University of Baghdad
College of Pharmacy
Clinical Laboratory Sciences
Department

Association of Macrophage Immunometabolism Regulator *MACIR* rs26232 Gene Polymorphism with the Serum Levels of Some Biomarkers Involved in the Pathogenesis of Rheumatoid Arthritis in Iraqi Patients

Ph.D. Student
Amena Jassim Lafta
Under Supervision of
Assist. Prof.
Dr. Ali Abdulhussain Kasim

2025 A.D

Introduction:

- Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that affects the joints, typically causing pain, swelling, and stiffness
- It is the most common type of inflammatory arthritis and can affect people of all ages, although it is most common in middle-aged and older adults
- The prevalence of RA varies around the world, but it is estimated to affect approximately 1% of the population globally
- However, the prevalence can vary significantly between different regions and countries and it can be as high as 5%

- The pathogenesis of RA involves a complex interplay of environmental, genetic, and immunological factors. It is characterized by an abnormal immune response that leads to chronic inflammation and joint damage
- Environmental factors, such as smoking, hormonal changes, and exposure to certain infections, may trigger the onset of RA in individuals with genetic predisposition
- Certain genetic markers are associated with an increased risk of developing RA. These genetic factors can influence the immune system's response to environmental triggers shown in figure below

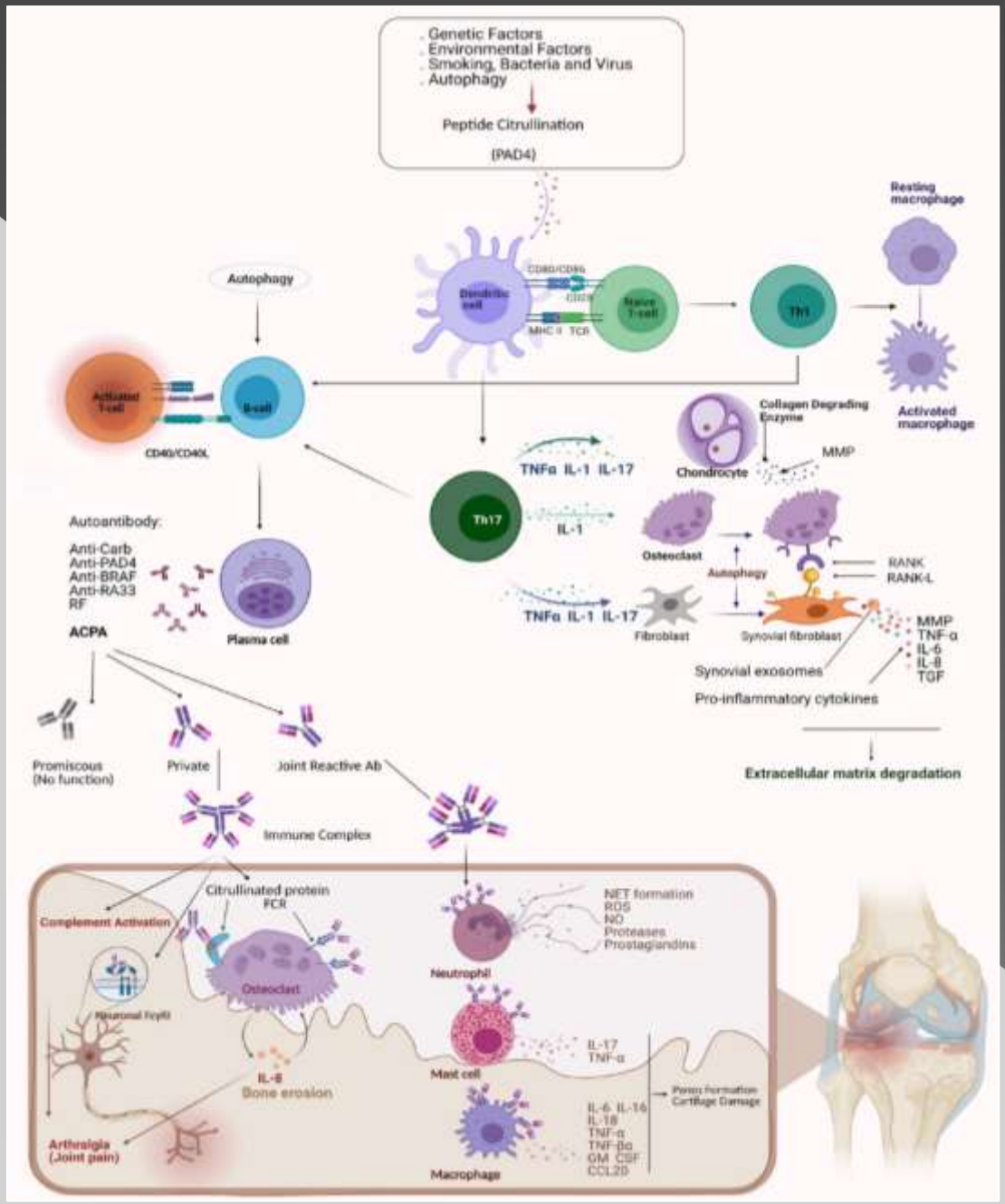

Figure: Pathogenesis of Rheumatoid Arthritis[49].

- The *MACIR* gene (previously known as *C5orf30*), specifically the rs26232 polymorphism, has been associated with the susceptibility to and severity of RA
- This polymorphism has been linked to the invasive activity of synovial fibroblasts and the expression of inflammatory mediators such as intracellular adhesion molecule-1 (ICAM-1) and IFN-γ-inducible protein-10 (IP-10)
- These findings suggest that the *MACIR* gene may play a role in the pathogenesis of RA by modulating the inflammatory response and the invasive behaviour of synovial fibroblasts

Several markers have been studied in the context of RA:

- Matrix Metalloproteinase 3 (MMP3) and Tissue Inhibitor of Metalloproteinase 3 (TIMP3) are involved in the remodeling of the extracellular matrix and have been implicated in the destruction of articular cartilage and bone in RA

- Complement factors, including complement factor I (FI) and the complement regulatory protein CD59, have also been implicated in the pathogenesis of RA
- Increased levels of FI have been observed in the synovial fluid and tissues of affected joints. This suggests that FI contributes to the excessive inflammation and tissue damage characteristic of RA
- Decreased expression of CD59 has been reported in synovial fibroblasts and endothelial cells in RA that impairs the ability of these cells to resist complement-mediated lysis, leading to increased tissue destruction and inflammation

- Dysregulation of the complement system and complement activation in RA has been linked to the production of pro-inflammatory cytokines and the recruitment of immune cells to the inflamed joints
- Monocyte chemoattractant protein 1 (MCP1) and Macrophage inflammatory protein 1 alpha (MIP1α) are chemokines that are involved in the recruitment of monocytes and macrophages to the site of inflammation in RA

Aim of the study

Evaluate the association of the *MACIR* rs26232 gene polymorphism with the suceptibility and with the serum levels of MMP3, TIMP3, FI, CD59, MCP1, and MIP1α in Iraqi patients with RA

Study Design

- The study will be a cross-sectional study involving newly diagnosed RA Iraqi patients.
- The study will compare the serum levels of the aforementioned markers between RA patients and healthy control individuals per group; as well as per genotype of the *MACIR* rs26232 polymorphism.

Subjects:

- Forty five newly diagnosed Iraqi RA patients

based on the ACR/EULAR 2010 criteria; along with 45 normal healthy individual to serve as the control group will be enrolled in the study.

The ACR/EULAR 2010 criteria are as follows:

- ✓ Morning stiffness
- ✓ Arthritis in at least one joint
- ✓ Arthritis in multiple joints
- ✓ Symmetrical arthritis
- ✓ Rheumatoid nodules
- ✓ Elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
- ✓ Positive rheumatoid factor (RF) or anti-citrullinated peptide (anti-CCP) antibody test

A person must meet at least four of these criteria to be diagnosed with RA.

Inclusion Criteria

- Newly diagnosed rheumatoid arthritis (RA) patients.
- Patients with active RA.
- Patients who have not received any disease-modifying anti-rheumatic drugs (DMARDs) or biologic therapies prior to enrolment.

Exclusion Criteria

- Patients with other autoimmune or inflammatory diseases, such as systemic lupus erythematosus or psoriatic arthritis.
- Patients with a history of malignancy or chronic infectious diseases, such as HIV or hepatitis.
- Patients with chronic renal or hepatic diseases.
- Patients who are pregnant or breastfeeding.

Methodology

- **Genotyping:** DNA will be extracted from the whole blood samples, and genotyping of the *MACIR* rs26232 polymorphism will be performed using polymerase chain reaction (PCR) and sequencing.
- **Biochemical investigations:** The serum levels of MMP3, TIMP3, FI, CD59, MCP1, and MIP1α will be measured using enzyme-linked immunosorbent assay (ELISA), shown in figure below.
- **Severity of RA assessment:**

$$DAS28 - ESR = 0.56 * \sqrt{(\text{Tender Joint Count} - 28)} + 0.28 * \sqrt{(\text{Swollen Joint Count} - 28)} + 0.70 * ln(ESR) + 0.014 * (General\ Health)$$

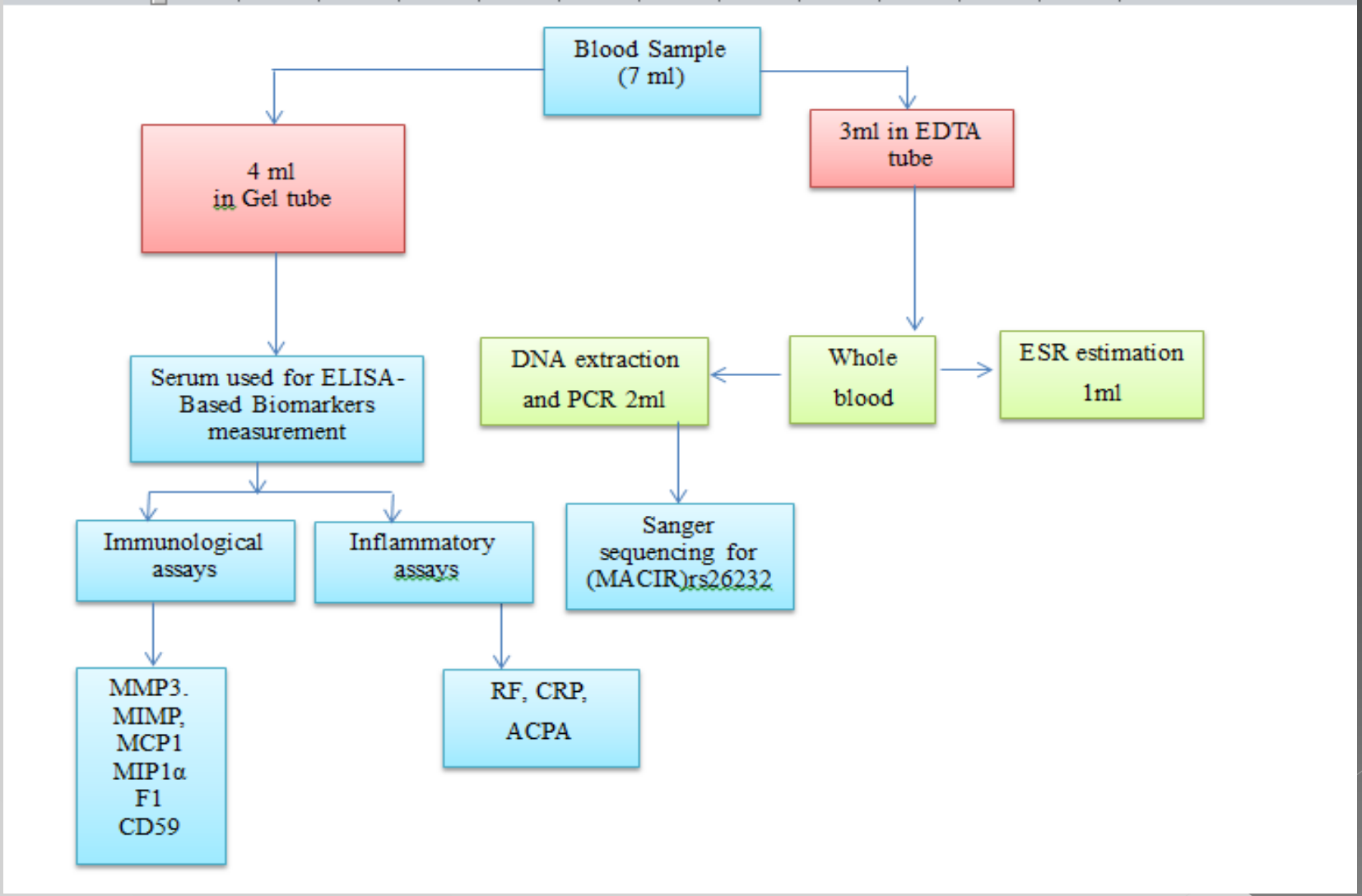

Figure: Sample processing flowchart for the distribution of the venous blood sample into ESR, Genotyping, and serum biomarker assays .

Significance of the Study

This study will contribute to the understanding of the genetic and molecular factors associated with RA in the Iraqi population. The findings may have implications for the development of personalized approaches to the management of RA.

Conclusion:

The study highlights the significance of the MACIR (rs26232) gene in Iraqi patients with rheumatoid arthritis.

MACIR is associated with several inflammatory biomarkers, reflecting its potential role in disease development.

Analysis of the biomarker panel provides deeper insight into the molecular mechanisms underlying disease progression.

Findings offer a foundation for supporting precision medicine and personalized disease management in Iraq.

Recommendations:

Conduct larger-scale studies to confirm the role of MACIR in disease.

Implement longitudinal studies to further clarify the impact of MACIR on disease progression and treatment response.

Integrate genetic and biomarker profiling into clinical practice to improve early diagnosis and risk stratification.

Explore the functional mechanisms of MACIR and its interaction with inflammatory pathways in greater detail.

References:

1. Dorris ER, Linehan E, Trenkmann M, Veale DJ, Fearon U and Wilson AG. Association of the Rheumatoid Arthritis Severity Variant rs26232 with the Invasive Activity of Synovial Fibroblasts. *Cells*. 2019; 8.
2. Aldabbagh KAO and Al-Bustany DA. Relationship of serum copper and HLADR4 tissue typing to disease activity and severity in patients with rheumatoid arthritis: A cross sectional study. *Annals of medicine and surgery*. 2022; 73:103193.
3. Ding Q, Hu W, Wang R, et al. Signaling pathways in rheumatoid arthritis: implications for targeted therapy. *Signal Transduction and Targeted Therapy*. 2023; 8: 68.
4. Murayama MA, Shimizu J, Miyabe C, Yudo K and Miyabe Y. Chemokines and chemokine receptors as promising targets in rheumatoid arthritis. *Frontiers in immunology*. 2023;14.
5. Kay J and Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. *Rheumatology*. 2012; 51: vi5-vi9.


Thank
you!