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SYSTEMATIC REVIEW OPEN ACCESS

Role of Post-Translational Modifications in Pathogenesis of Rheumatoid Arthritis and Therapeutic Targeting: A Comprehensive Systematic Review

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ABSTRACT

Background: Post-translational modifications (PTMs) such as phosphorylation, acetylation, and ubiquitination played a critical role in pathogenesis of inflammatory diseases including rheumatoid arthritis (RA). This systematic review aimed to synthesize evidence of principal role of PTMs in RA and to evaluate the therapeutic potential of agents targeting these dysregulated modification pathways. **Methods:** This systematic review followed PRISMA guidelines 2020. Research was conducted in PubMed, Scopus, Web of Science, and Google Scholar from 2015 to 2025. The studies which explored the role of particular PTMs in the RA pathophysiology and their therapeutic potential, were considered. Articles and reviews that were not written in English and where mechanistic or therapeutic outcomes were not described were excluded. The JBI Critical Appraisal Checklist, Newcastle-Ottawa Scale, and SYRCLE tool were used for evaluating risk of bias whereas, quality of study was evaluated using GRADE approach. **Results:** The findings of twelve studies demonstrated that dysregulation of PTMs played a substantial role in RA immunopathology. Mechanistically, acetylation, ubiquitination, and phosphorylation are involved in dysregulated T-cell metabolism, Th17/ Treg imbalance, synovial fibroblast activation, and pro-inflammatory signaling. Preclinical studies supported the therapeutic potential of targeting associated regulatory enzymes. The risk of bias of most studies was measured as moderate and certainty of evidence was found to be low. **Conclusion:** Phosphorylation, ubiquitination, and acetylation played a critical role in the pathogenesis of RA and could be exploited as potential therapeutic targets.

Keywords: Rheumatoid Arthritis; Protein Processing, Post-Translational; Phosphorylation; Ubiquitination; Acetylation; Autoimmunity; Signal Transduction; Cytokines

Rheumatoid arthritis (RA) is a systemic autoimmune disease, associated with chronic synovial inflammation and destruction of the joints [1,2]. Although its etiology remained multifactorial, an imbalanced immune response was central to its pathogenesis [3]. Recent studies had emphasized the importance of post-translational modifications (PTMs) in regulating the protein structure, activity, and immunogenicity [4]. These modifications played a critical role in the attenuation of immune tolerance and inflammation in RA [5]. Acetylation, ubiquitination, and phosphorylation were the main PTMs involved in altering the autoantigens, destabilizing the cellular signaling pathways, and regulating the activity of immune cells [6-8].

Mechanistic understanding of PTMs revealed its dual role in disease progression as well as in therapeutic applications [9]. Antibodies targeting PTM-derived neoepitopes were established as diagnostic biomarkers [10]. Emerging evidence suggested that acetylated peptide autoantibodies hold clinical significance [11]. Furthermore, enzymes regulating PTMs, such as kinases, acetyltransferases, deacetyltransferases, and ubiquitin ligases, became a promising frontier for targeted therapy [12]. The enzymatic machinery was able to regulate specific pathogenic pathways as compared to traditional immunosuppression pathways. Despite growing interest, the comprehensive role of PTMs in the pathogenesis of RA and their translational prospects was still missing. Most of the available evidence was based on discrete, usually small-scale studies involving individual PTMs, which left a knowledge gap about the synergistic or differential functions of individual PTMs in disease stages and subsets [13]. Systematic review of existing evidence was thus required to elucidate the pathophysiological processes, to evaluate their findings, and to identify consistent therapeutic targets. This review was conducted to fill this gap by critically reviewing recent literature on the role of major PTMs in RA. The main aim of this narrative review was to synthesize and critically analyze the evidence of twelve studies evaluating the role of the main PTMs acetylation, ubiquitination, and phosphorylation in the immunopathology of RA and evaluate their potential as diagnostic biomarkers or therapeutic targets.

Methodology

The systematic review followed PRISMA 2020 guidelines, to ensure the transparency of the study process [14].

Databases and Search Strings Used: Research published from 2015 to December 2025 were retrieved using databases i.e., PubMed, Scopus, Google Scholar, Web of Science, and Cochrane Library. The search strategy employed a combination of MeSH terms and free-text keywords related to PTMs, inflammatory diseases, and therapeutic targeting. Core search terms included: "post-translational modification," "ubiquitination," "acetylation," "phosphorylation," "chronic inflammation," "rheumatoid arthritis," and " therapeutic target". Boolean operators (AND, OR) were applied, and reference lists of included studies were also screened to identify additional eligible articles.

Inclusion and Exclusion Criteria: Those studies were included that were original research articles, such as experimental, observational, or clinical investigations, examining the mechanistic role or therapeutic potential of specific PTMs in the pathogenesis of RA. Only articles published in English were considered. Studies were excluded if they were non-primary research including reviews and editorials, or if they did not focus on a chronic inflammatory condition, explored PTMs without a direct link to disease mechanisms or treatment, or if the full text was unavailable.

Study Selection: The title and abstract of studies were reviewed independently by two researchers until proper inclusion requirement were met. The reviewers settled their selection differences either through group agreement or expert consultation.

Data Extraction: Two independent reviewers performed data extraction, which included information about study design, targeted disease, PTMs, outcome measures, and key results. The reviewers either achieved consensus or consulted a third person to settle any differences between their findings. When necessary, corresponding authors were contacted for missing or clarifying data.

Primary Outcome and Quality Assessment: The primary outcome of this review was to evaluate the role of specific PTMs in the pathogenesis of RA and to assess their potential as therapeutic targets. Risk of bias among the included studies were assessed through the Adapted JBI Critical Appraisal Checklist for observational cross-sectional studies, Newcastle-Ottawa Scale for observational cohort studies, SYRCLE risk of bias tool in animal studies and modified in vitro risk of bias tools for experimental studies [15-17]. The level of evidence was determined based on the GRADE approach.

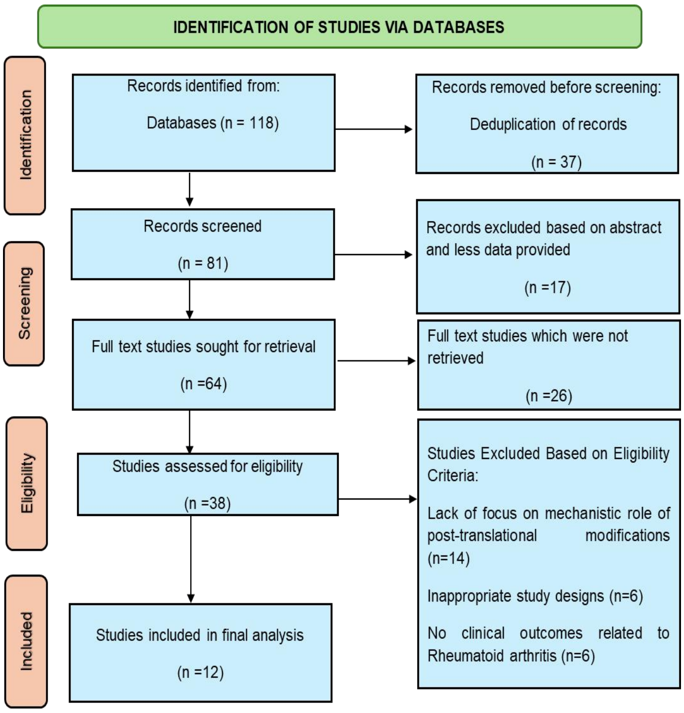

Figure 1: PRISMA Flow Diagram

Results

The study demonstrated the role of PTMs including phosphorylation, acetylation, and ubiquitination in pathogenesis of RA. Among the searched electronic databases and other sources, 118 research articles were initially selected. The number was reduced to 81 after removing the duplicates. Title and abstract screening further eliminated 17 studies. From the remaining 64 articles, 26 were removed due to unavailability of access to the full-texts. Further 38 articles were screened, and 26 were eliminated due to a lack of stratified data and studies including animals, in vitro findings, reviews, case reports, or languages other than English. Ultimately, twelve studies that passed the inclusion criteria were included in this systematic review. The PRISMA flow diagram presented in Figure 1 illustrates the selection process. A structured overview summarizing the characteristics and key findings of the twelve included studies, illustrating the association of specific PTMs with disease mechanisms and their proposed therapeutic implications is presented in Table 1.

Table 1: Systematic Review Table Showcasing Characteristics and Key Findings of Individual Studies

Author & Year	Country of Study	Disease Context	PTM(s) Investigated	Study Design & Model(s)	Sample Size / Population Characteristics	Key Findings	Therapeutic Implications
Haro et al., 2024 [18]	Spain	RA	Acetylation, Citrullination, Carbamylation,	Cross-sectional observational study	RA patients: n=178 Healthy donors: n=120	IgG, IgA, and IgM antibodies against acetylated, citrullinated and carbamylation peptides are elevated in RA	Incorporating anti-acetylated antibodies into RA diagnostics, early detection and highlight the pathogenic role of these PTMs.

						patients.	
Arito et al., 2015 [19]	Japan	RA	Acetylation	Case-control observational study design (with proteomic analysis)	7 RA patients, 7 healthy donors (PBMCs)	Hyperacetylation of ENO1 in PBMCs of RA patient enhances glycolytic activity, promoting T-cell activation and inflammation.	Modulating acetylation via HDAC1 or acetyltransferase inhibitors could reduce pathogenic T-cell metabolism in RA.
Nijjar et al., 2021 [20]	United Kingdom	RA	Acetylation, Citrullination, carbamylation,	Observational cohort study	362 RA patients	Autoantibody profile against acetylated, citrullinated, and carbamylated peptides predicts severe radiographic progression in RA.	AMPA profiling could guide early aggressive therapy in high-risk RA patients. Therapeutic strategies targeting PTM-specific B cell or antibody responses may slow radiographic damage.
García-Moreno et al., 2021 [21]	Spain	RA and interstitial lung disease.	Acetylation, Citrullination, carbamylation	Cross-sectional observational study	RA patients: n=178 (37 with ILD, 141 without ILD)	IgA/IgM AMPAs against multi-PTMs peptides correlate with severe RA phenotype and interstitial lung disease.	Multi-PTM peptides could improve RA stratification and predict severe ILD phenotypes. AMPA-specific therapies may benefit for RA subsets.
Wang et al., 2022 [22]	China	RA	Ubiquitination	Comparative observational (case-control) study	Human: 22 RA patients, 20 HC (blood); 8 RA, 8 OA (synovial fluid).	STUB1 is upregulated in RA patient. It promotes Th17/Treg imbalance via K63-linked ubiquitination, enhancing pro-inflammatory pathways.	Targeting STUB1 or its interaction with AHR could correct the pathogenic Th17/Treg imbalance in RA.
Su et al., 2024 [23]	China	RA	Ubiquitination	Experimental study	Rats: CIA model (n=6/group); In vitro: EL-4 cells, primary T cells from C57BL/6 mice	IAA reduces Foxp3 ubiquitination, promotes Treg differentiation, and alleviates arthritis in CIA rats.	IAA supplementation may serve as a therapeutic strategy for RA by modulating Treg/Th17 balance via AhR-TAZ-Tip60-mediated Foxp3 stabilization.
Kong et al., 2016 [24]	China	RA	Ubiquitination	Comparative experimental laboratory study	Human FLS cell lines from RA patients	TRIP overexpression promotes K48-linked ubiquitination, TAK1 degradation, suppress NF-κ-β activation, and reduce pro-inflammatory cytokine production.	TRIP may be a potential therapeutic target for RA by inhibiting TAK1/NF-κ-β-mediated inflammation.
Singh et al., 2016 [25]	United States	RA	Ubiquitination	Experimental study	Human RASFs from RA patients	EGCG suppresses RA synovial fibroblast activation by inhibiting K-linked autoubiquitination of TRAF6 and TAK1 phosphorylation.	EGCG represents a novel small-molecule strategy to target the ubiquitin–TRAF6 axis in RA, offering a potential oral alternative to biologic therapies.

Yang et al., 2024 [26]	China	RA	Phosphorylation	Experimental study	Mouse model (n=5/group)	Phosphorylated Au44MBA26-P nanoclusters exhibit enhanced bone targeting, and suppress pro-inflammatory cytokines via NF-κB inhibition.	Au44MBA26-P serves as a probe for bone-targeted imaging and improved RA therapy with good biocompatibility.
Zhang et al., 2021 [27]	China	RA	Phosphorylation	Experimental study	Synovial tissues from 8 RA patients, 8 healthy controls, cell culture experiments	ATF2 phosphorylation is upregulated in RA synovium. SPRY2 overexpression inhibits ATF2 phosphorylation and ERK signaling.	SPRY2/ERK/ATF2 axis may be targeted to suppress FLS activation and synovial inflammation in RA.
Novak-Kotzer et al., 2025 [28]	United Kingdom	RA	Phosphorylation	Experimental study	CD4+ T cells from 21 RA patients, 15 healthy controls	Lck mediates the TCR-dependent phosphorylation of STAT3 at the immunological synapse.	Targeting Lck-mediated phosphorylation of STAT3 at synapse presents a novel therapeutic approach for RA.
Wei et al., 2024 [29]	China	RA and interstitial lung disease	Phosphorylation of JAK2, STAT3, and SMAD3	Experimental study	Rats: n=30 (10 per group) Cell line: HFL1	A JAK2 inhibitor attenuated RA progression and lung fibrosis by suppressing the pathogenic phosphorylation of JAK2/STAT3/SMAD3	Inhibiting the phosphorylation of JAK2 and its downstream STAT3 reduces joint inflammation in rheumatoid arthritis.

RA = Rheumatoid Arthritis; PBMCs = Peripheral Blood Mononuclear Cells; HCs = Healthy Controls; HDACs = Histone Deacetylases; HAT = Histone Acetyltransferase; Treg cells = Regulatory T cells; OA = Osteoarthritis; ACPA = Anti-Citrullinated Protein Autoantibodies; mAbs = Monoclonal Antibodies; NETs = Neutrophil Extracellular Traps; HFLS-RA = Human Fibroblast-Like Synoviocytes from RA patients; CIA = Collagen-Induced Arthritis; TRAF2 = Tumor Necrosis Factor Receptor-Associated Factor 2; FLS = Fibroblast-Like Synoviocytes; SLB = Supported Lipid Bilayer; BMMs = Bone Marrow-Derived Macrophages; MTHFD2 = Methylenetetrahydrofolate Dehydrogenase 2; IAA = β-Indole-3-Acetic Acid; AhR = Aryl Hydrocarbon Receptor; TAZ = Transcriptional Co-activator with PDZ-binding motif (WWTR1); TRIP = TRAF-Interacting Protein (TRAIP); TAK1 = Transforming Growth Factor β-Activated Kinase 1; AMPAs = Anti-Modified Protein Antibodies; RASFs= Rheumatoid Arthritis synovial fibroblasts; EGCG= epigallocatechin-3-gallate

The synthesis of twelve studies proved that dysregulated PTMs were central to the immunopathology of RA. Autoantibodies against acetylated peptides were associated with a severe disease phenotypes and radiographic progression. Mechanistically, acetylation played a role in dysregulated T-cell metabolism. Ubiquitination critically controlled T-cell polarization (Th17/Treg balance) and synovial fibroblast activation via enzymes such as STUB1 and TAK1. Phosphorylation drove pathogenic signaling in fibroblasts and T cells through pathways involving JAK2/STAT3, ERK/ATF2, and TCR-STAT3. Preclinical data supported the therapeutic potential of targeting the PTM associated enzymes. In all the twelve studies, risk of bias was evaluated using specific tools according to study designs such as Adapted JBI Critical Appraisal Checklist for observational cross-sectional studies, Newcastle-Ottawa Scale for observational cohort studies, SYRCLE risk of bias tool in animal studies, and modified in vitro risk of bias tools for experimental studies were used (Table 2). The overall risk was moderate.

Table 2: Risk of Bias for Included Studies

Risk of Bias for Observational Cross-Sectional Studies						
Author & Year	**Inclusion Criteria**	**Exposure Measurement**	**Confounding Control**	**Outcome Measurement**	**Statistical Analysis**	**Overall**
Haro et al., 2024 [18]	Low	Low	High	Low	Low	**Moderate**
Arito et al., 2015 [19]	Low	Low	High	Low	Low	**Moderate**
García-Moreno et al., 2021 [21]	Low	Low	High	Low	Low	**Moderate**
Risk of Bias for Observational Cohort Study						
Author & Year	**Selection**	**Comparability**	**Outcome Assessment**	**Follow-Up**	**Overall**	

Nijjar et al., 2021 [20]	Low	Low	Low	Low	**Low**	
Risk of Bias for Pre-clinical Studies						
Author & Year	**Randomization**	**Blinding**	**Outcome Assessment**	**Selective Reporting**	**Sample Size Justification**	**Overall**
Su et al., 2024 [23]	Unclear	High	Low	Low	High	**High**
Yang et al., 2024 [26]	Unclear	High	Unclear	Low	High	**High**
Wei et al., 2024 [29]	Unclear	High	Unclear	Low	High	**High**
Risk of Bias for Experimental Studies						
Author & Year	**Cell/Tissue Source**	**Intervention Detail**	**Controls**	**Blinding**	**Replicates/Statistics**	**Overall**
Wang et al., 2022 [22]	Low	Low	Low	High	Low	**Moderate**
Kong et al., 2016 [24]	Low	Low	Low	High	Low	**Moderate**
Singh et al., 2016 [25]	Low	Low	Low	High	Low	**Moderate**
Zhang et al., 2021 [27]	Low	Low	Low	High	Low	**Moderate**
Novak-Kotzer et al., 2025 [28]	Low	Low	Low	High	Low	**Moderate**

The observational cohort study was characterized by low bias because of strict selection of patients and standardized assays. The risks were moderate in observational cross-sectional and experimental studies due to lack of confounding controls and blinding, respectively.

Discussion

The synthesized evidence from the twelve reviewed studies highlighted the central and complex roles of PTMs in the pathogenesis of RA. One of the common themes found in clinical observational studies was the diagnzostic and prognostic importance of anti-modified protein antibodies (AMPAs) [30]. The studies revealed that citrullination was not the only response to autoantibodies, as they also responded to acetylated forms of the peptide [31]. Interestingly, these AMPA profiles were related to severe disease phenotypes, radiographic evolution, and extra-articular manifestation such as interstitial lung disease [32]. Moreover, Environmental exposures have also been shown to induce persistent molecular regulatory alterations [33]. Experimental studies have similarly demonstrated that environmental and chemical exposures can induce long-lasting molecular and epigenetic alterations affecting disease-related pathways [34,35]. This evidence collectively supported the utility of multiplexed AMPA profiling to capture a broader "autoantibody landscape," which could enhance patient stratification, thereby enabling the early identification of high-risk individuals for more aggressive or targeted therapeutic intervention [36].

On a mechanistic level, PTMs controlled key processes in the cell that fueled inflammation [37]. The acetylation regulated metabolic processes in immune cells, stimulate glycolysis in T cells and a pro-inflammatory condition [38]. Ubiquitination became a major homeostatic regulator of immune signaling [39]. The studies demonstrated its key role in T-cell polarization via destabilization of Treg transcription factor Foxp3 or imbalance of Th17/Treg by E3 ligases such as STUB1. Its regulation of key inflammatory mediators like TAK1 in synovial fibroblasts had also been previously reported [40,41]. Phosphorylation events played a key role in driving signal transduction in fibroblast-like synoviocytes and T cells [42]. The therapeutic targeting of PTM-related enzymes, such as Histone Deacetylases, ubiquitin ligases, or kinases like JAK2, showed promise in preclinical models, which provides a route to further specific immunomodulation. The overlap of two or more PTMs on common downstream pathways, especially NF-κ-β and metabolic reprogramming, reinforced their strategic importance in the inflammatory network of RA. Comparable alterations in cellular signaling, metabolic regulation, and disease-related pathways have also been observed in experimental models investigating neurobiological and inflammatory disorders [43,44].

However, the evidence incorporated in this review had a number of limitations. The most important were moderate risks of bias in experimental and preclinical studies, which are frequently related to the uncertainty of blinding practices, and the absence of full information on randomization. Moreover, the heterogeneity in study designs, model systems and patient populations limited the direct comparability of the findings. Despite the fact that the evidence suggested the PTMs association in RA, the articles associated with the studies had severe limitations that limit conclusive results. The researchers were limited to three main types of PTMs (phosphorylation, acetylation, ubiquitination) and a one chronic inflammatory disease, which might exclude the other types of modifications, such as sumoylation, and rarer diseases [42].

The search and selection were systematic but limited to 12 key studies for in-depth analysis, which, although representative, but may not cover the entire scope of relevant research.These findings had many implications. To practice in the clinical field, integrating multiplex AMPA testing could be used to narrow down RA diagnosis and prognosis. For therapeutic development, inhibiting PTM enzymes was an attractive approach to next-generation and pathway-specific drugs. The future research should be focused on standardized and longitudinal clinical cohorts to confirm AMPA panels, as well as mechanistic experiments using conditional knockouts and highly selective inhibitors to elucidate the specific role of individual PTM regulators in a particular cell type, followed by translation of these findings into specific clinical treatment.

Conclusion

This review confirmed that ubiquitination, acetylation and phosphorylation deregulation were key elements in the pathogenesis of RA that instigated immune cell dysfunction, synovial inflammation and the production of autoantibodies. The main limitations were the heterogeneity of available literature and preclinical nature, and little clinical validation. The future studies required massive PTMs profiling in patients to extract biomarkers and development of specific tissue-targeted modulators to convert these processes into effective precision therapies.

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References

1. Jahid M, Khan KU, Ahmed RS. Overview of rheumatoid arthritis and scientific understanding of the disease. Mediterr J Rheumatol. 2023;34(3):284-91. https://doi.org/10.31138/mjr.20230801.oo
2. Alivernini S, Firestein GS, McInnes IB. The pathogenesis of rheumatoid arthritis. Immunity. 2022;55(12):2255-70. https://doi.org/10.1016/j.immuni.2022.11.009
3. Babaahmadi M, Tayebi B, Gholipour NM, Kamardi MT, Heidari S, Baharvand H, et al. Rheumatoid arthritis: the old issue, the new therapeutic approach. Stem cell res ther. 2023;14(1):268. https://doi.org/10.1186/s13287-023-03473-7
4. Mnatsakanyan R, Shema G, Basik M, Batist G, Borchers CH, Sickmann A, et al. Detecting post-translational modification signatures as potential biomarkers in clinical mass spectrometry. Expert Rev Proteomics. 2018;15(6):515-35. https://doi.org/10.1080/14789450.2018.1483340
5. Mastrangelo A, Colasanti T, Barbati C, Pecani A, Sabatinelli D, Pendolino M, et al. The role of posttranslational protein modifications in rheumatological diseases: focus on rheumatoid arthritis. J Immunol Res. 2015;2015(1):712490. http://dx.doi.org/10.1155/2015/712490
6. Willems P, Sterck L, Dard A, Huang J, De Smet I, Gevaert K, et al. The Plant PTM Viewer 2.0: in-depth exploration of plant protein modification landscapes. J Exp Bot. 2024;75(15):4611-24. https://doi.org/10.1093/jxb/erae270
7. Wen J, Wang D. Deciphering the PTM codes of the tumor suppressor p53. J Mol Cell Biol. 2021;13(11):774-85. https://doi.org/10.1093/jmcb/mjab047
8. Stastna M. Post-translational modifications of proteins in cardiovascular diseases examined by proteomic approaches. The FEBS J. 2025;292(1):28-46. https://doi.org/10.1111/febs.17108
9. Zhong Q, Xiao X, Qiu Y, Xu Z, Chen C, Chong B, et al. Protein posttranslational modifications in health and diseases: Functions, regulatory mechanisms, and therapeutic implications. MedComm. 2023;4(3):e261. https://doi.org/10.1002/mco2.261
10. Safa A, Vruzhaj I, Gambirasi M, Toffoli G. Antigenic dark matter: unexplored post-translational modifications of tumor-associated and tumor-specific antigens in pancreatic cancer. Cancers. 2025;17(21):3506. https://doi.org/10.3390/cancers17213506
11. Haro I, Sanmartí R, Gómara MJ. Implications of post-translational modifications in autoimmunity with emphasis on citrullination, homocitrullination and acetylation for the pathogenesis, diagnosis and prognosis of rheumatoid arthritis. Int J Mol Sci. 2022;23(24):15803. https://doi.org/10.3390/ijms232415803
12. Sun C-F, Li Y-Q, Mao X-M. Regulation of protein post-translational modifications on metabolism of actinomycetes. Biomolecules. 2020;10(8):1122. https://doi.org/10.3390/biom10081122
13. Ortiz AM, Silva Fernández L, Villaverde V, Abad MÁ, Maneiro JR, Candelas G, et al. Gaps between research and recommendations in rheumatoid arthritis. Rheumatol Int. 2021;41(1):57-66. https://doi.org/10.1007/s00296-020-04724-z
14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. bmj. 2021;372. https://doi.org/10.1136/bmj.n71
15. Barker TH, Stone JC, Sears K, Klugar M, Tufanaru C, Leonardi-Bee J, et al. The revised JBI critical appraisal tool for the assessment of risk of bias for randomized controlled trials. JBI evidence synthesis. 2023;21(3):494-506. https://doi.org/10.11124/JBIES-22-00430
16. Hooijmans CR, Rovers MM, De Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014;14(1):43. https://doi.org/10.1186/1471-2288-14-43
17. Carra MC, Romandini P, Romandini M. Risk of bias evaluation of cross-sectional studies: Adaptation of the Newcastle–Ottawa Scale. J Periodontal Res. 2025 Apr;60(2):e13405. https://doi.org/10.1111/jre.13405
18. Haro I, Castellanos-Moreira R, Sanmartí R, Gómara MJ. Anti-Modified Peptide Antibodies (AMPAs) in Rheumatoid Arthritis: Study of the Diagnostic Value of Citrullinated, Homocitrullinated, and Acetylated Fibrin/Filaggrin Chimeric Peptides. Diagnostics. 2024;14(22):2485. https://doi.org/10.3390/diagnostics14222485
19. Arito M, Nagai K, Ooka S, Sato T, Takakuwa Y, Kurokawa M, et al. Altered acetylation of proteins in patients with rheumatoid arthritis revealed by acetyl-proteomics. Clin Exp Rheumatol. 2015;33(6):877-86. https://doi.org/10.55563/clinexprheumatol/8d0gx3
20. Nijjar JS, Morton FR, Bang H, Buckley CD, van der Heijde D, Gilmour A, et al. The impact of autoantibodies against citrullinated, carbamylated, and acetylated peptides on radiographic progression in patients with new-onset rheumatoid arthritis: an observational cohort study. Lancet Rheumatol. 2021;3(4):e284-e93. https://doi.org/10.1016/S2665-9913(20)30381-7

21. García-Moreno C, Gómara MJ, Castellanos-Moreira R, Sanmartí R, Haro I. Peptides bearing multiple post-translational modifications as antigenic targets for severe rheumatoid arthritis patients. Int J Mol Sci. 2021;22(24):13290. https://doi.org/10.3390/ijms222413290
22. Wang W, Xiang T, Yang Y, Wang Z, Xie J. E3 ubiquitin ligases STUB1/CHIP contributes to the Th17/Treg imbalance via the ubiquitination of aryl hydrocarbon receptor in rheumatoid arthritis. Clin Exp Immunol. 2022;209(3):280-90. https://doi.org/10.1093/cei/uxac072
23. Su X, Wang X, Zhang X, Sun Y, Jia Y. β-Indole-3-acetic acid attenuated collagen-induced arthritis through reducing the ubiquitination of Foxp3 via the AhR-TAZ-Tip60 pathway. Immunologic Research. 2024;72(4):741-53. https://doi.org/10.1007/s12026-024-09480-x
24. Kong Q-Z, Guo L-T, Yang J-N, Wang Y-F, Zhao J-X, Kong S-H, et al. Anti-inflammatory effects of TRAF-interacting protein in rheumatoid arthritis fibroblast-like synoviocytes. Mediators Inflamm. 2016;2016(1):3906108. https://doi.org/10.1155/2016/3906108
25. Singh AK, Umar S, Riegsecker S, Chourasia M, Ahmed S. Regulation of transforming growth factor β–activated kinase activation by epigallocatechin-3-gallate in rheumatoid arthritis synovial fibroblasts: suppression of K63-linked autoubiquitination of tumor necrosis factor receptor–associated factor 6. Arthritis & Rheumatology. 2016;68(2):347-58. https://doi.org/10.1002/art.39447
26. Yang G, Liu K, Wang Y, Pan X, Ye J, Li Y, et al. Phosphorylation of NIR-II emitting Au nanoclusters for targeted bone imaging and improved rheumatoid arthritis therapy. Aggregate. 2024;5(2):e435. https://doi.org/10.1002/agt2.435
27. Zhang X, Zhang D, Wang Q, Guo X, Chen J, Jiang J, et al. Sprouty2 inhibits migration and invasion of fibroblast-like synoviocytes in rheumatoid arthritis by down-regulating ATF2 expression and phosphorylation. Inflammation. 2021;44(1):91-103. https://doi.org/10.1007/s10753-020-01311-z
28. Novak-Kotzer H, Capera J, Jainarayanan A, Elanchezhian M, Valvo S, Mayya V, et al. STAT3 phosphorylation in the rheumatoid arthritis immunological synapse. J Autoimmun. 2025;15(5):103456. https://doi.org/10.1101/2025.01.20.633875
29. Wei Y, Wang D, Wu J, Zhang J. JAK2 inhibitors improve RA combined with pulmonary fibrosis in rats by downregulating SMAD3 phosphorylation. Int J Rheum Dis. 2024;27(5):e15164. https://doi.org/10.1111/1756-185X.15164
30. Zhang G, Yao L, Zhu Q, Herrmann M, Zhao Y. Cross-reactivity of anti-modified protein antibodies in rheumatoid arthritis. Clin Exp Rheumatol. 2024;43(7):1332-44. https://doi.org/10.55563/clinexprheumatol/c0eeg7
31. Trouw LA, Rispens T, Toes RE. Beyond citrullination: other post-translational protein modifications in rheumatoid arthritis. Nat Rev Rheumatol. 2017;13(6):331-9. https://doi.org/10.1038/nrrheum.2017.15
32. Sebastiani M, Manfredi A, Croci S, Faverio P, Cassone G, Vacchi C, et al. Rheumatoid arthritis extra-articular lung disease: new insights on pathogenesis and experimental drugs. Expert Opin Investig Drugs. 2024;33(8):815-27. https://doi.org/10.1080/13543784.2024.2376567
33. Bano U, Memon S, Shahani MY, Shaikh P, Gul S. Epigenetic effects of in utero bisphenol A administration: Diabetogenic and atherogenic changes in mice offspring. Iran J Basic Med Sci. 2019 May;22(5):521-528. https://doi.org/10.22038/ijbms.2019.29909.7357
34. Memon S, Bano U, Shahani MY. Maternal exposure to Bisphenol-A induces epigenetic changes in metabolic syndrome markers of offspring. FASEB J. 2018 Apr;32(S1):774-2. https://doi.org/10.1096/fasebj.2018.32.1_supplement.774.2
35. Memon S, Bano U, Singha SP, Shahani MY, Shaikh P, Shahani SB, et al. Chromium restriction in the intrauterine environment and development of metabolic diseases in mice offspring. J Taibah Univ Med Sci. 2025;20(3):365–75. https://doi.org/10.1016/j.jtumed.2025.06.001
36. Volkov M, van Schie KA, van der Woude D. Autoantibodies and B Cells: The ABC of rheumatoid arthritis pathophysiology. Immunological reviews. 2020;294(1):148-63. https://doi.org/10.1111/imr.12829
37. Hsieh H-C, Ling L-L, Wang Y-C. Post-translational modifications of immune checkpoints: molecular mechanisms, tumor microenvironment remodeling, and therapeutic implications. J Biomed Sci. 2026;33(1):3. https://doi.org/10.1186/s12929-025-01202-1
38. Li X, Yu T, Li X, He X, Zhang B, Yang Y. Role of novel protein acylation modifications in immunity and its related diseases. Immunology. 2024;173(1):53-75. https://doi.org/10.1111/imm.13822
39. Sasaki K, Iwai K. Role of linear ubiquitination in inflammatory responses and tissue homeostasis. Int Immuno. 2023;35(1):19-25. https://doi.org/10.1093/intimm/dxac047
40. Jiang W, Li M, Peng S, Hu T, Long Y, Zhang J, et al. Ubiquitin ligase enzymes and de-ubiquitinating enzymes regulate innate immunity in the TLR, NLR, RLR, and cGAS-STING pathways. Immunol Res. 2023;71(6):800-13. https://doi.org/10.1007/s12026-023-09400-5
41. Liu J, Cheng Y, Zheng M, Yuan B, Wang Z, Li X, et al. Targeting the ubiquitination/deubiquitination process to regulate immune checkpoint pathways. Signal Transduct Target Ther. 2021;6(1):28. https://doi.org/10.1038/s41392-020-00418-x
42. Maglaviceanu A, Wu B, Kapoor M. Fibroblast-like synoviocytes: role in synovial fibrosis associated with osteoarthritis. Wound Repair Regen. 2021;29(4):642-9. https://doi.org/10.1111/wrr.12939
43. Huang C-H, Yang T-T, Lin K-I. Mechanisms and functions of SUMOylation in health and disease: a review focusing on immune cells. J Biomed Sci. 2024;31(1):16. https://doi.org/10.1186/s12929-024-01003-y
44. Singha SP, Memon S, Bano U, Isaac AD, Shahani MY. Evaluation of p21 expression and related autism-like behavior in Bisphenol-A exposed offspring of Wistar albino rats. Birth Defects Res. 2022;114(11):536–50. https://doi.org/10.1002/bdr2.2022
45. Singha SP, Memon S, Kazi SAF, Nizamani GS. Gamma aminobutyric acid signaling disturbances and altered astrocytic morphology associated with Bisphenol A induced cognitive impairments in rat offspring. Birth Defects Res. 2021;113(12):911–24. https://doi.org/10.1002/bdr2.1886