of patient-centred and integrated care models.

Conclusion

Rheumatoid arthritis is a complex autoimmune disease, which is manifested as the interaction of different dimensions, including immunological, genetic, and environmental factors, which leads to persistent inflammation and destructions. Despite increased treatment possibilities due to the introduction of targeted biologics and small-molecule drugs, a patient population has refractory disease and recurrent flares and comorbid complications. The research on multi-omics, pharmacogenomics, and biomarkers have also established the platform of precision medicine in RA through the possibility of making specific treatment decisions provided molecular profiles. Recent agents like JAK and BTK inhibitor, tolerogenic therapies and regenerative approaches have a potential of addressing unmet clinical needs. Moreover, patient stratification is becoming improved with the help of artificial intelligence and digital tools which will enable optimization of treatment in real-time. In spite of the fact that these innovations are of rather significant potential, its use mostly demands thorough testing, availability, and transdisciplinary cooperation. There must be a shift, therefore, to integrated, patient-centered care, where those with inflammation seek not only control but also, where comorbidities are involved, management. The connection between translational research and a practice will be key in the process of ensuring sustained remission and the long-term outcome of rheumatoid arthritis is improved.

Conflict of Interest

The authors declare that there is no conflict of interest related to the content, authorship, or publication of this manuscript.

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