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REVIEW ARTICLE

Role of Innate lymphoid cells in pathogenesis of Rheumatoid arthritis

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ABSTRACT

Background: Innate lymphoid cells (ILCs) populate within lymphoid and non-lymphoid tissues. They bridge the gap between the immune system and parenchymal tissues in non-lymphoid organs, ensuring tissue homeostasis and stabilizing immunity. Unlike T-and B-lymphocytes, the adaptive antigen receptors are not present in ILCs.

Aim: This review aims to examine the cell biology of ILCs, along with the cytokines they generate, and the current understanding of their likely pathogenic involvement in the initiation of inflammation in Rheumatoid arthritis (RA).

Conclusion: Disruption in ILC activation may lead to persistent inflammation. Patients with RA exhibit an aberrant distribution pattern and function of ILCs, which can reverse the immune system's homeostasis to inflammation, indicating ILCs' potential role in the pathophysiology of RA. Athorough analysis of ILC activity and signaling pathways would highlight these cells as possible therapeutic targets for the future.

Keywords: ILC; rheumatoid arthritis; NK cells

INTRODUCTION

According to immunologists, the immune system comprises two primary divisions, innate and adaptive. The most basic form of generic defense against invasive infections is provided by innate immunity, whereas adaptive immunity triggers a particular immune response. The adaptive immune system is primarily responsible for the development of immunological memory for future encounters with the same pathogen to accelerate the immune system's responsiveness [1].

Innate lymphoid cells (ILCs) are a recently identified subpopulation of cells that have been incorporated into the existing pool of innate immune cells. These cells make up the T-lymphocytes' innate variety. Notably, ILCs lack the manifestation of antigen receptors that usually occur in standard T- and B-subsets. ILCs generally reside amidst tissues and exhibit significant tissue-specific roles, including responding to microbial infections [2].

A growing body of research indicates that ILCs are essential for preserving tissue homeostasis. Their thrown-off reaction might lead to immunopathology, which would then lead to tissue death, autoimmune illnesses, metabolic problems, and inflammatory ailments. Individuals diagnosed with systemic sclerosis exhibit an increased quantity of cutaneous ILC2, which is directly correlated with the degree of fibrosis. Patients suffering from systemic lupus erythematosus (SLE) had altered levels of peripheral ILC1, ILC2, and ILC3 in both quantity and percentage[3] . ILCs are believed to be involved in the pathophysiology of RA, much like in other autoimmune diseases [4].

A chronic inflammatory disease, rheumatoid arthritis (RA) causes painful, rigid, and inflamed joints that eventually destroy bone and cartilage. The latest research has identified that individuals with active RA have a deregulated level of peripheral ILC1 and ILC2, which indicates their engagement in the pathogenicity of the disease[4]. RA patients' synovium is also characterised by a higher frequency of CCR6+ ILC3 cells, which generate IL-22 and IL-17[5].

The correlation between each kind of ILC and RA will be covered in depth in the following sections, with an emphasis on their promising implication in emerging immunotherapy to reduce inflammatory conditions associated with RA.

Biology of Innate Lymphoid Cells

Research on humans and animals has validated the origination of ILCs from cells of the lymphoid lineage known as common lymphoid progenitors (CLPs). This cell lineage would develop into common innate lymphoid progenitors (CILP), the precursor population of ILCs and natural killer (NK) cells. Ag-receptor reorganization does not occur in the differentiation of CILP, indicating that this mechanism is VDJ-free. The formation of NK cell precursors (NKP) and common helper innate lymphoid precursors (CHILP) is the first step in this differentiation. The generation of NK cells from NKPs requires specific transcription regulators such as “inhibitor of DNA-binding-2” (Id2), “thymocyte selection- associated high mobility group box protein” (TOX) and “nuclear factor IL-3 regulated” (NFIL-3). Conversely, CHILP generates various ILC subsets under the influence of the above mentioned three transcription elements in addition to a few additional transcription regulators, namely, GATA-3 and T-cell factor-1 (TCF-1) and interleukin-17 (IL-7) [6].

The CHILP population that expresses the transcription regulator Id2 can generate all ILC types including LTis. Owing to the non-homogenous nature of the CHILP population, cells positive for promyelocytic leukaemia zinc finger (PLZF), which is an essential transcription regulator of cell development, including type specification and cell stage expression, express all ILC variants barring LTis [7].

CHILP-progenitors' power to generate the homing receptor "lymphocyte Peyer patch adhesion molecule (LPAM)," also known as α4β7, is an additional attribute that characterises them as potential lymphoid tissue inducers (LTi) α4β7. LPAM is functionally responsible for facilitating the entry of T-cells into "gut-associated lymphoid tissue" (GALT) by adhering to the "mucosal adhesion cell adhesion molecules (MadCAM-1) present on the endothelial cells of mucosal blood vessels [6] and[8].

ILCs are classified into two groups based on their functional distinctions: cytolytic and non-cytolytic versions. ILC1 and conventional NK (cNK) cells, contributing to the cytolytic ILC group, eliminate target cells by producing the effector molecules perforin and granzyme-B and destroy the tumour and virus-infected cells. Conversely, non-cytolytic or helper ILCs, regulated by the transcription agent GATA-3, originate from a common helper innate lymphoid precursor (CHILP) [9].

Additionally, in 2018, ILCs were categorised into five groups based on their unique immunological characteristics, transcription variables, and cytokine panel generated. Specifically, natural killer (NK) cells are the inherent analogue of CD8+T-lymphocytes.

Conversely, ILC1, ILC2, and ILC3 serve as the phe notypic reflectors for the innate variations, CD4+ T-helper cells, Th-1, Th-2, and Th-17 respectively. Cytotoxic behavior is exhibited by ILC1 and NK cells only [10] and [4]. The fifth type includes lymphoid tissue inducers (LTi), playing a significant part in lymphoid organogenesis in the lymphotoxin-reliant pathway [11] and [12].

It is important to note that since the definitive identification of all ILC subsets cannot be done solely by a standard marker, it requires the application of a combination of numerous phenotypic markers to characterize mature ILCs, which renders them heterogeneous [10].

Besides their diversity, LCs are known to be CD3-negative, CD45-positive, and capable of expressing the IL-7 receptor (CD127) abundantly. Nevertheless, CD56bright NK cells demonstrate an intermediate level of CD127 expression, whereas the cytotoxic variety of NK cells (CD56 dim NK cells) lack the expression of CD127 [2].

Genesis of ILCs involves the inhibitory interplay of several transcription factors that are responsible for the differentiation of lymphocytes while stimulating the growth of ILCs. Significant molecules of E-protein transcription elements play an integral role in the initial phases of lymphocyte development, such as the production of B-lymphocytes in the bone marrow and T-cell differentiation in the thymus. Three genes, namely (*tcf3*), (*tcf4)* and (*tcf12*), encode different versions of E2A, E2-2, and HEB proteins, respectively. However, by dimerising with E-proteins through the helix-loop-helix region, an assortment of inhibitory differentiation (Id) proteins, including Id1- Id4 would hinder the functionality of these proteins. This balance between E-proteins and Id proteins is crucial for regulating the differentiation of ILCs from conventional lymphocytes [13].

Unlike adaptive immune cells, innate lymphocytes (ILCs) do not have reconfigured antigen-specific receptors, and they are mostly found in non -lymphoid tissues rather than lymphoid organs (14). The presence of ILCs in the mucosal layers of the colon, respiratory tract, bladder, skin, and decidua,

renders them a strategic position [15].

ILCs are considered an innate variation of T lymphocytes owing to their engagement in the same transcriptional mechanisms that control T lymphocytes' development and cytokine profile. T cells and ILCs function together coherently to combat external pathogens. Th-1 and ILC1 cells fight tumours, intracellular infections, and viruses. Allergens and parasites that live outside of cells are repelled by the ILC2 and Th2 subsets, whereas ILCs and T-h17 cells target external infections [14].

Numerous autoimmune diseases have been linked to dysregulated expression of ILCs, highlighting the need for a comprehensive study of ILCs' functions and signalling pathways to determine these cells' potential as effective treatment options.

Rheumatoid arthritis and immunity

Rheumatoid arthritis, characterised by a persistent inflammatory alteration in the synovial membrane, is an exceptionally widespread chronic autoimmune disease, affecting 1% of the world's population. Its basic clinical symptom manifests as symmetrical polyarthritis in minor joints along with exhaustion, fever, pain, stiffness, and oedema in several joints. The presence of autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), can precede the appearance of clinical manifestations by many years [16].

Joint deformity and gradual, irreversible bone loss a re often the end results of rheumatoid arthritis. The disease can progress to cause irreversible damage and deformity of joints, with potential complications like cardiovascular, renal, pulmonary, and mental health issues due to extra-articular inflammation [17].

Understanding the underlying mechanisms of RA is crucial for determining the cause of rheumatoid arthritis, which involves intricate interactions between genetic, environmental, and epigenetic factors, inducing disruption in immune tolerance and adaptive immune responsiveness, and stimulating the development of proinflammatory cytokines, chemokines, and autoantibodies by both T and B lymphocytes, ultimately causing chronic joint injury [12] and [16].

RA pathogenicity is related to disruption of the innate and/or adaptive immune responses. The pathophysiology of rheumatoid arthritis is defined by inflammatory cells invading the synovium, producing copious amounts of cytokines, and then destroying adjacent tissues, bones, and cartilage. Innate cells, such as macrophages are pivotal to causing synovitis by producing large amounts of proinflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-17, indicating Th1 and Th17 cells' supremacy in the surrounding environment of damaged joints [12].

Rodriguez Carrion and colleagues' (2017) analysis revealed the varying ILC subgroup distribution on the lymph nodes of RA patients, high-risk individuals (ACAP-positive patients with high IgM-RF levels, experiencing arthralgia without arthritis) and healthy subjects [18].

According to newly published studies, asthma, psoriasis, inflammatory bowel disease, and rheumatoid arthritis exemplify persistent inflammation and autoimmune conditions that can be initiated or aggravated by abnormal ILC functioning, impacting the IL-17/ IL-23 axis [19].

Role of cytolytic Innate Lymphoid cells in Rheumatoid Arthritis:

1. Conventional natural killer cells:

The initial category of ILCs to be discovered includes conventional natural killer cells that are recognised as massive granular lymphocytes, constituting 5–20% of the lymphocytes in the peripheral bloodstream. While sharing phenotypic characteristics with lymphoid cells, cNK cells lack antigen specificity due to the paucity of somatically altered antigen-specific receptors found on adaptive immune cells. As a primary defence against viral infections and tumours, cNK cells synthesise cytotoxic molecules of perforin and granzyme-B to knock out target cells [20] and [21].

The differentiation and growth of conventional NK cells rely on certain transcription regulators such as T-bet, Eomes, and homolog of Blimp-1 (HOBIT) (22). T-bet appears to be prevalent in adult NK cells, promoting responsiveness to IL-12, whereas extensive expression of Eomes in immature NK cells triggers lineage specification [23].

IL-15 is a prerequisite for the endurance, differentiation and functionality of conventional NK cells. In response to IL-12 and IL-18, cNK cells synthesise INF-γ and TNF-α ([22].

Numerous studies have demonstrated the abundance of NK cells in RA patients' synovial fluid that are pivotal in the degeneration of bones and cartilages. RA patients' synovial fluid exhibits a high concentration of the CD3- and CD56 bright NK subset. While reacting to the cytokine environment of IL-12 and IL-15, these cells induce the synthesis of the Th1 cytokine profile, TNF-α and INF-γ, and activation of cNK cells. TNF-α and INF-γ both

appear to contribute to the onset and advancement of RA [12].

Evidence has shown that conventional NK cells generate higher levels of INF-γ in comparison to their equivalents prevailing in peripheral blood. This, in turn, triggers CD14+ monocytes in the synovium to release TNF-α [12].

By decreasing osteoblast differentiation and increasi ng osteoclastogenesis, TNF-α becomes critical to bone remodelling. TNF-α receptors, TNFR1 and TNFR2, are synthesised by osteocytes; this signalling promotes t he transformation of osteocytes into osteoclasts. Exorbitant bone resorption among RA patients caused by an imbalanced increase in osteoclastogenesis is also a hallmark of periodontitis. Anti-TNF-α treatments have a strong track record of reducing inflammatory bone loss in RA [24].

TNF-α plays a critical role in the development of chronic inflammatory bone symptoms like periodontitis and RA, either directly by increased osteoclastogenesis due to synergistic reaction of TNF-α with two additional inflammatory cytokines, namely RANKL and IL-6. Alternatively, TNF-α might indirectly upregulate the synthesis of c-Fms and RANK on precursor osteoclasts, along with producing RANKL and M-CSF on osteoblasts, synovial fibroblasts and stromal cells. Consequently, it intensifies osteoclastogenesis by contending cytokines and other types of cells [25].

Additionally, NK cells serve as a primary source of INF-γ synthesis, which encourages the expression of MHC class II on antigen-presenting cells (APCs) and "INF-γ- inducible protein-10" (IP-10), referred to as CXCL10, capable of highly selective attachment with CXCR3 produced in hematopoietic cells, like NKs, CD4+, CD8+ and APCs. As a consequence, this would trigger the synthesis of osteoclastogenic cytokines from CD4+ T lymphocytes, RANKL and TNF-α [26].

RA patients experiencing bone erosion and deformation possess a unique subset of NK cells occupying their blood and synovia, sharing phenotypic similarities with non-deformative RA patients. On the other hand, the secretion of huge quantities of proinflammatory cytokines, such as TNF-α and INF-γ, after being activated by IL-2 and IL-15, renders them more vigorous. These findings pointed to the significance of synovial NK cells as potential biomarkers for disease severity in RA patients [27].

M-CSF and RANKL are the primary osteoclastogenic cytokines that control osteoclastogenesis in a physiological setting. Alternatively, oversynthesis of INF-γ, IL-6, and TNF-α greatly promotes osteoclastogenesis under particular circumstances of pathology, such as inflammatory processes in RA patients [28].

2. Group-1 Innate lymphoid cells:

Numerous identical characteristics of conventional NK and ILC1 include their reliance on HOBIT-1 and T-bet as transcription regulators (22). ILC1s have been found in large quantities in the synovial fluid and tissues of individuals suffering from inflammatory bone disorders like RA, suggesting their pathogenic function in bone destruction [31]

The primary definition of ILC1 represents them as a form of NK cells residing in tissues of the salivary glands, skin, gut, liver, and uterus. Despite possessing low levels of cytotoxicity than cNK cells, the primary effector compounds of ILC1 include INF-γ, TNF-α, and granzyme-B. The synthesis of IL-7 R is manifested by ILC1 cells [4] and [29]. TNF-α and IL-1β increase the synthesis of IL-7 in synovial stromal cells, as a result of which the macrophages synthesize increased quantities of TNF-α. IL-7 levels in synovial fluid have been found to be elevated in RA patients. IL-7 stimulates the transition of synovium-resident CD14+ monocytes into gigantic osteoclasts with multiple nuclei, which accelerates the breakdown of bones [30].

Additionally, cNK, as well as ILC1 subsets, are equitably reactive to IL-12, IL-15, and IL-18 (previously referred to as INF-γ inducer factor or IGIF). Moreover, IL-12 functions in tandem with IL-18 to increase INF-γ synthesis [11].

Fang et al.'s (2020) research indicated an abundance of ILC1 and ILC3 in the synovial fluid of juvenile patients suffering from arthritis. This finding corresponded to the increased synthesis of T-bet and INF-γ. However, findings suggest a substantial link between the extent of clinical illness and NKp44-negative ILC3 cells [12].

Role of non-cytolytic Innate Lymphoid cells in Rheumatoid Arthritis:

1. Group-2 Innate Lymphoid cells

The presence of transcription factor BCL-11B characterises group-2 innate lymphoid cells. Research conducted both *in vitro* and *in vivo* has demonstrated that innate lymphoid cell progenitors (BCL-11B ILPs) producing BCL-11B are essential

for ILC2 development, which may be hampered by the inhibition of this transcription factor in BCL-11B ILPs. Moreover, GATA3 plays a crucial role in transcriptional regulation that limits ILCs to the ILC2 lineage. The widespread synthesis of IL-33 receptors on the exterior of ILC2 cells leads to the generation of Th2 cytokine profile, IL-4, 5, 9, 13, and amphiregulin (31), demonstrating high responsiveness to this cytokine [31].

IL-33 serves as a reactive biomarker among RA-affected individuals. Elevated levels of IL-33 and its receptor ST2 in serum and synovium correlate with poor disease prediction, excessively severe symptoms, and increased disease activity [32].

Peripheral ILC2 level is lower in RA patients enduring the active stage of the disease than in the patients undergoing remission. Although peripheral ILC2 counts are inversely correlated with the "disease activity score-28" (DAS-28), they surge significantly following the anti-inflammatory medication (12). RA patients' blood and synovial fluid have greater quantities of IL-9,

which is a pleiotropic cytokine that has been linked to inflammatory remission [33].

IL-9, a cytokine produced by both ILC2 and Th9 cells, has crucial significance in coordinating the treatment of RA. Mice lacking IL-9 (IL-9 -/- mice) suffered from severe arthritis with significant bone and cartilage loss, as well as decreased ILC2 and Treg cell propagation and stimulation. Conversely, administration of IL-9 to mice increased the activation of Treg cells that are reliant on ILC2, alongside the reduction of inflammation and articular safety [34].

IL-9 contributes to bone destruction and osteoclastogenesis among RA patients through increased synthesis of metalloproteinase. Therefore, inhibiting IL-9 may stop progressive bone degradation among RA patients. The treatment of the IL-9 axis and/or the osteoclastogenesis mechanism may prove to be a promising therapeutic approach to avert bone deterioration in RA patients. It has been proposed that ILC2 may have an immunoregulatory and anti-inflammatory function in mitigating the effects of RA.[34].

Mechanism underlying the healing process of arthritis relies on the activation of ILC2, depending on IL-9, which consequently stimulates activation and synthesis of T reg cells, and enhances inhibitory function in GITR/GITRL and ICOS/ICOSL-dependent approaches [34].

According to an *in-vivo* investigation, mice with ILC2 deficiency displayed exacerbated arthritis, whereas the augmented concentration of these cells via adoptive transfer technique or IL-25/IL-33 gene treatment would considerably ameliorate arthritis and stop bone deterioration [35].

Another *in-vivo* investigation showed that inhibiting the IL-33/IL-33 R axis by deleting the IL-33 R gene, administering ST2, or using certain anti-IL-33 R antibodies would lessen the severity of arthritis. On the other hand, the mouse model with collagen-induced arthritis suffers from exacerbated illness upon systemic treatment with IL-33. The physiological activity of IL-33 is facilitated by its receptor, IL-33 R, which is widely expressed in immune cells such as Th2, T regs and ILC2. Furthermore, IL-33's implication in Th2 immunity and regulation of inflammatory reactions by proactively encouraging ILC2 proliferation has been proven in a number of earlier studies. Conversely, immunosuppressive T regs function is ceased by IL-33 R deficit [36].

In 2018, Hirota K. et al. identified the release of IL-2, IL-33, and CD289 (TLR9) ligands as a result of injury to synovium tissues. This triggers ILC2 cells to release GM-CSF, which is a major cause of osteoarthritis and pain in mice; however, ongoing treatment with certain monoclonal antibodies would eliminate pain entirely and lessen the severity of arthritis [37].

2. Group- 3 Innate Lymphoid cells:

ILC3s, along with Th17 cells, have a common transcription regulator RORγt and produce similar cytokines, namely IL-17, IL-22, and GM-CSF while responding to IL-23 and IL1β, thus reflecting Th17. LTi participate in immunological regulation [22] and [38].

ILC3 representing the predominant cytokine manufacturers of IL-17 and IL-23 are present in two varieties: NKP46+ and NKP46-, CCR6+. Individuals suffering from RA may

partake in the development of the disease's pathoph ysiology due to the elevated levels of the ILC3 cells in their swollen joints.

The experimental arthritis group with a greater percentage of CCR6+ ILC3 cells generated more molecules of IL-17A and IL-22 in comparison to the control group. CCR6+ ILC3 cells are abundant in the synovial fluid of inflamed joints in RA patients, generating a signific ant quantity of IL-17, and favourably correlated with fragile and inflamed joints [39].

The synovial fluid of RA patients' joints encompasses high concentrations of ILC1 and ILC3, which reflects a positive correlation with the disease intensity. ILC3 cells, expressing CD3, CD56+, NKp44+, and CCR6+, were found in greater quantities in RA patients' synovium and peripheral blood, linked to the increased synthesis of IL-17 and IL-22, which in turn exacerbates clinical acuity [5].

3. Lymphoid tissue inducer cells:

The identification of lymphoid tissue inducer cells (LTi), dating back to the late 20th century, precedes the conceptualisation of ILCs in 2008-2009 [14].

The CHILP population producing the transcription regulator Id2 is capable of generating all ILCs, including LTis. Considering the non-homogeneous nature of the CHILP population, PLZF-positive cells express all ILC versions except LTis. PLZF is a vital transcription factor required for cell development activity, including type specification and cell stage expression (7). According to *in vivo* research, LTi is not involved in the formation of the spleen or tertiary lymph nodes, but it is necessary for the subsequent growth of secondary lymphoid tissues and the payer's patch [14].

Like ILC3, LTi cells' dependence on ROR-yt for growth renders them a part of the ILC3 subset. While the specific cytokines that induce LTi remain unknown, these cells have been shown to generate GM-CSF, IL-8, IL-17, IL-22, TNF-α, TNF-β, and lymphotoxin [4]. Lymphotoxin, a member of the TNF superfamily, is important for immunological homeostasis and coordinating the growth and maintenance of lymphoid tissues. Notably, LTi cells are imperative for lymphoid organ development via the synthesis of lymphotoxin and TNF-α .Surface CCR6, extensively produced by LTi, is important for secondary lymphoid organ development throughout embryogenesis.[40].

In comparison to the healthy controls, Rodriguez Carrio et al.'s (2017) study found less LTi in LN samples obtained from RA patients who tested positive for IgM-RF and/or ACAP. Additionally, the expression of adhesion molecules VCAM and ICAM on stromal cells in RA patients may contribute to altered LTi cell distribution, highlighting the role of these cells in RA pathogenicity in a stromal cell-dependent pattern [18].

In comparison to the healthy controls, RA patients' lymph node biopsies revealed a higher proportion of ILC1 and ILC3, but reduced counts of LTi (P-values ≤0.05, 0.05, and 0.001, respectively). ILC1 levels were higher in those at risk of developing RA than in the healthy subjects (P-value < 0.01) [18].

Conclusion:

Twelve separate studies have discovered a novel het erogeneous subpopulation of non-T and non-B lymphoid cells during 2008-2009. These cells vary from traditional lymphoid cells in the expression of antigen-specific receptors and are also devoid of the recombination activating genes. These cells are designated as ILCs because of their potential to serve as effective innate immune responders. ILCs are responsible for wound healing, immunological homeostasis, tissue repair, and pathogen removal. Unlike conventional lymphoid cells, the inhibition of specific transcription regulators influences the development of immature lymphocytes (ILCs) from appropriate progenitor cells.

ILCs build up in bodily fluids and tissues in inflammatory illnesses such as autoimmune diseases. Abnormal ILC distribution has been observed in RA patients since the early stages of the disease, highlighting the significance of these cells as possible contributors to the pathogenicity and progression of RA. This disorder is characterised by dysregulated frequency and percentage of ILCs, implying an increase in cNK, ILC1, ILC2, and ILC3, alongside a deficit of LTi cells. These findings have garnered interest in these cell divisions as potential targets for future therapeutics aimed at treating or preventing RA.

Conflict of interest: Author declares none.

I declare that this review article has not been submitted to any other journal.

REFERENCES

1- Borgia F, Li Pomi F, Alessandrello C, Vaccaro M, Gangemi S. Potential Role of Innate Lymphoid Cells in the Pathogenesis and Treatment of Skin Diseases. J Clin Med. 2023;12(8).

2- Meininger I, Carrasco A, Rao A, Soini T, Kokkinou E, Mjösberg J. Tissue-Specific Features of Innate Lymphoid Cells. Trends Immunol [Internet]. 2020;41(10):902–17. Available from: https://doi.org/10.1016/j.it.2020.08.009

3- Jiang Y, Zhao Y, Liu Y, Huang Q, Meng W, Xu H, et al. Imbalanced innate lymphoid cells are associated with disease activity and arthritis involvement in patients with systemic lupus erythematosus. Arch Rheumatol. 2020;35(4):521–32.

4- Clottu AS, Humbel M, Fluder N, Karampetsou MP, Comte D. Innate Lymphoid Cells in Autoimmune Diseases. Front Immunol. 2022;12(January):1–10.
5- Takaki-Kuwahara A, Arinobu Y, Miyawaki K, Yamada H, Tsuzuki H, Irino K, et al. CCR6+ group 3 innate lymphoid cells accumulate in inflamed joints in rheumatoid arthritis and produce Th17 cytokines. Arthritis Res Ther. 2019;21(1):1–9.
6- Lai DM, Shu Q, Fan J. The origin and role of innate lymphoid cells in the lung. Mil Med Res [Internet]. 2016;3(1):1–10. Available from: http://dx.doi.org/10.1186/s40779-016-0093-2
7- Liu TM, Lee EH, Lim B, Shyh-Chang N. Concise Review: Balancing Stem Cell Self-Renewal and Differentiation with PLZF. Stem Cells. 2016;34(2):277–87.
8- van de Pavert SA. Lymphoid Tissue inducer (LTi) cell ontogeny and functioning in embryo and adult. Biomed J [Internet]. 2021;44(2):123–32. Available from: https://doi.org/10.1016/j.bj.2020.12.003
9- Fol M, Karpik W, Zablotni A, Kulesza J, Kulesza E, Godkowicz M, et al. Innate Lymphoid Cells and Their Role in the Immune Response to Infections. Cells. 2024;13(4):1–22.
10- Chung DC, Jacquelot N, Ghaedi M, Warner K, Ohashi PS. Innate Lymphoid Cells: Role in Immune Regulation and Cancer. Cancers (Basel). 2022;14(9):1–22
11- Castellanos JG, Longman RS. The balance of power: Innate lymphoid cells in tissue **inflammation and** repair. J Clin Invest. 2019;129(7):2640–50
12- Fang W, Zhang Y, Chen Z. Innate lymphoid cells in inflammatory arthritis. Arthritis Res Ther. 2020;22(1):1–7
13- Pankow A, Sun XH. The divergence between T cell and innate lymphoid cell fates controlled by E and Id proteins. Front Immunol. 2022;13(August):1–12.
14- Vivier E, Artis D, Colonna M, Diefenbach A, Di Santo JP, Eberl G, et al. Innate Lymphoid Cells: 10 Years On. Cell. 2018;174(5):1054–66
15- Vacca P, Vitale C, Munari E, Cassatella MA, Mingari MC, Moretta L. Human innate lymphoid cells: Their functional and cellular interactions in decidua. Front Immunol. 2018;9(AUG):1–8.
16- Jang S, Kwon EJ, Lee JJ. Rheumatoid Arthritis: Pathogenic Roles of Diverse Immune Cells. Int J Mol Sci. 2022;23(2).
17- Wang T, Rui J, Shan W, Xue F, Feng D, Dong L, et al. Imbalance of Th17, Treg, and helper innate lymphoid cell in the peripheral blood of patients with rheumatoid arthritis. Clin Rheumatol [Internet]. 2022;41(12):3837–49. Available from: https://doi.org/10.1007/s10067-022-06315-8
18- Rodriguez-carrio J, Hahnelin J, Ramwadhdoebe TH, Semmelink J. Brief Report: Altered Innate Lymphoid Cell Subsets in Human Lymph Node Biopsy Specimens Obtained During the At-Risk and Earliest Phases of Rheumatoid Arthritis. Arthritis Rheumatol. 2017;69(1):70–6.
19- Schinocca C, Rizzo C, Fasano S, Grasso G, La Barbera L, Ciccia F, et al. Role of the IL-23/IL-17 Pathway in Rheumatic Diseases: An Overview. Front Immunol. 2021;12(February):7–10.
20- Shin E, Bak SH, Park T, Kim JW, Yoon SR, Jung H, et al. Understanding NK cell biology for harnessing NK cell therapies: targeting cancer and beyond. Front Immunol. 2023;14(July):1–21.
21- Yang F, Luo X, Zhu W, Li J, Zheng Z, Zhu P. Dysregulation of Innate Lymphoid Cells in Patients with Active Rheumatoid Arthritis and Mice with Collagen-Induced Arthritis. Mediators Inflamm. 2021;2021(di).
22- Calvi M, Di Vito C, Frigo A, Trabanelli S, Jandus C, Mavilio D. Development of Human ILCs and Impact of Unconventional Cytotoxic Subsets in the Pathophysiology of Inflammatory Diseases and Cancer. Front Immunol. 2022;13(May):1–13.
23- Zhang J, Le Gras S, Pouxvielh K, Faure F, Fallone L, Kern N, et al. Sequential actions of EOMES and T-BET promote stepwise maturation of natural killer cells. Nat Commun [Internet]. 2021;12(1):1–17. Available from: http://dx.doi.org/10.1038/s41467-021-25758-2.
24- Kitaura H, Marahleh A, Ohori F, Noguchi T, Nara Y, Pramusita A, et al. Role of the Interaction of Tumor Necrosis Factor-α and Tumor Necrosis Factor Receptors 1 and 2 in Bone-Related Cells. Int J Mol Sci. 2022;23(3).
25- Kitaura H, Marahleh A, Ohori F, Noguchi T, Nara Y, Pramusita A, et al. Role of the Interaction of Tumor Necrosis Factor-α and Tumor Necrosis Factor Receptors 1 and 2 in Bone-Related Cells. Int J Mol Sci. 2022;23(3).
26- Kato M. New insights into IFN-γ in rheumatoid arthritis: role in the era of JAK inhibitors. Immunol Med. 2020;43(2):72–8.
27- Yamin R, Berhani O, Peleg H, Aamar S, Stein N, Gamliel M, et al. High percentages and activity of synovial fluid NK cells present in patients with advanced stage active Rheumatoid Arthritis. Sci Rep. 2019;9(1):1–12
28- Gao Y, Grassi F, Ryan MR, Terauchi M, Page

K, Yang X, et al. IFN-γ stimulates osteoclast formation and bone loss in vivo via antigen-driven T cell activation. J Clin Invest. 2007;117(1):122–32.
29- Taggenbrock RLRE, van Gisbergen KPJM. ILC1: Development, maturation, and transcriptional regulation. Eur J Immunol. 2023;53(2):1–12.
30- Churchman SM, Ponchel F. Interleukin-7 in rheumatoid arthritis. Rheumatology. 2008;47(6):753–9.
31- Yao H ci, Zhu Y, Lu H yan, Ju H min, Xu S qing, Qiao Y, et al. Type 2 innate lymphoid cell-derived amphiregulin regulates type II alveolar epithelial cell transdifferentiation in a mouse model of bronchopulmonary dysplasia. Int Immunopharmacol [Internet]. 2023;122(April):110672. Available from: https://doi.org/10.1016/j.intimp.2023.110672
32- Ouyang T, Song L, Fang H, Tan J, Zheng Y, Yi J. Potential mechanistic roles of Interleukin-33 in rheumatoid arthritis. Int Immunopharmacol [Internet]. 2023;123(August):110770. Available from: https://doi.org/10.1016/j.intimp.2023.110770
33- Kar S, Gupta R, Malhotra R, Sharma V, Farooque K, Kumar V, et al. Interleukin-9 facilitates osteoclastogenesis in rheumatoid arthritis. Int J Mol Sci. 2021;22(19).
34- Rauber S, Luber M, Weber S, Maul L, Soare A, Lin N, et al. HHS Public Access. 2018;23(8):938–44
35- Omata Y, Frech M, Primbs T, Lucas S, Andreev D, Scholtysek C, et al. Group 2 Innate Lymphoid Cells Attenuate Inflammatory Arthritis and Protect from Bone Destruction in Mice. Cell Rep. 2018;24(1):169–80
36- Yi XM, Lian H, Li S. Signaling and functions of interleukin-33 in immune regulation and diseases. Cell Insight [Internet]. 2022;1(4):100042. Available from: https://doi.org/10.1016/j.cellin.2022.100042.
37- Hirota K, Hashimoto M, Ito Y, Matsuura M, Ito H , Tanaka M, Watanabe H, et al. Autoimmune Th17 Cells Induced Synovial Stromal and Innate Lymphoid Cell Secretion of the Cytokine GM-CSF to Initiate and Augment Autoimmune Arthritis. Immunity . 2018; 48(June), 1220–1232
38- Zhang J. The role of group 3 innate lymphoid cell in intestinal disease. Front Immunol. INF2023;14(April):1–13.
39- Wu X. Innate Lymphocytes in Inflammatory Arthritis. Front Immunol. 2020;11(September):1–12.
40- Sato Y, Silina K, van den Broek M, Hirahara K, Yanagita M. The roles of tertiary lymphoid structures in chronic diseases. Nat Rev Nephrol. 2023;19(8):525–37.

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