الجمهورية الجزائرية الديمقراطية الشعبية
People's Democratic Republic of Algeria
وزارة التعليم العالي والبحث العلمي
Ministry of Higher Education and Scientific Research

Higher Normal School of Technological Education of Skikda المدرسة العليا لأساتذة التعليم التكنولوجي بسكيكدة

Department of Natural Sciences قسم: العلوم الطبيعية

Graduate dissertation
مـذكـــرة التخرج

من إعــداد :

Bougueroua Malak بوقروة ملاك

For graduation diploma of : Secondary School Teacher

لنيل شهادة : أستاذ التعليم الثانوي

Theme
الموضوع

New therapeutic avenues for Sarcoidosis

Supervisor : Dr MEZIRI Fayçal «MCA» تحت إشراف الأستاذ : *د. مزيري فيصل*

Examining committee : Dr KHELFAOUI Mohamed Sabri «MCA » (President)
Dr OUCHETATI Imene « MCB » (Examiner)

Promotion June 2024 *دفعة جوان*

Acknowledgments

At the end of this academic journey, it is incumbent upon us to dedicate moments where words scatter like ink and love on the pages, to all those who have contributed to building an educational institution over several years.

First and foremost, praise and thanks to God, without whose help no effort is completed, and no endeavor is sealed without his grace and favor.

Certainly, those who do not thank people do not thank God.

With my pen, I cannot adequately express simple words of thanks and gratitude that I wish to extend to my teacher, and supervisor, Doctor "Mezîrî Fayçal" for his invaluable and continuous guidance and support, as well as his encouragement at every step I took in preparing this thesis. The most important aspect of this, Is the trust he placed in me, the flexibility of his work, and his professional dealings, for which he was known as a teacher, department head, and finally as a supervisor.

Sir, you are a dynamic myocardium, nourishing our curiosity and stimulating our thinking at every educational moment.

I also express my heartfelt thanks to all those who have contributed significantly to my educational journey from its beginning to the last letter I write in this thesis, including the examination committee who agreed to participate in the discussion of this research.

Dedication

Be proud of how hard
You're working to get to
Where you want to be
After all,
We are never a finished piece.
Thanks to Allah, I did my best and God did the rest.
I would like to dedicate this humble work:
To my father, my hero because when I said I wanted to touch the moon you took my hand, held me close, and taught me how to fly.
To my mother, the queen of my heart, in every moment, near and far, you've been my guiding northern star.
To my best friend Ines, thank you for standing by my side when times get hard.
To my siblings, Dounia, Randalina and Chemeseddine, when the path seems too long hard, you take my hand and remind me that I don't ever have to walk it alone.
To my self, thank you for everything I have offered, endured, and faced.
To my grand brother not only supervisor, Doctor "Meziri Fayçal", thank you for being the best teacher, you are a precious gem.

Never stop dreaming, never stop believing never give up, never stop trying and never stop learning…

Content

List of figures and tables

Abbreviations

6AN	6-Aminonicotinamide.
ACE	Angiotensin-converting enzyme
AID	Autoimmune disease
AIDs	Autoimmune diseases
AIRE	Autoimmune Regulator
APECED	Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy
AS605240	Aobious -605240
AV	Atrioventricular
BCRs	B cell receptors
CAL-101	Calistoga Pharmaceuticals -101
cAMP	Cyclic adenosine monophosphate
CCL2	C-C chemokine ligand 2
CCL-4	C-C chemokine ligand 4
CD+4T	Cluster of Differentiation 4-positive T cell
CD+8	Cluster of Differentiation 8- positive
CD20	Cluster of differentiation 20
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CD8+T	Cluster of Differentiation 8-positive T cells
CREB	cAMp Response Element-Binding protein
CS	Cardiac Sarcoidosis
CT	Computed Tomography
CTLA4	Cytotoxic T-Lymphocytes –Associated Protein 4
CXCL10	C-X-C motif Chemokine Ligand 10
DC	Dendritic Cell
DHODH	Dihydroorotate Dehydrogenase
DL	Deep Learning
DNA	Deoxyribonucleic Acid
dUMP	Deoxyuridine Monophosphate
Fas	Fas Cell Surface Death Receptor
FasL	Fas ligand

FBP1	Fructose-1,6-Bisphosphatase
FKBP	FK-Binding Protein
G1k	IgG1 kappa subclass
G6PDi	Glucose-6-Phosphate Dehydrogenase
GI	Gastrointestinal
HIF	Hypoxia-Inducible Factor
HIF-1α	Hypoxia-Inducible Factor-1α
HLA-A1	Human Leukocyte Antigen –A1
HLA-B8	Human Leukocyte Antigen-B8
HLA-DR3	Human Leukocyte Antigen-DR3
HLA-DRB1*3	Human Leukocyte Antigen –DRB1*3
iDC	Immature Dendritic cell
IL-1	Interleukin 1
IL-1α	Interleukin 1 α
Il-1β	Interleukin 1 β
IL-6	Interleukin 6
IL-12	Interleukin 12
IL17A	Interleukin 17 A
IL-23	Interleukin 23
JAK-STAT	Janus Kinase-Signal Transducer and Activator of Transcription .
JEM	Journal of Experimental Medicine
LncRNAs	Long Non-coding RNAs
MHC	Major Histocompatibility Complex
MHCII	Major Histocompatibility Complex Class II
mKatG	mycobacterial catalase peroxidase
ML	Machine Learning
mTOR	Mammalian Target of Rapamycin
NAAbs	Natural Autoantibodies
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NF-kB	Nuclear Factor kappa-B
NN	Neural Networks
NOX	NADPH Oxidase

NRP-2	Neuropilin-2
OATD-01	OncoArendi Therapeutics drug-01
P40	Protein 40.
PD1	Programmed Cell Death Protein 1
pDC	Plasmacytoid Dendritic Cell
PDE4	Phosphodiesterase 4
PET	Positron Emission Tomography
PI3K γ / δ	Phosphoinositide-3 kinases γ / δ
PKA	Protein kinase A
PPP	Pentose Phosphate pathway
RA	Rheumatoid Arthritis
RCI	Repository Corticotropin injection
RNA	Ribonucleic acid
RNAs	Ribonucleic Acids
ROS	Reactive Oxygen Species
SAA	Serum Amyloid A
SLE	Systemic Lupus Erythematous
Smad3	Mothers against decapentaplegic homolog 3
TCR	T cell Receptor
TGFβ	Transforming Growth Factor-beta
Th1	T helper 1 cell
Th17	T helper 17 cell
Th2	T helper 2 cell
TLR9	Toll-like Receptor 9
TNF	Tumor Necrosis Factor
TNFα	Tumor necrosis factor α
Treg	Regulatory Tcell
Tregs	Regulatory T cells
Vα2.3+	variable alpha2.3-positive
Vβ22+	variable beta 22-positive

Introduction

Introduction

Autoimmunity arises from self-reactive elements within the adaptive immune system, resulting in clinically observable pathology in autoimmune diseases. There is growing evidence indicating a rise in both autoimmunity and autoimmune diseases. Likely factors contributing to this increase encompass significant recent shifts in dietary patterns, lifestyle choices, exposure to xenobiotics... **(Miller, 2024).**

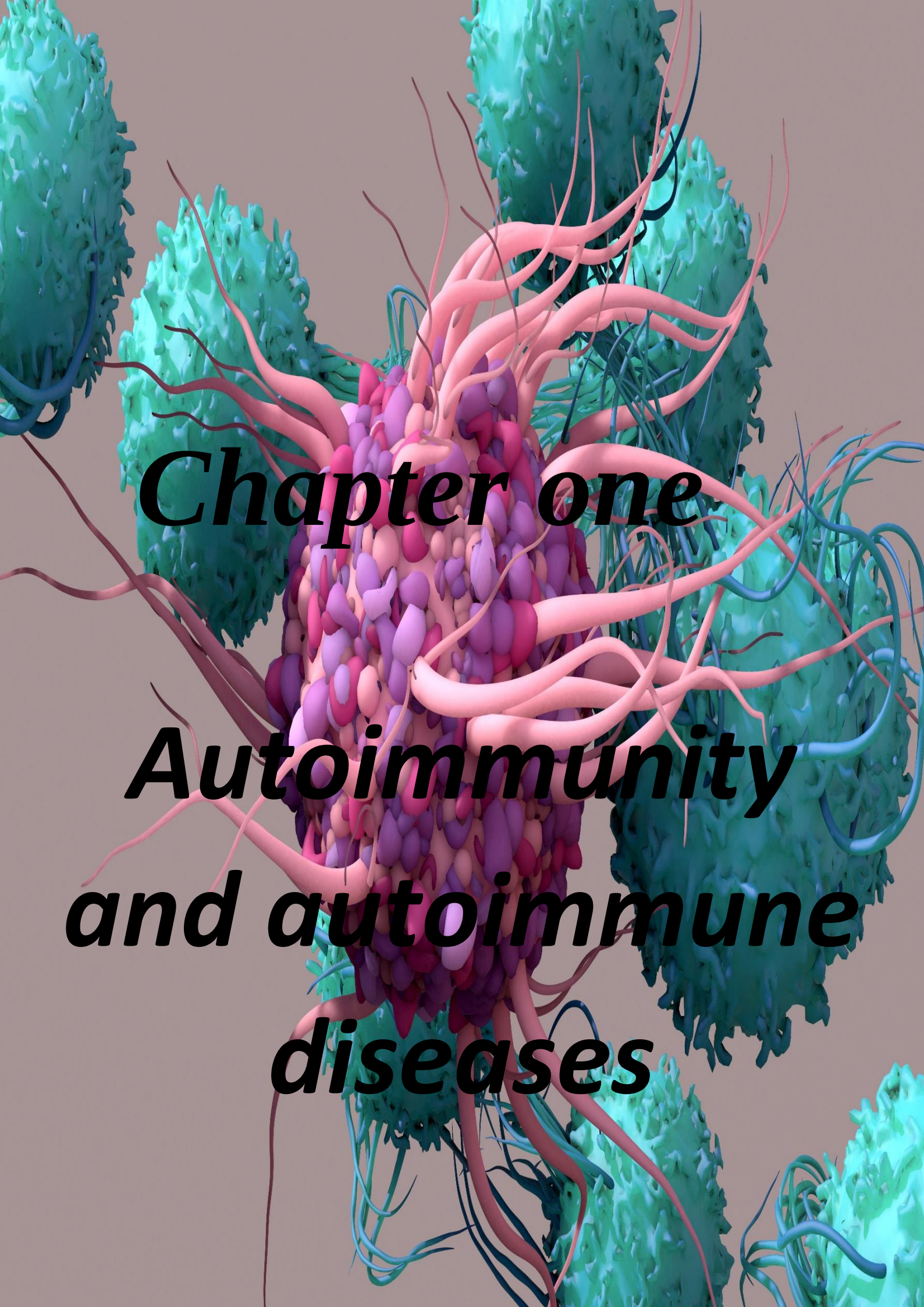
Previously, autoimmune diseases were linked to sarcoidosis, but now it's recognized that sarcoidosis itself might involve an autoimmune process **(Alzghoul *et al.*, 2020).**

This is what sparked our interest in studying sarcoidosis as an autoimmune disease and its connection to autoimmunity through conducting a comprehensive analysis of the disease.

Sarcoidosis is a chronic, multi-system granulomatous disorder with an unknown cause. Its prevalence ranges from 2.2 to 160 cases per 100,000 individuals, affecting women more than men. While the lungs are commonly involved, extrapulmonary manifestations are also observed. Sarcoidosis can affect any organ or tissue and often presents with diverse clinical symptoms, from mild to severe and serious symptoms. Although its exact mechanism remains elusive **(Gaddam *et al.*, 2021).**

The management of sarcoidosis is complex and demands continuous meticulous attention. Corticosteroids have traditionally been the primary treatment for sarcoidosis. Additionally, many medications used in treating various autoimmune diseases have been utilized in sarcoidosis treatment, alongside ongoing clinical trials targeting different causative elements of the disease **(Obi *et al.*, 2022).**

Our research reviews ongoing and anticipated drug trials in sarcoidosis, detailing drug targets at the molecular and cellular levels. We also review several recently completed trials and others that have laid the groundwork for their initiation.



Chapter one

Autoimmunity and autoimmune diseases

Chapter I. Autoimmunity and autoimmune diseases

Introduction:

The immune system comprises an intricate system of organs, cells and proteins working together to safeguard the body from infections while preserving its own cells. This defense mechanism also maintains a memory of every defeated germ, allowing it to swiftly identify and eliminate any returning microbes.

In addition to that, our Immune system is capable of recognizing between: self and tolerating it, and non- self and rejecting it. The self refers to the body's regular components, while non self includes foreign substances, infectious agents and altered self -components.

Occasionally our immune system can malfunction, resulting in a medical condition.

It has the potential to respond to harmless external agents, causing allergies. It might not be sufficiently responsive to combat microbes, resulting in immunodeficiency. Additionally, there are instances when the immune system targets and destroys normal body components, which are referred to as autoimmune diseases (figure 1) **(Moore, 2015).**

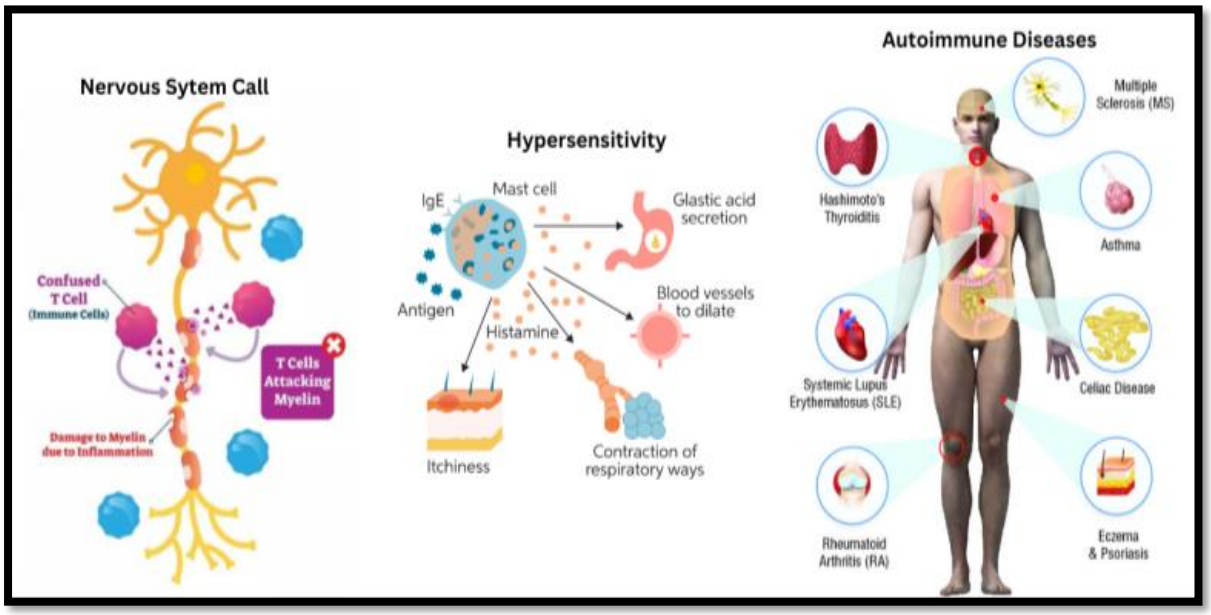


Figure 1. Categories of immune dysfunction (Immune Dysfunction,2021).

1. Autoimmunity:

1.1. Definition of autoimmunity:

The concept of autoimmunity was first introduced approximately a century ago by the German scientist and Nobel laureate Paul Erlich, coining the term 'autotoxicus'. It describes the immune system's tendency to target foreign invaders while avoiding self-harm **(Silverstein, 2001).**

Chapter I. Autoimmunity and autoimmune diseases

Autoimmunity involves auto- reactive T lymphocytes and autoantibodies reacting against the body's own antigens (autoantigens). This phenomenon can be a natural part of the immune response (natural autoimmunity) induced pathologically, potentially leading to clinical abnormalities **(word health organization, 2006).**

1.2. Physiological autoimmunity:

Autoimmunity, is a natural physiological phenomenon, in every individual, there exists a degree of self-recognition. these includes self-reactive B cells, self-peptides, and self-Major Histocompatibility Complex (MHC) reactive T cells, except in individuals with severe immunodeficiency, these elements can be detected in the circulatory system of all of us as are "autoantibodies". A low level of autoimmunity is typically considered normal and usually doesn't lead to health issues. However, it tends to increase with age **(Delves *et al.*, 2017).**

Natural autoantibodies possess polyreactivity due to their inherent flexibility, enabling them to recognize various epitopes, which may include public determinants present in all individuals of the same species, and sometimes shared with different species **(Arakawa *et al.*, 2023).**

Numerous hypotheses have been proposed about the functions of Natural autoantibodies (NAAbs), they can be involved in shaping immune repertoires, expediting initial immune responses, assisting in the removal of apoptotic cells, exhibiting anti-inflammatory properties, and maintaining homeostasis **(Olasz, 2012).**

The immune system maintains natural self-immunity through the following mechanisms:

1.2.1. central tolerance:

Central tolerance takes place in primary lymphoid organs and promotes tolerance in developing T and B cells through clonal anergy, clonal deletion, and negative cell selection T cells tolerance is attained by eliminating self-reactive clones in the thymus, while B cells strongly binding self-antigens undergo apoptosis in the bone marrow **(Pathak, 2005).** Multiple studies involving human B cells have shown that the mechanism of 'receptor editing 'is crucial for shaping their repertoire and maintaining self-antigen tolerance **(Gururajan *et al.*, 2014).** A recent study published in Journal of Experimental Medicine (JEM) contests the typical understanding of central tolerance. It was previously believed that B cell receptors (BCRs) regulated this process, the study exposes that central tolerance also depends on a receptor called Toll-like Receptor 9(TLR9), situated inside B cells. TLR9 is

activated by binding to DNA fragments and play an important role in preventing the production of self-reactive B cells and antibodies. The depletion of TLR9 impairs central tolerance **(Çakan *et al.*, 2023).**

1.2.2. peripheral tolerance:

Despite clonal deletion mechanisms**,** a small number of self-reactive T and B cells may still make their way into peripheral organs, some mechanisms of peripheral tolerance include: anergy, suppression by regulatory T cells (Treg), clonal deletion, activation induced cell death, …

Anergy: A state of unresponsiveness to autoantigens occurs once the self-antigen is identified in peripheral tissues.

Regulatory T cells: They assume an inhibitory function in immune responses through the activity of various secreted cytokines and receptors.

Clonal deletion: This process involves the elimination of self-reacting clones **(Demir *et al.*, 2021).**

Immune checkpoints: These are proteins situated on the surfaces of T and B cells allowing the maintenance of immune tolerance and mitigate autoimmunity. Examples include CTLA4 protein, which blocks the activation of T cells autoreactive, and PD1 protein, which promoting the suppressive function of Treg cells (figure 2) **(González,2022).**

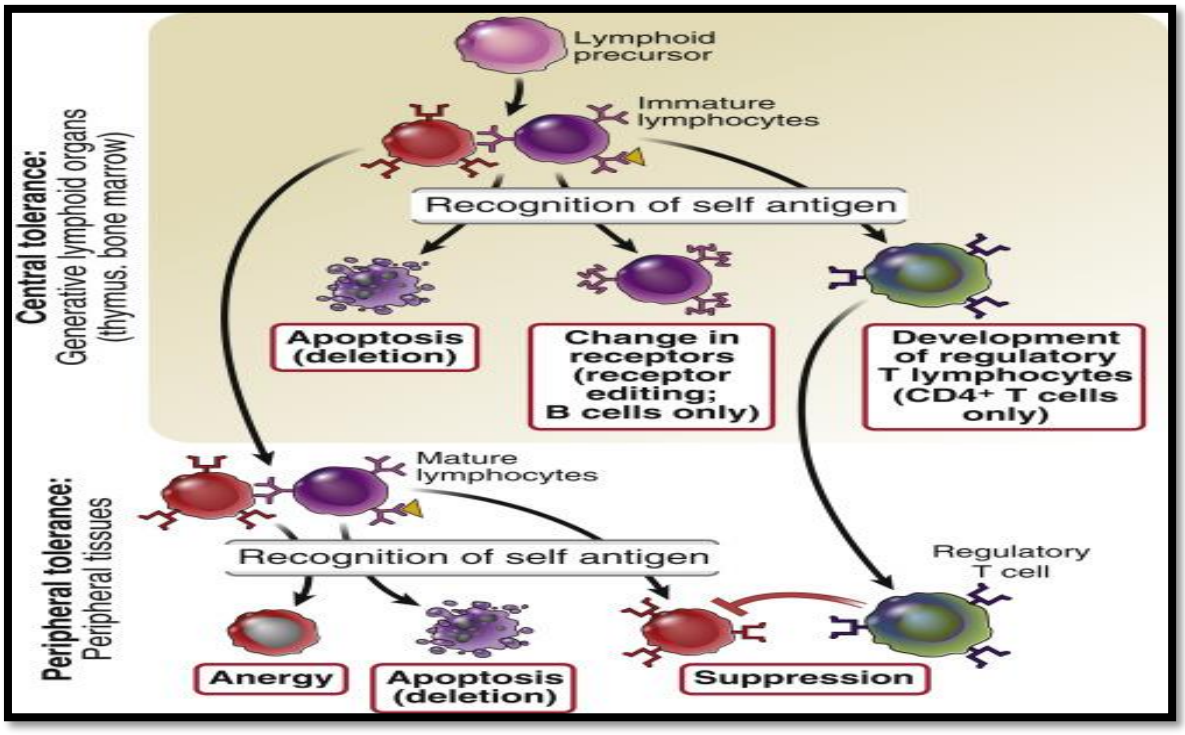


Figure 2. Central and peripheral tolerance to self-antigens (Karki, 2020).

1.3. Pathological autoimmunity:

Autoimmune responses occur when the immune system mistakenly attacks the host's own body, indicating a disruption in the regulation of the immune system **(Pollard, 2006).** When immune tolerance is compromised, autoantibodies and self-reactive lymphocytes contribute to inflammation, ultimately leading to the development of pathological autoimmunity, which can manifest in form of autoimmune diseases **(Wang *et al.*, 2015).**

2. Autoimmune diseases:

2.1. An overview of autoimmune diseases:

Autoimmune diseases (AIDs) constitute a distinct category of chronic illnesses, and they have a significant social impact on individuals. These diseases are characterized by complex mechanisms, occurring when the immune system loses its ability to recognize and tolerate the body's own antigens **(Arango *et al.*, 2013 ; Rentier, 2015).**

Autoimmune diseases habitually come with the development of inflammation, and inflammatory mediators such as inflammatory factors and inflammasomes, play a fundamental role in their development. These mediators facilitate the immune process by impacting both innate cells like macrophages and adaptive cells like T and B cells, ultimately, leading to the promotion of autoimmune responses **(Xiang, 2023).**

There are more than 80 types of AIDs known. A recent study conducted on 22 million individuals to investigate 19 types of the most common AIDs revealed that 10 % of the population were affected, with 13% being women and 7 %being men. This showed a significant increase compared to previous years when the percentage ranged from 3-9 % **(Conrad *et al.*, 2023).**

2.2. Classification of AIDs:

Autoimmune diseases can be categorized as:

2.2.1. Organ specific AIDs:

These diseases involve the production of autoantibodies that precisely target the tissue of a single organ, resulting a specialized effect on that organ. Examples include Grave's disease and insulin -dependent mellitus.

2.2.2. Systemic AIDs:

In this diseases, the immune system produces autoantibodies that attack a diverse tissue in the body. These diseases exhibit a distinctive issues in immune regulation, resulting an hyperactive T and B cells. As a result, tissue damage is pervasive tends to lead to disorders affecting various organ systems, such as Systemic Lupus Erythematosus (SLE) **(Parija, 2012).**

2.3. Factors influencing AIDs:

The causes of AIDs are not entirely understood. Therefore, conducting epidemiological studies on AIDs can offer valuable insights into potential factors that may play a role in the development of the disease **(Ye, 2023).**

2.3.1. Genetic factors:

Autoimmune diseases have a notable genetic component, but inheriting susceptibility doesn't ensure the development of the disease **(Zhang, 2023).** Some AIDs have a higher genetic predisposition than others. changes in genes like human leukocyte antigen (HLA) **(Cormack, 2019),** complement factors, cytokines, or cytokine receptor genes are frequently observed **(Hachulla *et al*., 2006).** Besides, research shows a relationship between epigenetic modification (DNA methylation, histone modifications, and noncoding RNAs) and the progression of AIDs **(Mazzone *et al*., 2019).**

2.3.2. Endogenous factors:

Other factors also thought to play a role in the development of AIDs, it is called endogenous factors such as cytokines, hormones …. Cytokines involved in the initiation and propagation of autoimmune inflammation **(Moudgil *et al*., 2011).**, and hormones like estrogens generally influence the immune system towards a type 2 helper cell (Th2), leading to increased B cell activation and the production of antibodies, on the other hand, androgens stimulate a (Th1) response, resulting activation of CD+8 T cells **(Miller, 2021).**

2.3.3. Environmental factors:

Many environmental determinants may play an important role in triggering the autoimmune response including diet (fatty acids, cow's milk, gluten iodine excess, vitamin D deficiency, obesity), chemicals, cigarette smoking **(Chowaniec *et al*., 2017)** viruses, bacteria and other infectious pathogens **(Delogu *et al*., 2011).**

2.4. Stages of autoimmune diseases:

AIDs is also a persistent disease that goes through three stages:

Stage 1: Silent autoimmunity

In this phase, the body has developed a reduced tolerance to its own tissues, but their impact on the normal functions of the body is minimal and no symptoms are present, also the level of antibodies increase this is indicated by laboratory tests. People in this stage can remain an extended period, often spanning several years **(Ryan, 2018).**

Stage 2: Reactive autoimmunity

We are aware that there are millions of people in this stage suffering considerable health issues. Even so, the level of tissue damage is limited, making it difficult to definitively diagnose a specific disease. These individuals offer a chance to preserve in advance their health.

Stage3: Autoimmune disease

When a patient is diagnosed with an AID, it frequently suggests that damage has been silently progressing for many years. At this stage the damage is extensive, making the process of healing considerably more difficult **(Wright *et al.*,2018).**

2.5 Mechanisms of AIDs:

2.5.1Mechanisms related to autoantigens:

A. The visibility of autoantigens to the immune system:

Certain constituents in the body, such as the heart, lens and sperm, keep their antigens hidden (sequestered) from the immune system to prevent the development of immunological tolerance. This is generally not a problem, except when incidents like physical trauma leads to the release of these antigens into circulation, potentially triggering self-reactive lymphocytes **(Delves *et al.*, 2017).**

B. Modification of the autoantigens:

This includes posttranslational modifications of autoantigens, encompassing a wide array of changes such as phosphorylation, proteolytic cleavage, isoaspartyl modification. In some instances, autoantibodies exclusively target the modified version of the antigen **(Johnson *et al.*, 2023).**

C. Molecular mimicry:

This mechanism occurs when a foreign antigen, such as one from an infectious pathogen, shares sequence or structural similarities with self-antigens within the body. This similarity can lead to disorder within the immune system, where immune cells may have difficulty distinguishing between self and foreign antigens.

As a result, the immune response that is presumed to target the invading pathogen may mistakenly target the body's tissues, initiating an AID **(Cusick *et al.*, 2012).**

2.5.2 Polyclonal activation of B lymphocytes:

Excessive sustained polyclonal B cell activation may lead to the production of nonspecific antibodies and trigger anti self-responses, potentially contributing to AIDs **(Montes *et al.*, 2007).**

2.5.3. Cytokines imbalance:

The imbalance between pro- and anti-inflammatory cytokines worsens immune function and leads to the development of AIDs **(Zou, 2018).**

2.5.4 Epitope spread:

Epitope spreading refers to the phenomenon where the immune response, induced by an initial antigen, diversifies to target new T cells and antibody specificities, which can contribute to the development and progression of autoimmune disease **(Venkatesha *et al.*, 2015).**

2.5.5. Idiotype bypass mechanism:

Idiotypes are the antigenic determinants of immunoglobulin molecules situated in the variable region of the antibodies. Idiotypic distribuance is a pivotal mechanism leading to AIDs through the production of pathological autoantibodies **(Abu shakra *et al.*, 2014).**

2.5.6. Abnormal expression of MHCII:

Aberrations in MHCII molecules play an important role in AID development by influencing different mechanisms. Irregular T Cell Receptor (TCR) interactions with self-antigens presented on MHC, posttranslational modifications of self-antigens, direct loading onto classical MHC, proinflammatory environments, and molecular mimicry between

foreign and self-antigens can all contributed to the emergence of autoreactive T cells and the loss of self-antigen tolerance **(Ishina *et al.*,2023).**

2.5.7. Dysfunction of the immune system:

A. Mutation in Fas and FasL:

Fas ligand is a protein produced by activated Tcells, and it induces cell death in target cells when it binds to the Fas receptor, which is also protein. Mutation in either Fas or FasL genes which encode these proteins can lead to certain AIDs through the dysregulation of self-antigen tolerance **(Maccari *et al.*, 2023).**

B. Mutation in AIRE gene:

The autoimmune regulator(AIRE) is a protein plays a crucial role in the negative selection of autoreactive Tcells in the thymus. Mutation in the autoimmune regulator(AIRE) gene can cause AID, such as Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED) **(Sakaguchi *et al*., 2021).**

C. Dysfunction of Tregs:

The malfunction of regulatory Tcells (Tregs), along with the ineffectiveness of effector T cells which are responsible for the immune system's response to pathogens, can lead to AID **(Rajendeeran *et al*., 2021).**

D. Dysfunction in complement system:

The dysregulation of the complement system can lead to uncontrolled immune responses, ultimately causing AIDs and damage to various tissues notably the kidneys **(Jia *et al*., 2022).**

2.6. Examples of some AIDs:

2.6.1. Psoriasis:

Psoriasis is a persistent skin disease often characterized by red, thickened patches of skin covered with silvery scales. Prevent forms of the disease include Scalp psoriasis, guttate psoriasis sand erythrodermic psoriasis **(Koo *et al.*, 2014).** Studies propose that the disease begins with the activation of Tcell by an unidentified antigen. This activation triggers the release of different cytokines by activated Tcells, leading to inflammation and affecting keratinocytes. The skin lesions seen in psoriasis are a result of the hyper-proliferation of keratinocytes (figure 3) **(Das, 2009).**

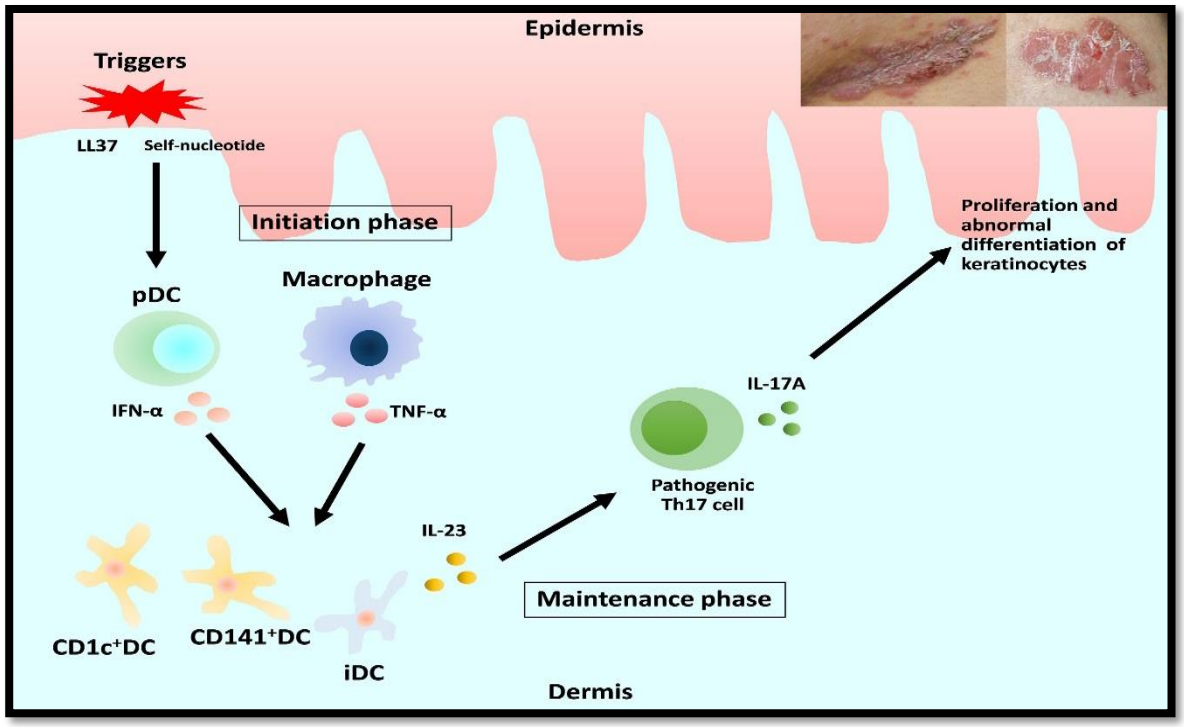


Figure 3. Overview of the current understanding of the pathogenesis of psoriasis and the roles of dendritic cells and macrophages. DC, dendritic cells; pDC, plasmacytoid DC; iDC, inflammatory DC (Kamata *et al.*, 2022).

2.6.2. Rheumatoid Arthritis:

Rheumatoid Arthritis(RA) is a chronic systemic AID, which is primarily characterized by proliferative synovitis and inflammatory arthritis with erosions **(Koarada *et al.*, 2018).** RA is associated with elevated production of inflammatory cytokines. T and B cells, as well as macrophages, are found in the synovial tissue of RA patients, indicating an ongoing local immune response. Recent research indicates that certain long non-coding RNAs (LncRNAs) are linked to notable inflammatory reactions and compromised immune responses (figure 4) **(Huang *et al.*, 2022).**

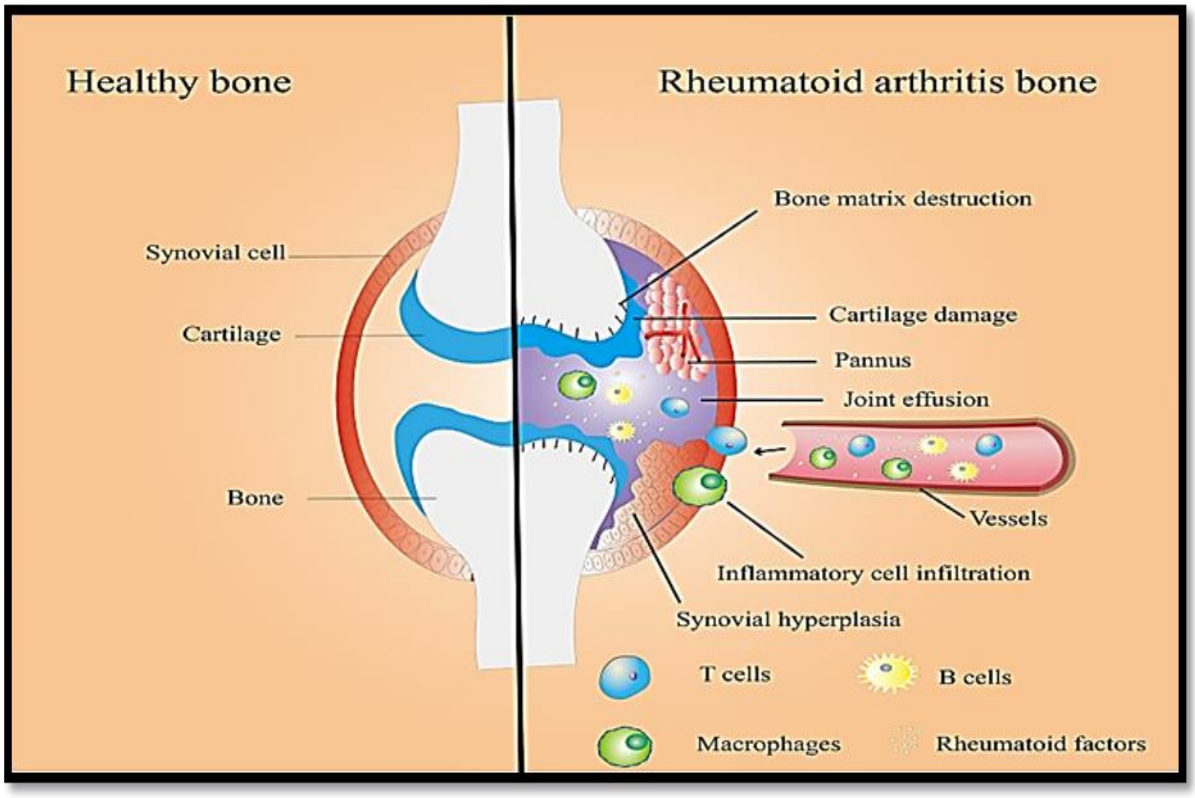
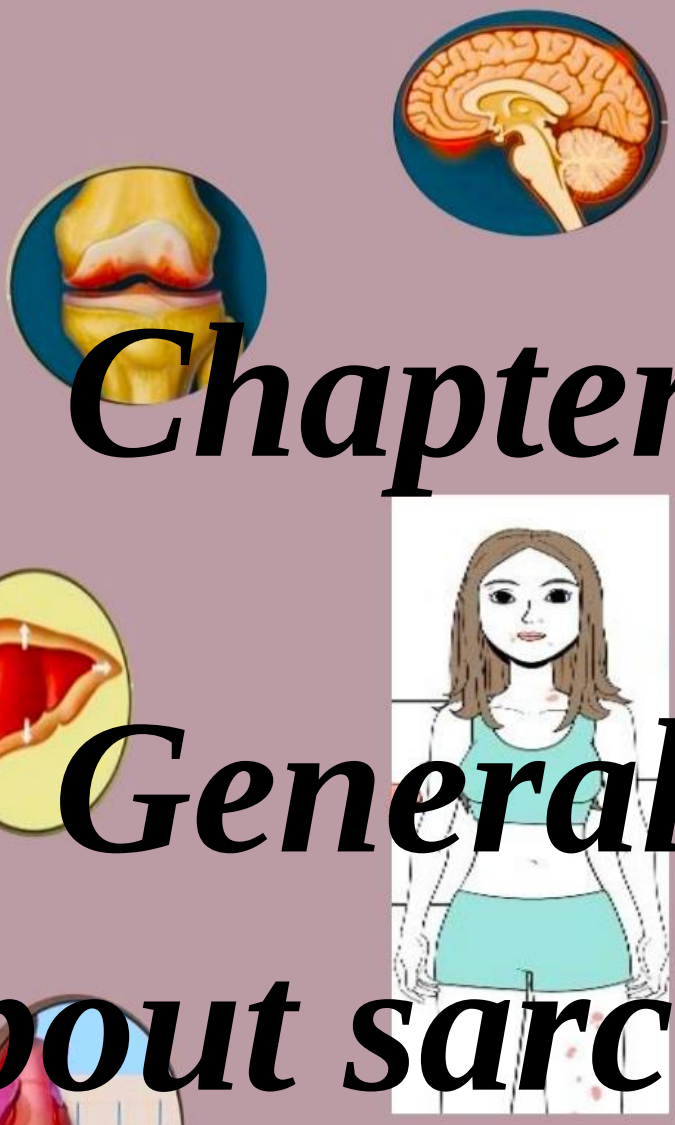


Figure 4. Bone microenvironment in healthy (left) and RA (right) bone. Healthy bones have thin and smooth synovium, smooth cartilage tissue and healthy bone matrix (left): Synovial hyperplasia, pannus formation, inflammatory cell infiltration, cartilage damage, bone matrix destruction, joint effusion and other symptoms in RA bone (right) (Huang *et al.*, 2022).

2.6.3. Pernicious Anemia:

Pernicious Anemia is an uncommon AID that leads to a reduction in the absorption of dietary vitamin B12, resulting in B12 deficiency and the development of megaloblastic anemia **(Vaqar *et al.*, 2023).**

Pernicious anemia results from the body's inability to transport vitamin B12 effectively across the intestinal mucosa due to a relative deficiency of intrinsic factor, which normally forms a complex with vitamin B12, facilitating its absorption by mucosal cells. The condition is believed to be primarily driven an autoimmune response targeting parietal cells in the stomach's mucosa, which are responsible for producing intrinsic factor **(Regezi *et al.*, 2012).**



Chapter two

Generalities about sarcoidosis

Chapter II. Generalities About Sarcoidosis

Introduction:

Inflammation is a typical physiological defense against pathogenic assault, infections, and tissue damage, usually terminating rapidly. However, the inflammatory response can persist in several chronic conditions, leading to substantial damage to organs and tissues. Lately manifestations revealed the relationship between abnormal inflammatory responses and various chronic diseases, notably AIDs, and this is clearly evident in sarcoidosis **(Shen *et al.*,2018; Chen *et al.*, 2019).**

Sarcoidosis is an autoimmune disease that can affect the entire body and is correlated with the evolution of non-necrotizing granulomas **(Zeron *et al.*, 2022).** It may initiate as an auto-inflammatory disorder, at which the activation of adaptive immunity happens accompanied by the presence of auto-specific Tand B cells that synthesize autoantibodies to a specific antigen **(Doria *et al.*, 2012).**

1. Definition and Epidemiology:

1.1. General presentation about sarcoidosis:

Sarcoidosis, also known as Besnier-Bock-Shaumann disease, is a systemic granulomatosis disease. At present, the cause of the disease is unknown. Histologically, it is marked by the presence of epithelioid and giant cell granulomas without caseous necrosis **(Tougorti *et al.*, 2017).** The granulomatous reaction can unfold in any tissue or organ; therefore, clinical signs may differ and vary, but the lung is the most commonly targeted organ.

Sarcoidosis can be associated with other AIDs, making diagnosis more complex and challenging **(Ceobanu *et al*., 2021).**

The term ‘Sarcoidosis’ originates from the Greek words “sarco”, which means “flesh”,” edos” which means “similar”, and “osis” meaning “condition”. In1877, Jonathan Hutchinson described the first case at King’s college hospital in London. Later, Cesar Boeck developed a description of sarcoidosis by focusing on the granulomatous inflammation that characterizes this disease. He was the first to use the term “sarcoid” because he considered the lesions to resemble sarcoma but benign.

In1953, Sven Lofgren described acute sarcoidosis syndrome with enlarged lymph nodes and the appearance of rosacea nodules, often associated with arthritis, fever, and eye inflammation. Over the past century, sarcoidosis has become known as a granulomatous disorder extending to multiple organs with diverse presentations **(Sterling *et al*., 2015).**

1.2. Epidemiology:

The yearly occurrence of sarcoidosis ranges from 1 to 15 cases per 100,000 individuals, contingent on geographical location. The incidence is at its minimum in Eastern Asian nations (0.5-1 per 100,000), elevated in North America and Australia (5-10), and reaches its peak in Northern European(Scandinavian)countries. Estimates in Southern Europe are lower compared to the north. The frequency and prevalence display variations even within countries, likely influenced by genetic disparities, environmental exposures, or differences in the detection and diagnosis of sarcoidosis **(Rossides *et al.*, 2023).**

Sarcoidosis is more prevalent among females, often manifesting between the ages of 20and 40. Interestingly, bimodal distribution patterns have been reported, revealing a secondary peak occurring around the age of 50 (figure 5) **(Ramachandran *et al.*, 2021).**

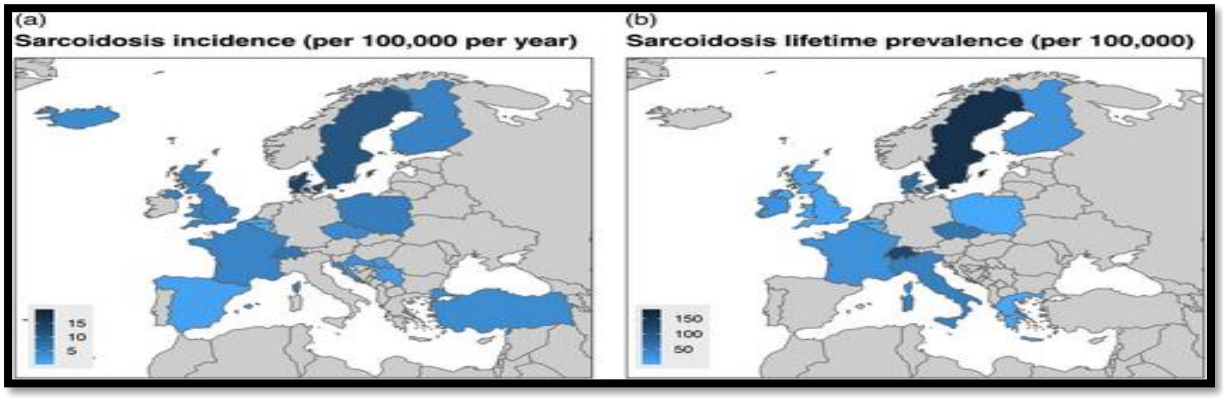


Figure 5. Incidence (panel a) and prevalence (panel b) of sarcoidosis in Europe showing the north-south gradient, with higher incidence in northern regions and lower incidence in southern regions (Rossides *et al.*, 2023).

2. Clinical manifestations:

Individuals with sarcoidosis develop abnormal granulomas consisting of inflamed tissues in different organs of the body. The symptoms differ from person to other based on the organs involved **(Synovec *et al.*, 2021).** Note that sometimes more than one organ may be affected at the same time **(Oya *et al.*, 2022).**

The most commons symptoms of sarcoidosis are: dry cough, skin and eye manifestations, weight loss, malaise, night sweats, fever, arthralgia and erythema nodosum **(Robert *et al.*, 2013; Jain *et al.*, 2020).**

Furthermore, sarcoidosis may be present with acute symptoms, such as in Lofgren syndrome which is a subtype of sarcoidosis with the presence of erythema nodosum and bilateral hilar

adenopathy. Moreover, Heerfordt –waldenstrom syndrome presents a subacute variant of sarcoidosis, represented by enlargement of the parotid glands, anterior uveitis and facial nerve paralysis. In addition to that, the symptoms of sarcoidosis could be chronic or self-remitting. Nonetheless, for the most part of cases, it is fully asymptomatic or incidentally detected **(Fraga *et al.*, 2017; Baughman *et al*., 2018).**

3.Types of sarcoidosis:

3.1Pulmonary sarcoidosis:

Pulmonary sarcoidosis presents non-caseating granulomatous inflammation dispersed along the interstitium of the lung, the pleura, and interlobular septa and around bronchovascular bundles. The granulomas are well-defined and composed of densely packed histocytes and multinucleated giant cells, as well as a few lymphocytes and other inflammatory cells.

During routine examination of an asymptomatic patient, pulmonary sarcoidosis can be detected on a chest radiograph. As lung disease progress, nonspecific respiratory symptoms including dyspnea during exercise and aspiration, may develop **(Lee et al., 2013 ; Reisner, 2013).** The stages of pulmonary sarcoidosis are illustrated in the table 1:

Table1. Stages of pulmonary sarcoidosis (Jane Smith *et al,* 2015).

Stage	***Chest X-ray findings***	***symptoms***
0	Normal	None
1	Bilateral hilar lymphadenopathy	None or mild cough
2	Parenchymal infiltrates and bilateral hilar lymphadenopathy	None ,breathlessness or cough
3	Parenchymal infiltrates only	Progressive breathlessness
4	Advanced pulmonary fibrosis	Progressive breathlessness

3.2. Extrapulmonary Sarcoidosis:

Even though sarcoidosis generally affects the lung, it may involve any organ, with the most commonly targeted organs being those outlined below:

3.2.1. Cutaneous Sarcoidosis:

There are two types of cutaneous sarcoidosis lesions: specific and nonspecific. Specific sarcoidosis lesions demonstrate granulomatous inflammation on histology, and their lesions may develop on any part of the skin and mucosa. Virtually, all forms have been stated,

including: papules, plaques, nodules, macules, and the dominant presentation is the popular form.

Lupus Pernio is a special specific sarcoidosis skin lesion. Habitually, these lesions are somewhat symmetric, violaceous indurated plaque-like and nodular occurring on the nose, ear lobes, and cheeks. Nonspecific skin findings are lesions resulting from reactive inflammation that do not show granulomas, such as erythema nodosum, and the skin biopsies here have no value in the diagnosis of sarcoidosis **(Baughman *et al.*, 2011).**

3.2.2. Cardiac Sarcoidosis:

Cardiac sarcoidosis(CS) is an infiltrating disease resulting from granulomatous inflammation affecting the heart. The frequent occurrences encompass atrioventricular blocks (AV) pursued by ventricular arrhythmias, bundle branch blocks, and supraventricular arrhythmias, of which atrial fibrillation is most common. The typical signs for (CS)comprise: palpitations, pre-syncope, and syncope **(Hussain *et al.*, 2023).**

3.2.3. Lymph nodes Sarcoidosis:

Effectively, all cases of sarcoidosis encompass lymph nodes, and any lymph nodes can be involved yet the frequent are the hilar and mediastinal lymph nodes. Generally, enlargement of these nodes is picked up on a chest radiograph **(Carton *et al*., 2007).**

3.2.4. Neurosarcoidosis:

Neurosarcoidosis alludes to central and peripheral nervous system engagement during sarcoidosis, related to granulomatous infiltration of several areas of the nervous system, where lymphocytes and mononuclear phagocytes enclose a noncaseating epithelioid cell granuloma **(Aubart *et al.*, 2019 ; Pirau *et al.*, 2023).**

Clinical manifestations are multifarious, varying from cognitive or psychiatric disruptions to motor or sensory deficiencies. The prevalent manifestation is cranial neuropathy, most frequently bilateral or unilateral facial-nerve palsy, pituitary dysfunction, seizures, headache, … **(Chen *et al.*, 2019)**

3.2.5. Ocular Sarcoidosis:

ocular sarcoidosis is an inflammatory state, that has the potential to affect any part of the eye, resulting in benign conjunctival masses, episcleritis/scleritis uveitis, optic neuropathy, and/or its accessory tissues leading to enlargement of the lacrimal glands and orbital inflammation **(Simakurthy *et al.*, 2023).**

3.2.6. Renal Sarcoidosis:

Renal sarcoidosis is an infrequent condition, but it may cause significant complications. The established pathology of renal sarcoidosis is granulomatous interstitial nephritis, which commonly presents with elevated creatinine. Confused calcium metabolism is the crucial manifestation of renal sarcoidosis and is defined by the uncontrolled synthesis of calcitriol by activated macrophages. Calcitriol augments the gastrointestinal absorption of ingested calcium and stimulates bone resorption, leading to increased hypercalciuria and /or hypercalcemia accordingly, can cause nephrocalcinosis and nephrolithiasis **(Wagner *et al.*, 2023).**

3.2.7. Gastrointestinal and Hepatic Sarcoidosis:

Each component of the gastrointestinal(GI) tract, from the oral cavity to continuum of (GI) and hepatic sarcoidosis, is extensive extending from asymptomatic disease to abrupt liver failure requiring transplantation.

The trademark of this condition is the development of epithelioid noncaseating granulomas. These granulomas prefer periportal and portal regions in the liver, while in the (GI) tract, they are situated in the mucosa and submucosa.(GI) sarcoidosis shows peptic ulcerations or narrowing of the gastric lumen as a consequence of granulomatous inflammation and/or allied fibrosis of the gastric wall, reduced peristalsis leading to abdominal fullness or satiety, on the other hand ,there are other markers such as epigastric pain ,nausea ,vomiting ,heartburn ,abnormal discomfort, diarrhea, and anorexia .

The pivotal sign of hepatic sarcoid is fatigue, accompanied by pruritis, weight loss, hepatomegaly, and the presence of portal hypertension **(Shah *et al.*, 2021).**

3.2.8. Musculoskeletal Sarcoidosis:

Musculoskeletal sarcoidosis is combined with the accumulation of granulomas in one or multiple areas of the musculoskeletal system, including joints, muscles, bones and vessels.

The first clinical manifestation possibly is muscular atrophy. Also, in the context of Lofgren’s syndrome, acute joint inflammation may appear; despite chronic joint inflammation, it is linked with swelling in multiple organs. Symptomatic muscular involvement in sarcoidosis is divided into two types: sterile, acute myositis, and chronic myopathy. Depending on the location of the affected bones, sarcoid bone lesions can be permeative, lytic, or sclerotic. Moreover, bone density can be reducing, elevating the risk of fractures especially in the distal forearm, due to the illness development and activation of osteoclasts.

Studies on vascular involvement in sarcoidosis are still rare. While vasculitis may sometimes coincide and be induced by sarcoidosis **(El Hasbani *et al.*, 2022).**

4. Etiology of sarcoidosis:

The cause of sarcoidosis is unknown, but research suggests that a combination of genetic and environmental factors may contribute to the development of the disease.

4.1. Genetic factors:

Sarcoidosis may be a polygenic genetic disease, and it is deemed that HLA-A1, HLA-B8, and HLA-DR3 in human leukocyte antigen (HLA) are intricately connected to the development of sarcoidosis **(Li *et al.*, 2023),** and is substantiated by various proofs: monozygotic twins are more commonly agreement for the disease than dizygotic twins, and people with sarcoidosis are more likely than healthy people to report the influence of a sibling or parent with the disease **(Spagnolo *et al.*, 2013).**

4.2. Environmental factors:

Several environmental factors, incorporating contact with wood stoves, inorganic particles, insecticides, nanoparticles, soil, tree pollen, and others, may contribute to the initiation of sarcoidosis. Some of these factors can be infectious **(Jain *et al.*, 2020).**

The environmental factors manifest their impact clearly through the following example:

4.2.1. Infectious agents in sarcoidosis:

It has been suspected that infectious agents may be a possible cause of sarcoidosis. These infectious agents include bacteria, mycobacteria, and fungi. One of the most important pieces of evidence for this is the presence of DNA from the bacteria *Propionibacterium acnes* in the lymph nodes of people with sarcoidosis **(Arevalo, 2012).**

On the other hand, molecular techniques in some studies have proven the presence of mycobacterial components in the tissues of sarcoidosis patients, especially mycobacterial catalase peroxidase (mKatG).mKatG has physiochemical properties similar to the Kveim-Siltzbach reagent that causes granulomatous inflammation in sarcoid patients.T cell responses to mKatG have been documented in peripheral blood cells of sarcoidosis patients, and their appear to be more robust responses in Broncho alveolar lavage fluid and stronger responses in active cases of the disease**(Thomassen *et al.*,2021).**

4.3. Autoimmunity:

Autoimmunity may be involved in some forms of sarcoidosis. Autoimmunity in sarcoidosis can be triggered by molecular mimicry, where antigens initiate inflammation, ultimately resulting in the exposure of self-peptides.

Immunologic resembling between the altered trigger and the self-peptide may contribute to the activation of autoreactive T and B cells in individuals prone to such responses. It is conceivable that the primary granulomatous reaction in sarcoidosis is a direct effect of an antigen exposure in a designated organ, but that ensuing granulomatous reactions in other organs are the consequence of molecular mimicry **(Thomassen *et al*., 2021).**

4.3.1. Vimentin and sarcoidosis:

Vimentin is a type of III filament protein, which is part of the cytoskeleton of human mesenchymal cells and certain bacteria, and is part of the components of Kveim solution reagent. Vimentin has also been suggested to be a sarcoidosis antigen causing expansion of the clonal proliferation of CD+4T lymphocytes bearing the TCR Vα2.3+/Vβ22+ antigen in Lofgren syndrome patients.

Whilst the response against the self-protein Vimentin suggests that sarcoidosis has an autoimmune component, the perfect fit of vimentin with the peptide-binding gap of HLA-DRB1*3 molecules may result from molecular mimicry.

Simple put, vimentin may resemble the structure of the antigen that causes granulomatous inflammation, and there may be other antigens/environmental factors that trigger granulomatous inflammation via molecular mimicry **(Bonella *et al.*, 2022).**

5. Pathogenesis:

While the exact pathogenesis of sarcoidosis remains obscure, there is a consensus that it represents an exaggerated helper/inducer T lymphocyte(Th17) response to exogenous or autologous antigens. These cells accumulate in the affected organs, where they secrete lymphokines and recruit macrophages activated by IFN-gamma. The activated macrophages, in turn, secrete increased amounts of interleukin-17(IL-17)**,** participating in the formation of noncaseating granulomas.

The organs containing sarcoid granulomas have CD4+to CD8+ T cell rations of 10:1 compared with 2:1 in uninvolved tissues. The basis for this abnormal accumulation of helper/inducer T lymphocytes is unclear. In addition, there is an increased production of tumor necrosis factor (TNF), contributing to disease symptoms. Nonspecific polyclonal activation of B cells by T-helper cells is evidenced by hyperglobulinemia, a characteristic of active sarcoidosis. Also observed in cases of sarcoidosis are an increase in the release of certain inflammatory cytokines, activation of Th1/Th17 cells, decreased regulatory T-cells, and impairment of CD4 cells. These factors promote the proliferation of cells and blood

vessels, tissue remodeling, and stromal growth leading to a tumor (figure 6) **(Reisner, 2013 ; Ramstein *et al.*, 2016)**.

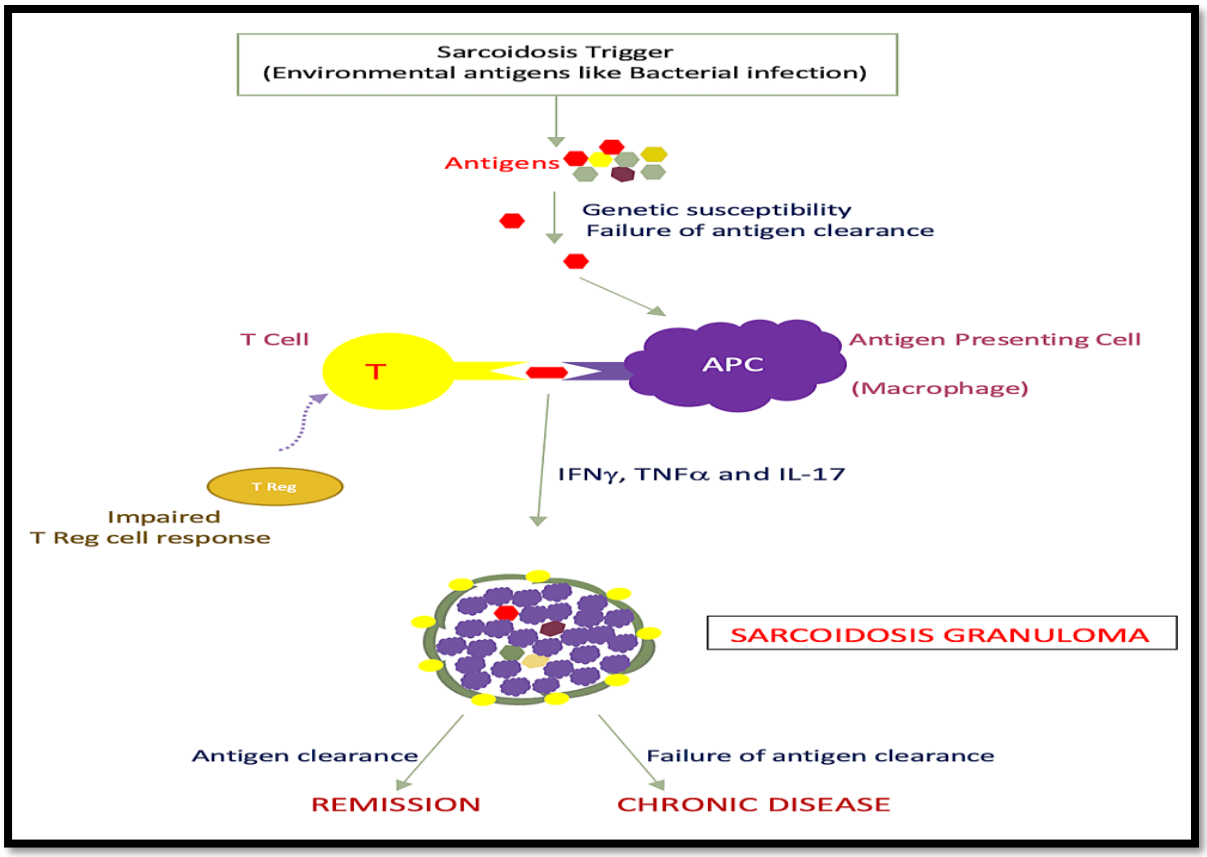


Figure 6. Pathogenesis of sarcoidosis granuloma (Ramstein *et al.*, 2016).

6. Complications of sarcoidosis:

The most serious and repeated complications of sarcoidosis are:

- Pulmonary fibrosis: The development of lung fibrosis can lead to chronic shortness of breath and a significate impact on lung function.
- Respiratory airways obstruction: Resulting from several mechanisms, such as deformation of the trachea due to pulmonary fibrosis or direct localization of granulomatous masses in the airways.
- High pulmonary arterial pressure: It occurs in cases of terminal pulmonary fibrosis and is considered a strong indicator of death.
- Granulosis formation: A complication considered to be associated with an increased risk of death due to severe bleeding or underlying respiratory failure.

- Heart complications: Such as cases of continuous tachycardia and left ventricular dilatation.
- Complications in the central nervous system: It can be the third cause of death after localization in the lungs and heart.
- Skin problems: Such as *Lupus Pernio* symptoms.
- Problems in the nose, throat, kidneys, and severe eye concentrations.
- Permanent effects:10-20% of patients with sarcoidosis experience permanent effects **(Nunes *et al.*, 2007).**

7. Diagnosis of sarcoidosis:

Diagnosing sarcoidosis is somewhat challenging due to the variability of symptoms and the affected organs. In most cases, the diagnosis relies on a thorough review of the medical and family history, followed by a physical examination, it is than complemented by a series of additional tests **(Chow, 2022).**

7.1. Medical family history:

Since the disease is associated with genetic factors, it is essential to consider the family history. Additionally, specific factors related to an individual's lifestyle and daily routine must be known for an accurate diagnosis **(Chow, 2022).**

7.2. Physical examination 'Footprints of sarcoidosis':

It is essential to investigate the effects of involvement in different organs through a complete physical examination. There are no distinctive clinical symptoms to confirm the disease based on physical examination **(Baughman, 2016)**

7.3. Laboratory:

The serum biomarkers identified in sarcoidosis are primarily generated by inflammatory cells participating in the formation of granulomas. Angiotensin-converting enzyme (ACE)is the crucial biomarker, which is increased in 60-90% of patients (figure 7) **(Kraaijvanger *et al.*, 2020),** and others are summarized in the picture below:

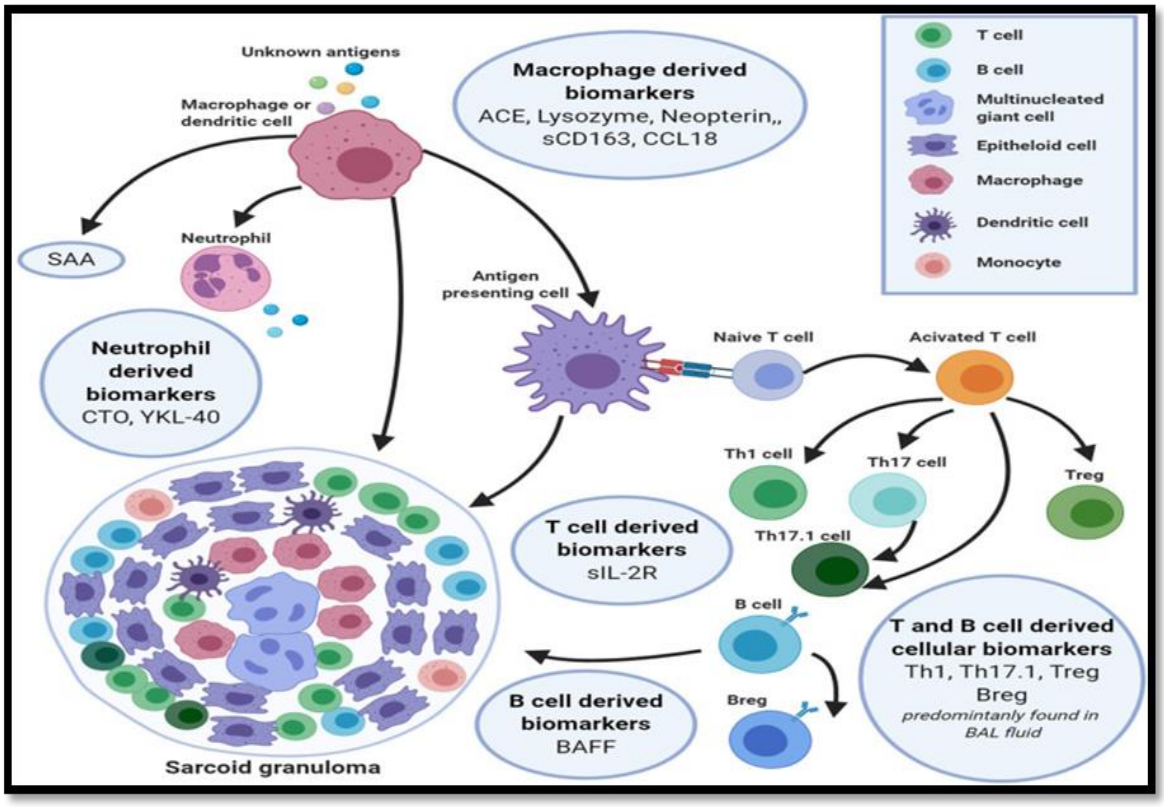


Figure 7. An integrated overview of serum and Broncho alveolar lavage fluid biomarkers produced by cells of the innate and adaptive immune system, involved in the formation of granulomas in sarcoidosis (Kraaijvanger *et al.*, 2020).

7.4. Imaging:

- ✓ Chest X-ray or computerized tomography(CT)scan is often used as adjunctive screening tests for sarcoidosis. Important findings for sarcoidosis include hilar or mediastinal nodal enlargement, interstitial air space-like opacities and peripheral cavitation.
- ✓ Bone X ray is used to assess bone involvement, like punched- out lesions.
- ✓ Gallium scan in order to perceive and assess lesions and swelling not revealed by ancients methods.
- ✓ (PET)scan is employed to detect inflammation, mostly in cardiac sarcoidosis **(Papaliodis, 2017).**

7.5. Biopsy:

- ✓ Doctors take a small sample of tissue, selecting the least invasive place to biopsy such as the skin, lymph nodes or lungs.

- ✓ Kveim or Kveim-Siltzbach reaction involves a preparation from the spleen of a patient whose histopathological examination has confirmed sarcoidosis. It causes the appearance of masses when injected intradermally in patients with sarcoidosis. The test is positive in 80%of cases with acute systemic sarcoid and negative in 90%of patients with long- term sarcoid.
- ✓ Pulmonary function testing might indicate a reduction in diffusion capacity and static lung volume.
- ✓ Skin testing might uncover a lack of immune response to Candida and Trichophyton indicating anergy.
- ✓ Pathologic findings: granuloma of sarcoidosis comprises multinucleated giant cells, epithelioid cells, and slender coating of lymphocytes. Additionally, the giant cells might consist of Shaumann or Lamellar bodies (basophilic inclusions constituted by calcium and iron) and asteroid bodies (acidophilic inclusions composed by intermediate filaments) **(Gold *et al.*, 2011).**

7.6. Differential diagnosis:

Causes of granulomatous nodules, searching for infections (fungal, mycobacterial,) and immunologic problems (allergy, autoimmunity…).

On the other hand, the latest studies presented by the lung journal showed the contribution of artificial intelligence in diagnosing sarcoidosis, as machine learning(ML), deep learning(DL), and neural networks(NN) represent subsets of technological development, increasing depth of analytical capacity, accuracy in diagnosis, and decreasing reliance on human supervision **(Klang *et al.*, 2023).**

8. Treatment of sarcoidosis:

Not all patients with sarcoidosis require systemic treatment, as sarcoidosis can develop in two different ways: the first has a specific duration, while the second takes a chronic nature.

8.1. Medical therapy:

Immunosuppressants are a class of drugs designed to attenuate the immune response, thereby alleviating the symptoms associated with sarcoidosis include:

8.1.1. Corticosteroids:

Corticosteroids persist as a cornerstone in therapy by suppressing pro-inflammatory cytokines and chemokines that participate in cell-mediated immune responses and granuloma formation, namely Prednisone and Prednisolone. Although corticosteroids

present the first line of medical therapy, research into alternative medications was conducted due to their negative effects **(Grutters *et al.*, 2006 ; Arcana *et al.*, 2023).**

8.1.2. Disease-modifying antirheumatic drugs (DMARDs):

DMARDs Are medications that dampen the immune system. They may prolong the progression of sarcoidosis and minimize symptoms to treat an overactive immune system, such as Methotrexate, Azathioprine and Leflunomide **(Chambers, 2019).**

8.1.3. Tumor necrosis factor (TNF) inhibitors:

Tumor necrosis factor alpha, plays a crucial role in the formation of granulomas. Recent clinical trials have highlighted the efficacy of TNF-alpha inhibitors in treating sarcoidosis that is resistant to conventional therapies, drugs like Infliximab and Adalimumab **(Wig *et al.*, 2018).**

8.1.4. Calcineurin inhibitors:

Calcineurin is an important protein that activates T lymphocytes. Although calcineurin inhibitors (Tacrolimus, Cyclosporine, and pimecrolimus) are among the most powerful immunosuppressant medications **(Jindal *et al.*, 2011).**

8.1.5. Immunomodulators:

Many drugs used in the treatment of inflammatory conditions, aimed at modulatory the immune response, are also recommended for use in the treatment of sarcoidosis. For example, Thalidomide modulate the effects of TNF-alpha **(Hay *et al.*, 2009).**

8.2. Surgical intervention:

Surgical intervention may be necessary in some cases when sarcoidosis leads to various complications in a specific organ that cannot be effectively managed with medications alone. whereas transplant surgery (commonly lung and liver) has been used as a treatment for sarcoid more than remove surgery. The aim for surgical intervention in sarcoidosis is not the elimination of disease but the anticipated elevation of life quality **(Rosen, 2022).**

Chapter three

New therapeutic avenues and clinical trials

Chapter III. New therapeutic avenues and clinical trials

Introduction:

About half of patients suffering from sarcoidosis will need systemic treatment for their disease, as the proposed medications aim to alleviate the severity of inflammation and symptoms through their effect on the immune system. There are cases that heal spontaneously.

Since the cause of sarcoidosis is unknown, specific treatment and distinct signs do not exist. Many medications have been studied, some of which have proven effective in reducing the severity of the disease, and some are still undergoing clinical trials. Therefore, several additional research efforts should be undertaken to develop improved and effective tools in the treatment of sarcoidosis **(Grunewald *et al.*, 2019 ; Zhou *et al.*, 2023).**

1. Therapeutic approaches for targeting cells and molecules:

Only two medications, Prednisone and Repository Corticotropin injection (RCI), are approved by the United States Food and Drug Administration for the treatment of sarcoidosis.

Corticosteroids continue to be considered the first-line treatment for sarcoidosis, but considerations must be given to corticosteroid-sparing medications for patients who require long-term therapy or who experience toxicity or side effects from corticosteroids.

Drug development is hindered due to the absence of suitable animal models and a basic understanding of its underlying causes. Moreover, most research on sarcoidosis focuses on pulmonary sarcoidosis as the most prevalent form.

Over the last twenty years, a significant portion of clinical trials has focused on investigating drugs initially approved for different medical purposes. This strategy is grounded in the recognition that many immunopathological pathways implicated in inflammatory and fibrotic diseases, akin to those observed in sarcoidosis, exhibit similarities. Consequently, by scrutinizing medications licensed for alternative uses, researchers seek to uncover potential treatments that might prove efficacious in managing sarcoidosis owing to their shared underlying mechanisms **(Obi *et al.*, 2022 ; Gerke, 2020 ; Gerke, 2024).**

1.1. Targeting B cells:

Many studies have demonstrated the role of B cells in the pathogenesis of sarcoidosis. The relevance of B lymphocyte activation in sarcoidosis can be proven by the effectiveness of anti-CD20 treatment **(Malkova *et al.*, 2019).**

“Rituximab”, a chimeric monoclonal antibody which, its association with the transmembrane protein CD20 leads to the destruction of B cells, through complement

mediated cytotoxicity and antibody, furthermore the onset of apoptotic path-ways (figure 8) **(Nelson *et al.*, 2024).**

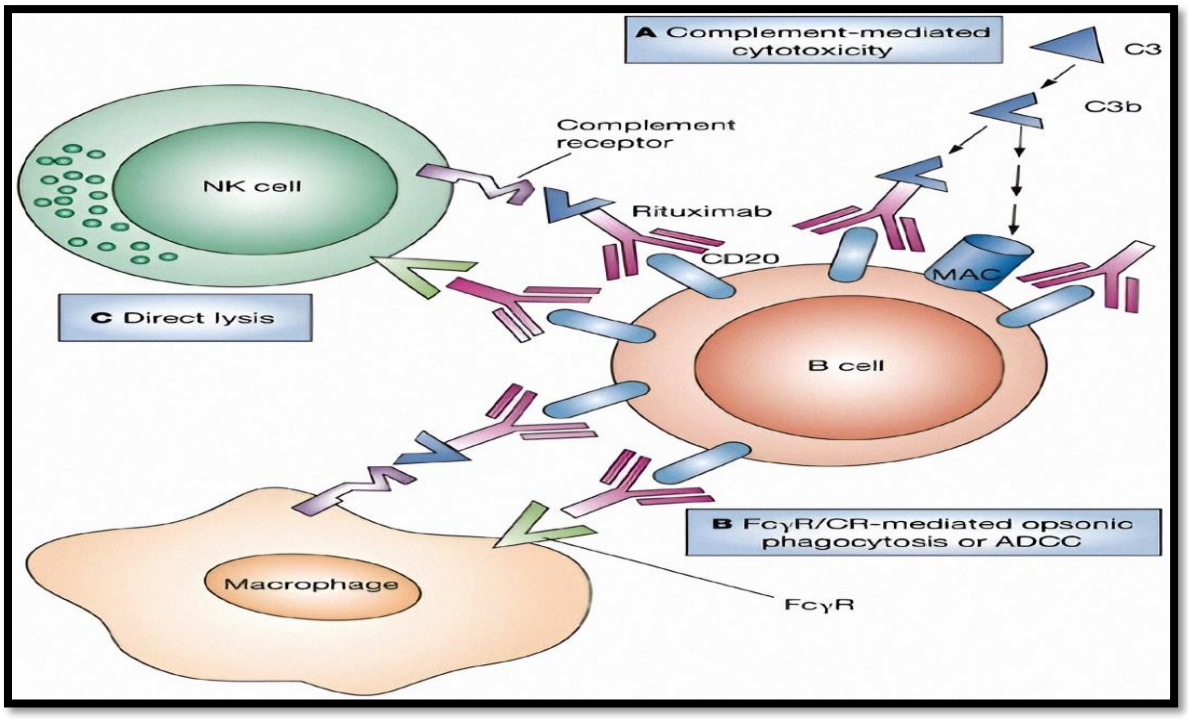


Figure 8. The mechanism of action of Rituximab (Taylor *et al.*, 2007).

1.2. Targeting T cells:

Recent studies have revealed the diverse contribution of CD4+T subsets in sarcoidosis, with the focus on the roles of Th17 cells, Th17.1cells and Tregs cells as active players involved in the formation of granuloma, beyond that CD8+T lymphocytes. We discussed the mechanism of action of certain drugs targeting Tcells **(Zhou *et al.*,2020; Zhang *et al.*,2021).** "Azathioprine"is an analogue of purine, undergoing conversion to the active 6-mercaptopurine by thiopurine -s-methyl transferase. The incremental amassment of 6-thioguanine nucleotides in target organs may play a pivotal role in immunosuppression. Working as an inhibitor of RNA/DNA, Azathioprine hinders the proliferation of T cells and impairing the function of cytotoxic T cells.

Various studies have emphasized the advantages of Azathioprine as a steroid-sparing agent in sarcoidosis. Though, because of its substantial toxicities, which include gastrointestinal effects, hepatitis, bone marrow suppression, the utilization of this drug in sarcoidosis is reserved for cases of progressive organ-threatening disease that do not respond to safer alternatives, such as low-dose corticosteroid therapy **(Moller, 2003).**

"Leflunomide"is an oral immunosuppressive agent. Its supposed mechanism of action involves inhibiting dihydroorate dehydrogenase (DHODH), an important enzyme in the novo synthesis of deoxyuridine monophosphate (dUMP). Activated T-lymphocytes, but not memory ones, rely on de novo pyrimidine production for membrane biosynthesis, clonal expansion, and terminal differentiation into effector cells. Leflunomide, selectively suppress lymphocyte responses in actively stimulated lymphocyte clones. In the absence of sufficient intracellular (dUMP), P53-mediated apoptosis (DNA-binding transcription factor) is triggered in activated, but not resting, lymphocytes.

After being approved in 2003, the prevalent side effects of "leflunomide" included diarrhea and increased liver enzyme levels **(Sahoo *et al.*, 2018).**

1.3. Targeting Cytokines:

Despite confirming the contribution of cells to the inflammatory and granulomatous response in sarcoidosis, numerous studies have demonstrated the involvement of several cytokines and chemokines in disease pathogenesis **(Weinberger *et al.*, 2008).**

"Infliximab" is a monoclonal antibody targeting tumor necrosis factor- alpha (TNFα), which is a crucial inflammatory cytokine in the pathophysiology of sarcoidosis. The mechanism of action of "Infliximab" involves binding to and neutralization of (TNFα) where it is considered a good therapeutic option, most notably in cases of neurologic and cutaneous sarcoidosis (figure 9) **(Sakhat *et al.*, 2022).**

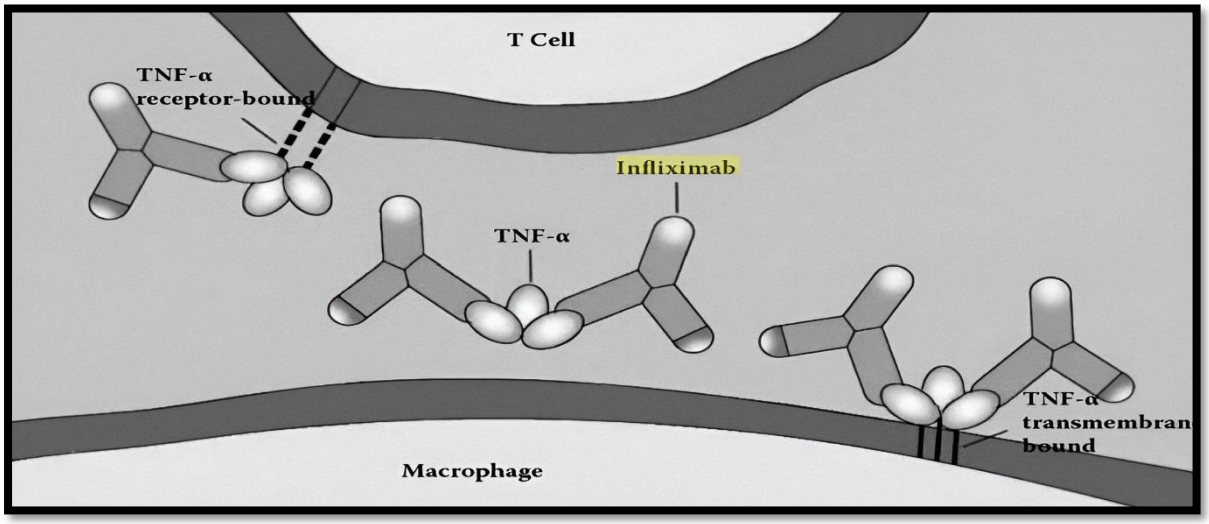


Figure 9. Mode of action of Infliximab (Grewal, 2009).

Interleukin 1(IL-1), is one of therapeutic targets of sarcoidosis, it activates the nuclear transcription factor NF-kB, which contributes to inflammation and granuloma formation.IL-1 inhibitors have paved the way for new therapeutic directions.

Chapter III. New therapeutic avenues and clinical trials

"Anakinra"is a recombinant human IL-1 receptor antagonist that blocks IL-1α and IL-1β. It can harmlessly modulate systemic inflammation in cardiac sarcoidosis according to the latest studies (figure 10) **(Kron *et al.*, 2021 ; Kron *et al.*, 2023).**

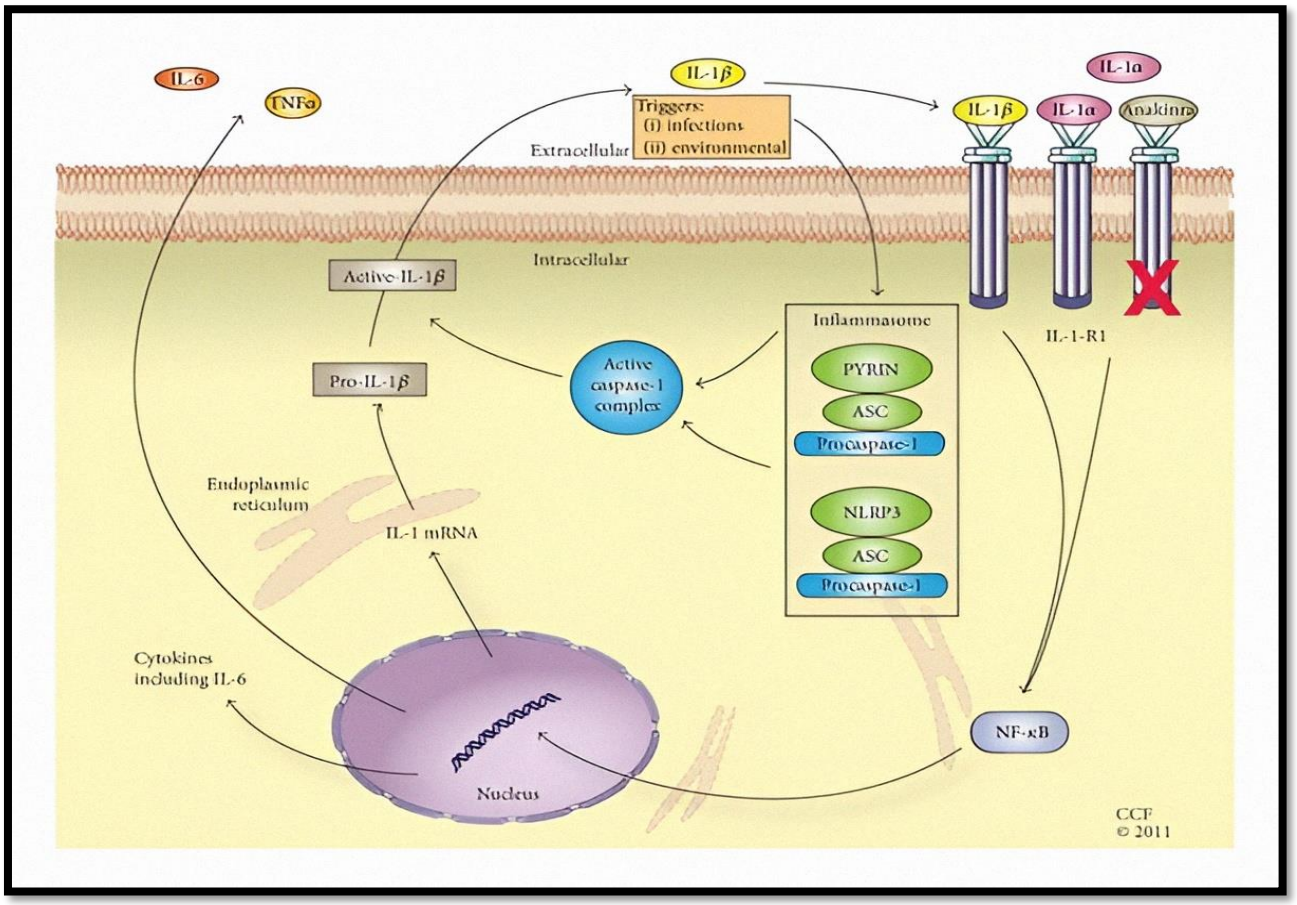


Figure 10. Mechanism of action of Anakinra (Baskar *et al.*, 2016).

"Tocilizumab" is a direct inhibitor of IL-6 monoclonal antibody, targeting the IL-6 pathway, proving advantageous in chronic sarcoidosis affecting multiple systems. The inhibition of IL-6 receptor in sarcoidosis aims to decrease the precursor protein SAA (Elevated Serum Amyloid A), concentrated within sarcoidosis granulomas (figure 11) **(Sharp *et al.*, 2019).**

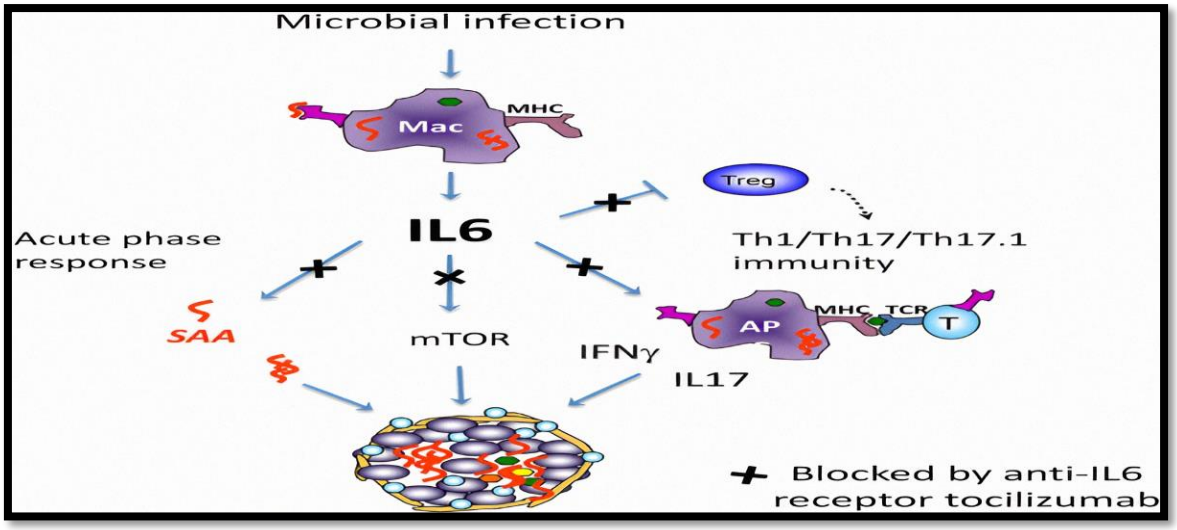


Figure 11. Hypothesized therapeutic role of blocking IL-6 pathway in Sarcoidosis (Sharp *et al.*, 2019).

An analysis of the genetic code in biopsies taken from sarcoid skin lesions revealed an increase in IL-12 and IL-23. This suggests a potential upregulation of Th1 and possibly Th17 pathways in sarcoidosis. Therefore, inhibiting of IL-12/IL-23 could potentially prove effective in treating chronic sarcoidosis.

"Ustekinumab" is a human monoclonal antibody of the immunoglobulin G1k class that binds strongly to the shared P40 submit of human IL-12 and IL-23. Despite demonstrating excellent safety, "Ustekinumab" did not meet the primary effectiveness endpoint moreover, literature reports various cases of induced or aggravated sarcoidosis with "Ustekinumab" (figure 12) **(Judson *et al.*, 2014 ; Boleto *et al.*, 2020).**

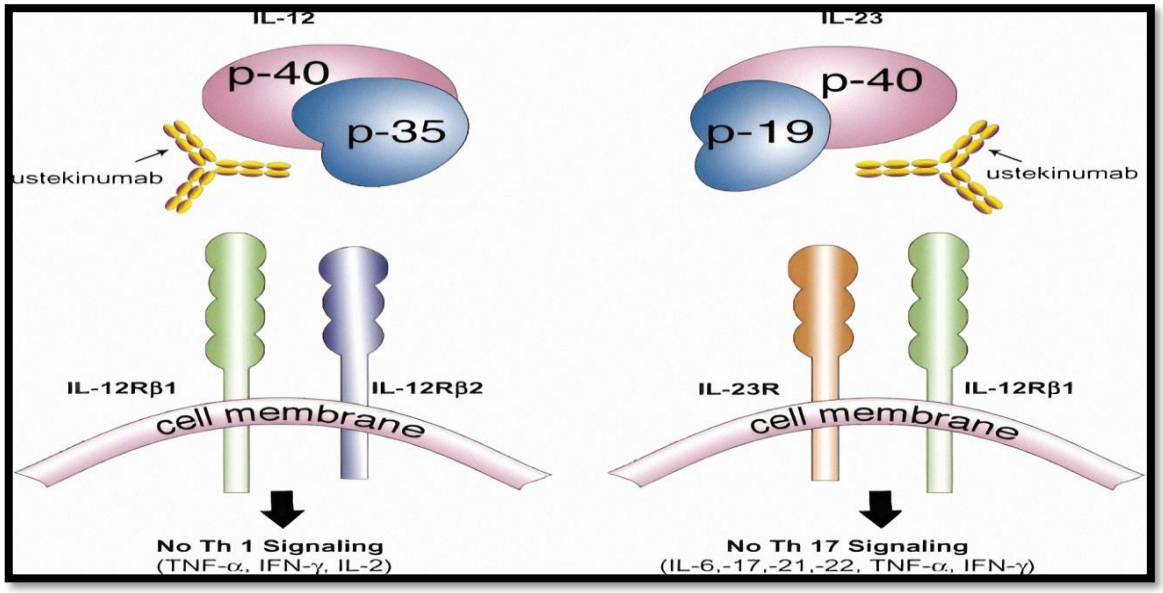


Figure 12. Mechanism of action of Ustekinumab, an interleukin-12 and interleukin-23 inhibitor (Koutruba et al., 2010).

Recent studies suggest that Th17 cells play a pivotal role in all phases of granuloma formation. The distinctive feature of the Th17 pathway is its production of IL-17. In individuals with sarcoidosis, the impact of inhibiting IL-17 remains unclear. Most information regarding IL-17 inhibitors are derived from case reports.

"Secukinumab" is a human monoclonal antibody to IL-17A.Generally, the use of "Secukinumab" leads to a lower concentration in IL-17. While many reports present paradoxical cases where the onset of sarcoidosis was associated with the use of an IL-17 inhibitor, and several cases have reported successful treatment with "Secukinumab", and diagnostic test results were completely normal **(Nychowski *et al*., 2017 ; Boleto *et al*., 2020 ; Kobac *et al*., 2020).**

1.4. Targeting Enzymes:

Angiotensin converting enzyme(ACE) is a serum marker that shows an increased presence in sarcoidosis. Several studies have demonstrated the positive effects of (ACE) inhibitors on patients with cutaneous and lymphatic sarcoidosis.

"Enalapril" and "Captopril" inhibit (ACE) through a direct contact with a different special site of (ACE). The use of these inhibitors in sarcoidosis patients has shown a positive response. Test results demonstrated significant improvement in lung function and prevented pulmonary fibrosis and skin tissue fibrosis in patients with sarcoidosis. Additionally,

experimental results showed an important remodeling of areas in diverse tissues **(Wang *et al.*, 2011 ; Kaura *et al.*, 2013).**

Targeting Phosphodiesterase-4 (PDE4), holds significant clinical promise as it focuses on a central pathological process that circumvents intricate antigen receptor-specific immunoregulatory mechanisms. Inhibiting (PDE4) leads to the accumulation of the intracellular second messenger (cAMP), subsequent activation of protein kinase A(PKA), and consequent phosphorylation of the transcription factor cAMP-response element binding protein (CREB). This pathway activation regulates the transcription of various cytokines, resulting in the suppression of their production **(Kumar *et al.*, 2013).**

"Apremilast"is a specific inhibitor of phosphodiesterase 4 (PDE4). This specificity allows for higher dosages with fewer side effects compared to other non-specific PDE4 inhibitors. Its effectiveness in treating cutaneous sarcoidosis was described in 2012 by Baughman et al **(El Jammal *et al.*, 2020).**

There is ample evidence indicating persistent activation of Janus Kinase-signal transducer and activation of transcription (JAK-STAT) signals in sarcoidosis **(Damsky *et al.*, 2020).** "Tofacitinib" is a Janus Kinase inhibitor that works to reduce JAK-STAT signaling pathways, thereby contributing to the reduction of inflammation and granuloma formation in sarcoidosis by decreasing cytokines levels. This medication demonstrated significant improvement in skin condition and effective healing in patients with cutaneous sarcoidosis. Moreover, it improved respiratory symptoms in those with pulmonary sarcoidosis **(Kerkemeyer *et al.*, 2020).**

1.5. Targeting fibroblasts:

Fibrosis results from the activation and proliferation of fibroblasts, leading to the production and deposition of collagen. In sarcoidosis, these process occur as an extension of granulomatous inflammation. Histopathologically, fibrotic changes initiate at the periphery of granulomas and extend centrally **(Patterson *et al.*, 2014).**

"Nintedanib" exhibits antifibrotic properties by inhibiting the proliferation and migration of fibroblasts. Additionally, it reduces the accumulation of extracellular matrix, demonstrating its anti-inflammatory effects**.** The use of Nintedanib as an antifibrotic treatment in pulmonary sarcoidosis has shown success and improvement in the decline of vital lung capacity (**Papanikolaou *et al.*, 2022; Bandyopadhyay *et al.*, 2023).**

1.6. Targeting genes expression:

Hypoxia-inducible factor(HIF-1α) is transcription factor. In sarcoidosis, granulomatous lung tissues, the in situ hybridization revealed a significant presence of HIF-1α concentrated

at the center of granulomas. The abundance of HIF isoforms was found to be intricately connected to heightened levels of IL1β and IL17, this connection was demonstrated through targeted downregulation of HIF-1α using short interfering RNA or a specific HIF-1α inhibitor, resulting in a reduction in their production. Additionally, pharmacological intervention with Chloroquine, a lysosomal inhibitor, led to decreased levels of HIF-1α, along with alterations in cytokine production **(Kietzmann *et al.*, 2016; Talreja *et al.*, 2019).**

2. Exploring innovative treatments in clinical trials:

It's expected that upcoming treatment will focus on preventing exposure, targeting antigens, reducing granulomatous inflammation, and blocking fibrotic pathways **(Gerke, 2020).**

2.1. mTOR inhibitor:

mTOR also known as mammalian target of rapamycin, is a protein kinase that plays a significant role in controlling and shaping the effective responses of innate immune cells. It configures cellular metabolism and regulates translation, cytokines responses, antigen presentation, macrophages proliferation and cell migration**.**

The activation of the mTOR pathway in sarcoidosis, supporting the hypothesis that mTOR plays a pivotal role in granuloma formation. The signaling mechanisms and the involvement of mTOR signaling during the early stages of sarcoidosis granuloma formation remain unclear **(Weichhart *et al.*,2018; Crouser *et al.*,2021; PiZZirni *et al.*,2021).**

"Sirolimus" binds to a cytoplasmic protein known as FK-binding protein(FKBP), forming a complex that inhibits the cytosolic enzyme mTOR **(Ali *et al.*,2024).**

One report has been published indicating the effectiveness of Sirolimus in treating pulmonary sarcoidosis by alleviating symptoms and inducing improvement in granuloma enlargement. Short-term systemic treatment with Sirolimus can be a safe and effective option for sarcoidosis. Currently, its impact on cutaneous sarcoidosis is being further investigated in large clinical trials **(Gupta *et al.*,2020; Redl *et al.*,2024)**.

2.2. Inhibitor of Pentose Phosphate Pathway:

Activation of the pentose phosphate pathway(PPP) in macrophages plays a vital role in the formation of granulomas in sarcoidosis. Elevated expression of pentose phosphate pathway enzymes was detected not only in the serum of sarcoidosis patients but also in systemic granuloma lesions.

Studies have shown that in sarcoidosis, the production of reactive oxygen species (ROS) increases through NADPH and NADPH oxidase (NOX) activation via (PPP). Additionally, free radicals contribute to granuloma formation and tissue destruction around the granulomas. The use of PPP inhibitors in both in vitro giant cell cultures and in vivo murine models resulted in a reduction of granuloma formation. After using FBP1,6AN, and G6PDi compounds, which inhibit the pentose phosphate pathway, the results showed inhibition of granuloma formation in vitro. Moreover, a significant decrease in cytokines was recorded. These findings indicate that targeting the PPP could hold promise for the development of treatments for sarcoidosis (figure 13) **(Nakamizo *et al.*,2023).**

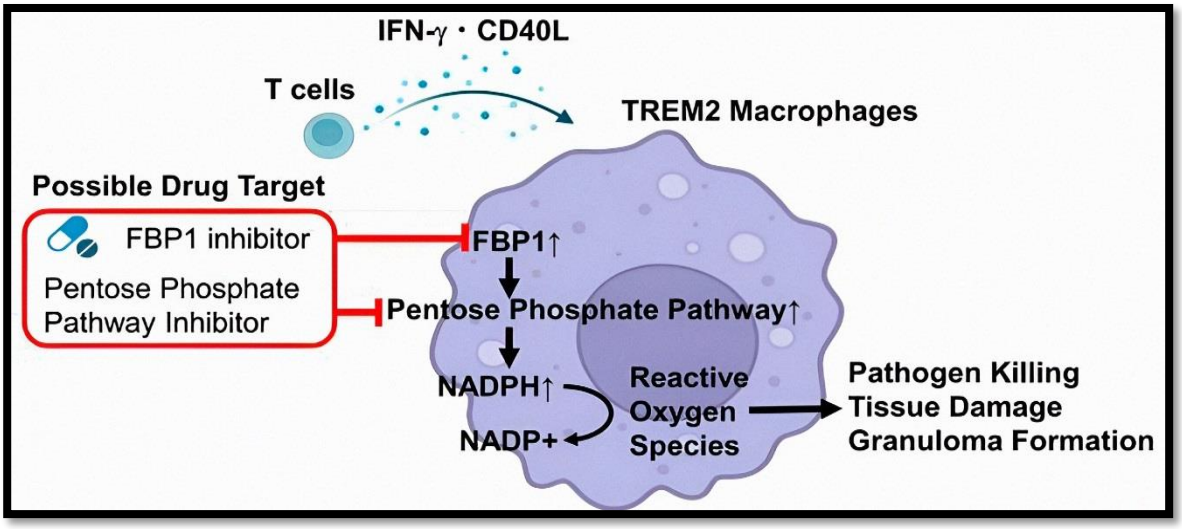


Figure 13. Pentose Phosphate pathway (Nakamizo *et al.*, 2023).

2.3. Inhibitor of Phosphoinositide-3 kinases γ / δ:

Phosphoinositide-3 kinases γ / δ (PI3K γ / δ) are crucial for maintaining a robust immune response, particularly in regulating the balance and stability of regulatory T cells (Tregs). Both patients and mice with sarcoidosis exhibited activation of the Phosphoinositide-3 kinases signaling pathway. After using CAL-101 and AS-605240 as inhibitors for (PI3K δ) and (PI3K γ), respectively, they played a role in restoring the balance of Tregs and Th1 cells and reducing granuloma formation, as tested in mice. Moreover, the effect of inhibiting (PI3K δ) was more effective than (PI3K γ). These inhibitors could potentially be a new therapeutic strategy for sarcoidosis **(Zhang *et al.*,2022).**

2.4. Activator of TGFβ/Smad3 pathway:

The TGFβ/Smad3 signaling pathway is involved in regulating the function of Tregs in sarcoidosis, where the TGFβ/Smad3 pathway is inactive in patients with sarcoidosis.

Dexamethasone, was used in a mouse model, there it was observed to activate TGFβ/Smad3 signals and promote rebalancing of Th17/Tregs in pulmonary sarcoidosis patients.

This study suggests the possibility of using Dexamethasone in the treatment of pulmonary sarcoidosis **(Zhang *et al.*, 2024).**

2.5. OATD-01:

Chitotriosidase, a biomarker secreted by activated macrophages and neutrophils, is still not fully understood in terms of its physiological function. However, its believed to be involved in breaking down chitin and similar substances. Elevated levels of chitotriosidase have been observed in the serum and Broncho alveolar lavage fluid of patients with active sarcoidosis **(Bergantini *et al.*, 2019).**

OATD-01, the first chit1 inhibitor of its kind, showed effectiveness in murine models of granulomatous inflammation. Where it inhibited the production of inflammatory mediators CCL4 and IL15, showed anti-inflammatory effects reducing the percentage of neutrophils, thereby decreasing granuloma formation, as the model was applied in the case of pulmonary sarcoidosis **(Daymek *et al.*, 2022).**

2.6. Efzofitimod:

Efzofitimod, a novel immunomodulatory molecule, is undergoing testing for the treatment of pulmonary sarcoidosis by targeting Neuropilin- 2 (NRP-2), a cell surface receptor pivotal in lymphanogiogenesis and implicating in some physiological conditions such as inflammation. The increased presence of Neuropilin 2 in the granulomatous model suggests that Efzofitimod could be an effective treatment option.

the preliminary experimental results showed that Efzofitimod reduced inflammation and key fibrosis indicators including IL6, CCL2, and CXCL10 in sarcoidosis animal models and this is after it is associated with Neuropilin 2. significant improvement in lung function was also observed, opening the door for further study of this drug in sarcoidosis patients, especially after the promising preliminary results **(Forster *et al*., 2023; Baughman *et al.*, 2023).**

Conclusion

Conclusion

Sarcoidosis is a systemic granulomatous disease that induces various changes in the immune system involving cells and molecules. This diversity in the targeted elements by the disease has necessitated the search for specialized medications for each, such as Infliximab, which binds and neutralizes TNFα whether soluble, transmembrane, or receptor-bound thereby guarding against the serious complications of the disease. Additionally, recent clinical trials have shed positive light on treatment, particularly with mTOR inhibitors due to their multi-targeting capabilities including cytokine response, antigen presentation, and macrophage proliferation and migration. This warrants the exploration of multi-targeted drugs or subjecting patients to a comprehensive therapeutic regimen with minimal side effects. The recent qualitative leap in trials underscores the positive research outlook pursued by researchers in treating the disease.

References

References

Abu-Shakra M, Shoenfeld Y. Idiotypes and anti idiotypes. Autoantibodies:75-82. 2014.

Ali E. S, Mitra K, Akter S, Ramproshad S, Mondal B, Khan I.N. Recent advances and limitations of mTOR inhibitors in the treatment of cancer. Cancer cell International.22(284).2022.

Arakawa T, Akuta T. Mechanistic Insight into Poly-Reactivity of Immune Antibodies upon Acid Denaturation or Arginine Mutation in Antigen –Binding Regions Review. Journal Antibodies.12(4):64.2023.

Arango M T, Shoenfeld Y, Cervera R, Anaya J M. Autoimmunity: From Bench to Bedside. National Library of Medicine.2013.

Arcana R, Dabija R, Cernomaz A, Buculei I, Buculei I, Zabara M.*et al*. The risk of sarcoidosis misdiagnosis and the harmful effect of corticosteroids when the disease picture is incomplete. biomedicines.2023.

Arevalo JF. Retinal and choroidal manifestations of selected systemic diseases:212.2012.

Aubart FC, Chazal T, Lhote R, Amoura Z. Neurosarcoidosis.Sarcoidosis a clinician's guide. (10): 115-125.2019.

Bandyopadhyay D, Mirsaeidi M.S. Sarcoidosis-associated pulmonary fibrosis: joining the dots. European Respiratory Review.32(169).2023.

Baskar S, Klein A, Zeft A. The use of IL-1 Receptor Antagonist (Anakinra) In idiopathic recurrent Pericarditis a Narrative Review.Cardiologie research and practice. (4):1-6.2016.

Baughman RP, Bois RM. Diffuse lung disease: A pratical approach:146.2011.

Baughman R, Niranjan V, Walker G, Burkart Ch, Paz S, Chong Y.E. Efzofitimod: a novel anti-inflammatory agent for sarcoidosis. Sarcoidosis Vasculitis and diffuse lung diseases.40(1).2023.

Baughman R. Sarcoidosis, an issue of clinics in chest medicine:590.2016

Baughman RP, Valeyre D. Sarcoidosis A clinician's guide. (25)305.2018.

References

Bergantini L, Bianchi F, Cameli P, Mazzei M. A, Fui A, Sestini P Et al. Prognostic Biomarkers of sarcoidosis: A comparative Study of Serum Chitotriosidase, ACE, Lysozyme. And KL-6. Hindawi Journal of disease markers.2019.

Bonella F, Culver DA. Biet D. sarcoidosis :34.2022.

Boleto G, Vieira M, Desbois AC, Saadon D, Cacoub P. Emerging Molecular Targets for the treatment of Refractory Sarcoidosis. Frontiers in Medecine.7:1-6.2020.

Carton J, Daly R, Ramani P. Clinical Pathology. (21): 482.2007.

Çakan E, Ah Kioon MD, Carmona Y G, Glauzy S, Oliver D, Yamakawa N *et al*. TLR9 ligand sequestration by chemokine CXL4 negatively affects central B cell tolerance.

Journal of Experimental Medicine.220 (12):1.2023.

Ceobanu G, Gheorghe G, Ionescu VA. Sarcoidosis associated with Rheumatic Autoimmune disease. Annals of Academy of Romanian Scientists Series of Medicine .2(2):7-11.2022.

Chambers J. Immune system disorders sourcebook,4th Ed.2019.

Chen Moller D. Sarcoidosis.Clinical Immunology principles and practice: 981-991.2019.

Chen Z, Bozec A, Ramming A, Shett G. Anti –inflammatory and immune regulatory cytokines in rheumatoid arthritis. Nature Reviews Rheumatology.15(1):9-17.2019.

Chow S. Sarcoidosis Diagnosis. Medical and life sciences.2022.

Chowaniec M, Kawalec A, Pawalas K. Environmental risk factors in autoimmune diseases: a review of literature. Environmental Medicine.20(3):12-20.2017.

Conrad N, Misra S, Verbakel J Y, Verbake G, Molenberghs G *et al*. Incidence, prevalence,

and autoimmune disorders over time and by age, sex, and socioeconomic status: a population –based cohort study of 22 million individuals in the UK The Talent. (10391):1878-1890.2023.

References

Cormack T. The role of genetics and environmental factors on autoimmune disease incidence with a focus on gender bias in family case study. Harvard Library office for scholarly communication:7.2019.

Crouser ED, Locke LW, Julian MW, Bicer S, Sadee W, White P *et al*. Phagosome-regulated mTOR signaling during sarcoidosis granuloma biogenesis. Interstitial Lung Disease and Basic Science.57(3).2021.

Cusick M, Libbey JE,Fujinami RS. Molecular mimicry as a mechanism of autoimmune disease. Clinical reviews in Allergy &Immunology.42(1):11-102.2012.

Das RP, Jain AK. Ramesh Current Concepts in the pathogenesis of psoriasis. Indian Journal of Dermatology .54(1):7-12.2009.

Damsky W, Young B. D, Sloan B, Miller E. J, Obando J. A, King B. Treatment of Multiorgan Sarcoidosis with Tofacitinib.ACR Open Rheumatol.2(2):106-109.2020.

Delogu LG, Deidda S, Delitala G, Manetti R. Infectious diseases and autoimmunity. Review article in Journal of infection in developing countries.5(10):679-687.2011.

Demir K, Gorgun S. Human autoimmunity and associated diseases:38-40.2021.

Delves PJ, Martin SJ, Burton DR, Roitt IM. Roitt's Essential Immunology:500.2017.

Doria A, Zen M, Bettio S, Gatto M, Bassi N, Nalotto L *et al*. Autoinflammation and autoimmunity: bridging the divide. Autoimmunity Rev. National library of Medicine .12(1) :22-30.2012.

Dymak B, Sklepkiewicz, Mlacki M, Guner NC, Gryz PN, Drzewicka K. Pharmacological Inhibition of Chitotriosidase (CHIT1) as a Novel Therapeutic Approach for Sarcoidosis. Journal of Inflammation research.15:5621-5634.2022.

El Hasbani G, Uthman I, Jawad A. Muscoloskeletal manifestations of sarcoidosis. Clinical medicine insights: Arthritis and musculoskeletal disorders.2022.

El Jammal T, Jamilloux, Valentin M. G, Valeyre D, Seve P. Refractory Sarcoidosis. Therapeutics and Clinical Risk Management:323-345.2020.

References

Fraga RC, Kakizaki P, Valente N, Portocarrero L, Teixeira M, Senise P. Do you know this syndrome? Heerfordt-Waldenstrom syndrome. Anais Brasileiros de dermatologia.92(4):571-572.2017.

Foster S, Chong YE, Siefker D, Becker Y, Bao R, Escobedo E *et al*. Development and characterization of a novel Neuropillin-2 Antibody for Immunohistochemically Staining of cancer and sarcoidosis Tissue samples. Monoclon Antib Immunodiagn Immunother.42(5):157-165.2023.

Gerke AK. Treatment of Sarcoidosis: A Multidisciplinary Approach. Frontiers in Immunology.11:1-11.2020.

Gerke AK. Anti-Granulomatous Therapy for Pulmonary Sarcoidosis.IntechOpen.2024.

Gold D, Lewis RA. Clinical Eye Atlas. (6): 472.2011.

González AA. Immune Checkpoint Inhibitors: A Review. Internal Medicine and Neumology.8:1-11.2022.

Grewal IS. Emerging Protein Biotherapies.6:138.2009.

Grunewald J, Grutters JC, Arkema EV, Saketkoo LA, Moller DR, Quernheim JM. Sarcoidosis. Nat Rev Dis Primers. National Library of Medicine.5(1):45.2019.

Grutters J, Bosch V. Corticosteroid treatment in sarcoidosis. European Respiratory journal :626.2006.

Gupta N, Bleesing JH, Cormack FX. Successful Responses to Treatment with Sirolimus in Pulmonary Sarcoidosis. American Journal of Respiratory and Clinical Care Medicine. 202:119-120.2020.

Gururajan M, Sindhava VJ, Bondada S. B cell Tolerance in Health and Disease.3:116-129.2014.

Hachulla É, Hatron PY. Détecter les maladies systémiques auto immunes : 7. 2006.

Hay LD, Wass H. Clinical endocrine oncology:334.2009.

Huang W, Li X, Huang C, Tang Y, Zhou Q, Chen W. LncRNAs and Rheumatoid Arthritis: From Identifying Mechanisms to Clinical Investigation.Frontiers in Immunology.12:3.2022.

Hussain k. Shetty Cardiac sarcoidosis. StatPearls.2023.

References

Immune Dysfunction.2021. http://biocode.org.uk. (consulted on20-10-2023).

Ishina IA, Zakharova M Y, Kurbatskaia I, Mamedov A, Belogurov A, Gabibov A. MHC class II presentation in Autoimmunity.12(2):314.2023.

Jain R, Yadav D, Puranik N, Guleria R, Ojin J. Sarcoidosis: causes, diagnosis, clinical features, and treatments .9(4): 1081.2020.

Jane Smith L, Brown J, Quint J. Eureka: Respiratory Medicine :179.2015.

Jia C, Tan Y, Zhao M. The complement system and autoimmune diseases. Chronic Dis Trans Med.8(3):184-190.2022.

Jindal S, Shankar PS, Gupta D, Suhail.Textbook of Pulmonary and critical care medicine voles 1and 2. (17): 181.2011.

Johnson TP, Antichos B, Rosen A. Mechanisms of autoimmunity clinical immunology:649-656.2023.

Judson MA, Baughman RP, Costabel U, Drent M, Gibson KG *et al*. Safety and efficacy of Ustekinumab or golimumab in patients with chronic sarcoidosis. European Respiratory Journal.44.1296-1307.2014.

Kamata M, Tada Y. Dendritic cells and Macrophages in the pathogenesis of Psoriasis. Frontiers in Immunology:2.2022.

Karki G. Immunological Tolerance: Central and Peripheral. Online BiologyNotes.2020.http://onlinebiologynotes.com. (consulted on 20_10_2023).

Kaura V, Kaura NV, Kaura BN, Kaura CS. Angiotensin-converting Enzyme Inhibitors in the Treatment of Sarcoidosis and Association with ACE Gene Polymorphism: Case Series. The Indian Journal of Chest Diseases and Allied Sciences.55.105-107.2013.

Kerkemeyer K, Meah N, Sinclair RD, Tofacitinib for cutaneous and pulmonary sarcoidosis: A case series. National library of Medecine.84(2):581-583.2021.

Kietzmann T, Mennerich D, Dimova EY. Hypoxia-Inducible Factors (HIFs)and Phosphorylation: Impact on Stability, Localization, and Transactivity.Frontiers in cell and Development Biology.4:11.2016.

References

Klang D, Morgenthau A. Current Applications of Artificial Intelligence in Sarcoidosis.Lung. Medicine and computer.2023.

Koarada S, Ono N, Tada Y. Basic Knowledge of Rheumatoid Arthritis. Frontiers in Arthritis.3:1-3.2018.

Kobac S, Gungen AC, Gungen BD, Tutpinar Y, Gulet M. Secukinumab in a patient with sarcoidosis. Scandinavian Journal of Rheumatology.00.1-2.2020.

Koo J, Levin E, Leon A, Wu J, Gottlieb A. Moderate to Severe Psoriasis Fourth edition:1-9.2014.

Koutruba N, Emer J, Lebwohl M. Review of Ustekinumab, an inteleukin-12 and interleukin -23 inhibitor used for the treatment of plaque psoriasis. Therapeutic and clinical Risk Management .6(1): 41-123.2010.

Kraaijvanger R, Bonas M, Veltkamp A, Vorselaars A. Biomarkers in the diagnosis and prognosis of sarcoidosis: Current use and future prospects. Frontiers in immunologie. National Library of Medecine.11:1443.2020.

Kron J, Crawford T, Mihalick V, Bogun F, Jordan JH *et al*. Interleukin-1 blockade in cardiac sarcoidosis: study design of the multimodality assessment of granulomas in cardiac sarcoidosis: Anakinra Randomized Trial (MAGIC-ART). Journal of Translation Medicine.19:460.2021.

Kron J, Crawford T, Bogun F, Jordan J, Koelling T *et al*. Interleukin-1 Blockade in Cardiac Sarcoidosis: A Pilot Study.Circulation: Arrhythmia and Electrophysiology.2023.

Kumar N, Goldminz AM, Kim N, Gottlieb AB. Phosphodiesterase 4-targeted treatments for autoimmune diseases. BMC Medicine.11:96.2013.

Lee KS, Han J, Chung M, Jeon YJ. Radiology illustrated: Chest Radiology:175.2013.

Li H, Liu J. Radiology of infectious and inflammatory diseases, heart and chest:325.2023.

Maccari ME, Schneider P, Smulski CR, Meinhardt A, Pinto F, Gonzalez-Grando LI *et al*. Revisiting autoimmune lymphoproliferative syndrome caused by Fas ligand mutations. American Academy of Allergy, Asthma &Immunology.151(5):1391-1401.2023.

References

Malkova AM, Kudryavtsev IV, Basantsova NYu, Zimchenko YuS, Starshinova AA, Churilov LP, Yablomsky PK. Analysis of the level of B-cell population in patients with pulmonary sarcoidosis.14(4):322-324.2019.

Mazzone R, Zwergel C, Artico M, Taurine S, Ralli M, Greco A *et al.* The emerging role of epigenetics in human autoimmune disorders Review. Clinical epigenetics.11(1):34.2019.

Miller LE, Stevens CD. Clinical Immunology&Serology Fifth Edition a Laboratory Perspective:3-6.2021.

Moller DR. Treatment of sarcoidosis-froma basic science point of view. Journal of Internal Medecine.253:31-40.2003.

Montes CL, Rodriguez EV, Merino MC, Bermejo DA, Gruppi A. Polyclonal B cell activation in infections: infectious agents devilry or defense mechanism of the host? National university of Cordoba, Argentina .82(5):1027-32.2007.

Moodily KD, Choubey D. Cytokines in autoimmunity: Role in induction, regulation, and treatment. Journal of Interferon of cytokine Research. Pub Med Central .31(10):695-703.2011.

Moore EA. Autoimmune Diseases and Their Environmental Triggers. (1):10.2015.

Nakamizo S, Sugiura Y, Ishida Y, Ueki Y, Yonrkura S, Tanizaki H. Activation of the pentose phosphate pathway in macrophages is crucial for granuloma formation in sarcoidosis. The journal of Clinical Investigation .133(23).2023.

Nakamizo S, Egawa G, Kabashima K. Activation of the pentose phosphate pathway in macrophages is crucial for granuloma formation in sarcoidosis. The journal of clinical investigation.133(23).2023.

Nelson NC, Kogan R, Condos R, Hena KM. Emerging Therapeutic Options for Refractory Pulmonary Sarcoidosis: The Evidence and Proposed Mechanisms of Action. Journal of Clinical Medecine.13(1):15.2023.

Nunes H, Bouvry D, Soler P, Valeyre D. Sarcoidosis.Orphanet Journal of rare diseases. (2): 46.2007.

Nychowski T, Ceilley R, Wilson J. Sarcoidosis Developing During Secukinumab Therapy: case Report. The national Society for cutaneous sarcoidosis.1(2).2017.

References

Obi ON, Saketkoo LA, Russell AM, Baughman RP. Sarcoidosis: Updates on therapeutic drug trials and novel treatment approaches. Frontiers in Medicine.9:1-272022.

Olasz K. Comparative Study of Physiological and Pathological Autoimmune

Models. Department of Immunology and Biotechnology University of Pécs, Faculty of Medicine:3.2012.

Oya F, Ostiz JAM, Barbera IC, Farre MG, Carrion JA, Monte CS. Multi –organ involvement in non-pulmonary sarcoidosis. Reumatol clin (18) 309-311.2022.

Papaliodis GN. Uveitis A Practical Guide to the diagnosis and treatment of intraocular inflammation:24.2017.

Papanikolaou IC, Antonakis E, Pandi A. State of the art Treatments for sarcoidosis. Methodist Debakey cardiovascular Journal.18(2):94-105.2022.

Parija SC. Microbiology & Immunology. ELSEVIER:158-160.2012.

Pathak S, Palan U. Immunology Essentia and Fundamenta:266.2005.

Patterson KC, Hogarth K, Husain AN, Sperling AI, Niewold TB. The clinical immunologic features of pulmonary fibrosis in sarcoidosis. The journal of library and clinical medicine.160(5):321-331.2014.

Pirau L, Forshing L. Neurosarcoidosis.National Library of Medecine.2023.

Pizzini A, Bacher H, Aichner M, Franchi A, Watzinger K, Tancevski I *et al*. High expression of mTOR signaling in granulomatous lesions is not predictive for the clinical course of sarcoidosis. Respir Med:177.2021.

Pollard KM. Autoantibodies and autoimmunity: Molecular mechanisms in health. (1):4.2006.

Principles and Methods for Assessing Autoimmunity associated with Exposure to Chemicals. World health organization:1.2006.

Rajendeeran A, Tenbrock K. Regulatory T cell function in autoimmune disease. Journal of Translational Autoimmunity. (4).2021.

References

Ramachandran M, Pamulapati S, Barlas A. Aqeel A. Elderly Onset Sarcoidosis: Case Report. National Library of Medicine.13(12).2021.

Ramstein J, Broos C, Simpson L, Ansel K, Sun S. Ho M .INF-gamma Producing T –Helper 17.1 Cells are increased in sarcoidosis and are more prevalent than T-helper type 1 cells. American thoracic society:1281-1291.2016.

Redl A, Doberer K, Unterluggauer L, Kleissl L, Krall C, Mayerhofer C. Efficacy and safety of mTOR inhibition in cutaneous sarcoidosis: A Single-Centre trial. Lancet Rheumatol .6(2).81-91.2024.

Regezi J, Sciubba J, Jordon R. Oral pathology clinical pathologic correlations :114-133.2012.

Reisner H. Essentials of Rubin's Pathology. (3)340.2013.

Reisner H. Essentials of Rubin's Pathology. (12): 339.2013.

Rentier C. Autoimmune diseases: design, synthesis and immunological screening of post-translationally modified peptides to characterize autoantibodies in patient's sera. University of Cergy pontoise and University of Firenze:13.2015.

Robert B, David AK. PhillipsM.Scherger JE. Taylor TA. Johnson Jr. Family Medicine principles and practice:758.2013.

Rosen CA. Bailey's Head and Neck Surgery.2022.

Rossides M, Darlington P, Kullbeg S, Arkema EV. Sarcoidosis: Epidemiology and Clinical insights. Journal of internal medicine. (6):668-680.2023.

Ryan M. The Hashimotos Healing Diet :76.2018.

Sahoo DH, Bandyopadhyay D, Xu M, Pearson K, Parambil JG *et al*. Effectiveness and safety of leflunomide for pulmonary and extrapulmonary sarcoidosis. European Respiratory Journal.38:1145-1150.2018.

References

Sakaguchi H, Mizuochi T, Haruta M, Takase R, Yoshida S, Yamashita Y *et al*. *Aire* Gene Mutation Presenting at Age 2 Years with Autoimmune Retinopathy and Steroid-Responsive Acute Liver Failure: A Case Report and Literature Review. Frontiers in Immunology. (12).2021.

Sakkat A, Cox G, Khalidi N, Larche M, Beattie K *et al*. Infliximab therapy in refractory sarcoidosis: a multicenter real-world analysis. Respiratory Research.23(54).2022.

Shah N, Mitra A. Gastrointestinal and Hepatic Sarcoidosis: A review article. Clinical liver disease.17(4): 301-307.2021.

Sharp M, Donnelly SC, Moller DR. Tocilizumab in sarcoidosis patients failing steroid sparing therapies and anti-TNF agents. Respir Med X:1.2019.

Shen H, Yang YX, Meng X *et al*. A promising therapeutic target for autoimmune diseases. Autoimmunity Reviews .17(7):694-702.2018.

Silverstein AM. Autoimmunity versus horror autotoxicus: the struggle for recognition. Nat Immunol.2(4):279-81.2001.

Simakurthy S, Tripathy K. Ocular Sarcoidosis National Library of Medecine.2023.

Spagnolo P,Shwartz D. Genetic predisposition to sarcoidosis: another brick in the wall:778-780.2013.

Sterling G,West. Sarcoidosis. Rheumatology.1392-1400.2015.

Synovec, Mark S. ICD-10-CM/PCS coding: Theory and practice. (12).277.2021.

Talreja J, Talwar H, Baurfeld Ch, Grosman LI, Zhang K, Tranchida P, Samavati L.HIF-1α Regulates IL-1βand IL-17 in sarcoidosis. Elifesciences :8.2019.

Taylor R, Lindorfer M.A. Drug Insight: the mechanism of action of rituximab in autoimmune disease-the immune complex decoy hypothesis. Nature Clinical Practice Rheumatology.3:86-95.2007.

Thomassen MJ, Judson MA, Barna BP. Novel insights into the immunology of pulmonary granulomatous diseases:40-41.2021.

References

Tougorti M, Aydi Z, Rachdi I, Daoud F, Ben Dahou B, Boussema F. Un syndrome inflammatoire biologique révélant une sarcoidose : une latence de 3ans ! La revue de Medecine Interne.A131. 2017.

Vaqar S, Shackelford K. Pernicious Anemia. Stat Pearls.2023.

Venkatesha SH, Durai M, Moudgil KD. Epitope spreading in autoimmune diseases. Infection and autoimmunity Second Ed. (4):45-68. 2015.

Wagner T, Humbert M, Wijsenbe M. Rare diseases of the respiratory system ERS monograph 100:300.2023.

Wang L, Wang FS, Gershwin ME. Human autoimmune diseases: a comprehensive update. J Intern Med. 278(4):369-395.2015.

Wig S. Proffitt R. Anti-TNF induces sarcoidosis: A peculiar paradox. Academic rheumatology.2018.

Wang W, Wu S, Xu D, Xie D, Guo H. Inhibitor and Substrate Binding by Angiotensin-Converting Enzyme: Quantum Mechanical/Molecular Dynamics Studies. Journal of Chemical information and modeling.51(5).1074-1082.2011.

Weichhart T, Hengstschlager.Linke M. Regulation of innate immune cell function by mTOR.Nat Rev Immunol.15(10):599-614.2015.

Weinberger S, Cockrill B, Mandel J. Principles of Pulmonary Medicine:160.2008.

Wright MA, Swartz MD. Keto smart: Heal your brain and body with the ten step action plan scientifically proven to prevent or reverse, obesity, memory loss, Alzheimer, diabetes:63-64.2018.

Xiang Y, Zhang M, Jiang D, Su Q, Shi J. The role of inflammation in autoimmune disease: a therapeutic target. Frontiers in Immunology Review:4.2023.

Ye DQ, Fang XY. Progress China Epidemiology:351-366.2023.

Zeron PB, Alvarez RP. Cassals MR. Sarcoidosis. Med clin. National library of Medecine.159(4):195-204.2022.

Zhang E. Educate Act Thrive for the immune system:131.2023.

References

Zhang H, Costabel U, Dai H. The role of diverse Immune Cells in Sarcoidosis. Frontiers in Immunology.12.2021.

Zhang X, Dai Q, Shan J, Zhang S, Zhang B, Liu S *et al*. Inhibition of phosphoinositide-3 kinases gamma/delta ameliorates pulmonary granuloma by rescuiring Treg function in a sarcoidosis model. Experimental and Therapeutic Medicine. 25(5):225.2023.

Zhang Y, Jiang X, Wang Q, Jiayi W, Zhou J. Dexamethasone alleviates pulmonary sarcoidosis by regulating the TGF-β/Smad3 signaling to promote Th17/Treg cell rebalance. Journal of cellular immunology:395-336.2024.

Zhou ER, Arce S. Key Players and Biomarkers if the Adaptive Immune System in the Pathogenesis of Sarcoidosis. International Journal of Molecular Sciences.21(19).2020.

Zhou Y, Jeny F, Baughman RP. Editorial: Diagnosis and treatment of sarcoidosis. Frontiers in medicine:1-3.2023.

Zou S. Management of Rheumatoid Arthritis: from the perspective of complex network. Scientific Research Publishing. (5):102.2018.

Abstract:

The term “autoimmunity” refers to the failure of the body’s immune system to recognize its own cells and tissues as part of the self, leading to the emergence of autoimmune diseases such as sarcoidosis, a systemic granulomatous disease of unknown cause. Genetics and lifestyle play a significant role in increasing the likelihood of developing it, resulting in various symptoms of varying severity, with the lungs being the most commonly affected organ.

For effective treatment, early and accurate diagnosis of the disease is essential, followed by the use of targeted medications against the cells and molecules involved in the disease process. It’s crucial to broaden the research perspective to develop specific treatments for sarcoidosis because the diversity of changes caused by the disease makes it difficult to reach a real and effective cure.

Key words: Sarcoidosis, Autoimmunity, Autoimmune diseases, Specific treatments, Effective cure.

Résumé :

Le terme “auto-immunité” fait référence à l’échec du système immunitaire à reconnaitre ses propres cellules et tissues comme faisant partie du soi, ce qui conduit à l’émergence de maladies auto-immunes telles que la sarcoïdose, une maladie granulomateuse systémique de cause inconnue. Les facteurs génétiques et le mode de vie jouent un rôle significatif dans l’augmentation de la probabilité de développer cette maladie, ce qui entraine divers symptômes de gravités variables, les poumons étant l’organe le plus fréquemment touché.

Pour un traitement efficace, un diagnostic précoce et précis de la maladie est essentiel, suivi de l’utilisation de médicaments ciblés contre les cellules et les molécules impliquées dans le processus pathologique. Il est crucial d’élargir la perspective de la recherche pour développer des traitements spécifiques pour la sarcoïdose car la diversité des changements causés par la maladie rend difficile l’obtention d’un véritable remède efficace.

Les mots clés : Sarcoïdose, Auto-immunité, Maladie auto-immune, Traitements spécifiques, Remède efficace.

الملخص:

مصطلح المناعة الذاتية يشير إلى فشل جهاز المناعة في التعرف على خلايا الجسم الأنسجة باعتبارها جزء من الذات، مما يؤدي إلى ظهور أمراض المناعة الذاتية كالساركويد، وهو مرض مناعي حبيبي يؤثر على عدة أعضاء أو أجزاء من الجسم , غير معروف السبب والتي تلعب الوراثة ونمط الحياة دورا هاما في زيادة احتمال الإصابة به، محدثة بذلك عدة أعراض مختلفة الشدة تكون فيها الرئة العضو الأكثر استهدافا.

ومن أجل العلاج لابد من التشخيص المبكر والصحيح للمرض، ثم الانتقال للأدوية المستهدفة للخلايا والجزيئات المحدثة للمرض، وأهم ما في ذلك ضرورة توسيع الرؤية البحثية للعلاجات النوعية للساركويد لأن تنوع التغييرات التي يحدثها المرض صعّب الوصول لعلاج حقيقي وفعال.

الكلمات المفتاحية: الساركويد، المناعة الذاتية، مرض مناعي ذاتي، علاجات نوعية، علاج فعال.