Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL09, ISSUE 04, 2018

A Multidisciplinary Study on the Pathophysiological and Molecular Link between Psoriasis and Psoriatic Arthritis: Dermatological and Orthopedic Perspective

Dr. Shefali Singhal[1], Dr. Neelesh Damani[*2]

1Assistant Professor Department of Dermatology (Skin & VD) Krishna Mohan Medical College & Hospital, Mathura (UP)

2Assistant Professor Department of Orthopedics Santosh Medical College & Hospital Ghaziabad

Corresponding Author

Dr. Neelesh Damani

Assistant Professor Department of Orthopedics Santosh Medical College & Hospital Ghaziabad

ABSTRACT

Psoriasis and psoriatic arthritis (PsA) are two inflammatory autoimmune diseases with significant genetic basis that share some clinical and pathological features but have different manifestations. This research paper is a multidisciplinary study examining skin joint interaction at pathophysiological and molecular levels concerning the IL-23/IL-17 axis, genetic biomarkers HLA-Cw6 and HLA- B27 along with cytokines such as TNF-α. The systematic literature review of secondary studies that was conduct with papers from 2010 to 2018 established that nail psoriasis and biomarkers could indicate the development of PsA in the future. The histopathological changes would also indicate the extent of organ involvement in psoriatic conditions. The research paper also discusses the diagnostic issues and focuses on the role of combination diagnosis of dermatological problems with orthopedic ones. The main identification of such symptoms and then providing the appropriate intervention needs to be a priority to ensure an improved prognosis for the condition.

Keywords: ***Psoriasis, Psoriatic Arthritis, IL-17, IL-23, TNF-α, HLA-Cw6, HLA-B27, Nail Psoriasis, Skin–Joint Transition, Biomarkers, Systemic Inflammation*****.**

Introduction

Immunologic skin disease, known as psoriasis, is estimate to occur in 2-3% of the world population and up to 30% of the individuals with psoriasis will develop psoriatic arthritis, a progressive joint inflammation. It is especially important to diagnose soon after the onset of the disease to avoid severe joint deterioration and complications. However, the clinical indicators exist under different specialty fields even though they have some immuno-pathological similarities. PsA represents a complex comorbid state with, independent autoimmune disease in itself and its relation to psoriasis is not clear, hereby presenting the possible molecular and pathophysiologic links between psoriasis and psoriatic arthritis, and why dermatologist and orthopedic approaches may needed. Thus, in covering these two perspectives, the research aims to improve the diagnostic accuracy of diabetes-related diagnoses and provide a comparative analysis for the holistic management of a patient.

Literature Review

Immunological and genetic overlap

According to Boutet *et al*.2018, In this study the author discuss about the determination of the fracture risk and assessment of the presence of Heidelberg Decision Score (HDS) independent of the progression of structural damage and the beginning of PsA demonstrate that there is a significant immunology link between psoriasis and PsA. While the author, state that this inflammatory pathway is common in both conditions, the manifestation of this pathway is different in the skin and joint tissues leading to clinical differences. IL-23 is known to promote the development of Th17 cells and maintain their lifecycle and Th17 cells in turn secrete IL-17 cytokine, which reportedly is involved in the proliferation of epithelial cells and synovial inflammation (Boutet *et al*.2018). In addition, human leukocyte antigen Cw6 is strongly relate to cutaneous psoriasis, while HLA B27 is attach to PsA and axial involvement. This shows a critical point like psoriatic disease and underlines the need for broad studies about common and different pathogenesis, as it will make a positive impact on the development of ameliorated therapies and the identification of new diagnostic methods.

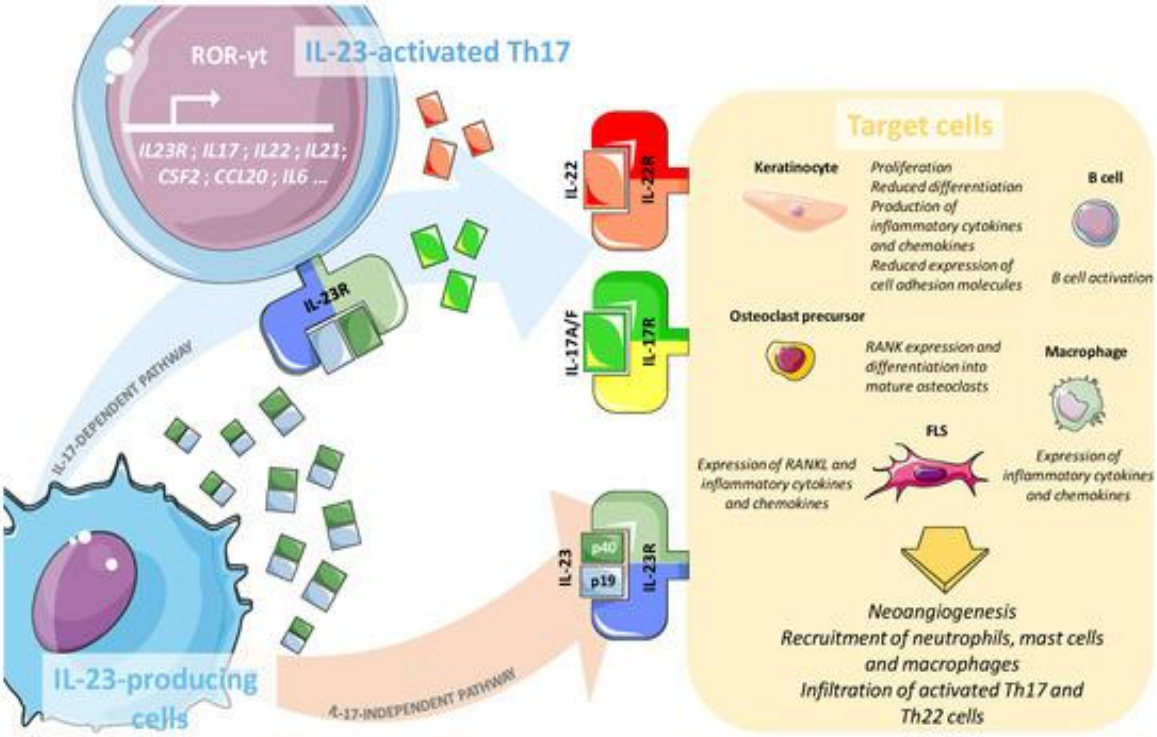

Figure 1: The main IL-23/IL-17 axis

(Source: Boutet *et al*.2018)

Skin-joint transition: theories of pathogenesis

According to Suzuki *et al*.2014, In this research, there is a detailed review of the transition of cutaneous psoriasis to PsA suggesting that IL-23/IL-17 plays major roles in progression. The authors suggest that this axis promotes a pro-inflammatory environment both in the skin and in joints, although the conversion may elicited by tissue-specific stimuli. According to key ideas, long-term skin inflammation causes systemic immune activation, effector T cells, and cytokines in enthuses and synovial tissues. In individuals carrying the HLA-B27 gene, mechanical stress may also increase essentially local inflammation of the joints (Suzuki *et al*.2014). This also has further validated the idea of psoriatic disease not just separate ailment but rather as a disease process involving different organs and tissues at the body's skin and joints. This is why knowledge of the characteristic skin–joint transition is crucial for early assessment of PsA and the initiation of treatment.

Role of cytokines

According to Mylonas, and Conrad 2018, this study discusses the immunological interplay between TNF and type I interferons in psoriasis and the focus is on diagnostics, challenges, and connection syndromes. They explain how classical psoriasis and psoriasis induced by anti-TNF therapies are clinically present in a similar manner while the biological mechanisms are different. This renders the diagnosis process challenging, particularly when attempting to determine the clinical status of patients who are under biologic therapy with atypical or new skin manifestations. Besides, clinical manifestations of psoriasis and psoriatic arthritis (PsA) somewhat mimic each other and joint involvement may remain undetected for some time (Mylonas, and Conrad 2018). It is not uncommon to have diagnostic errors, which may manifest as underdiagnoses or misdiagnosis especially in early or oligo symptomatic PsA. It is imperative to identify the differences in the difference and similarities between the immune system responses and biomarkers for the different subtypes of psoriatic disease and other related conditions.

Cytokine	Cellular source	Receptor	Targets	Role in Pso/PsA
IL1β	Macrophages, T cells	ILR1	Keratinocytes, FLS, ECs, OB	Inflammation, osteoclastogenesis, angiogenesis, Th17 amplification
IL6	Macrophages, T cells	IL6R/gp130	DC, macrophages, T cells	Inflammation, acute phase response
IL12	Th1, monocytes, macrophages	IL12Rβ 1/2		Th1 differentiation, inflammation, NK activation
IL17A, IL17F	Th17, mast cells, macrophages DCs, NK cells, CD8 T cells	IL17RA/IL17RC	Keratinocytes, FB, OC	Inflammation, neutrophil recruitment, osteoclastogenesis, angiogenesis
IL23	T cells, mast cells, macrophages, DC	IL12Rβ/IL23R	Th17, mDC, OC	Th17 differentiation, mDC activation, osteoclastogenesis
IL20	Monocytes	IL20Rα/β	Th17	Inflammation
IL22	Th17, NK cells, mast cells	IL22Rα/IL10Rβ	Keratinocytes, FLS	Host defence, Keratinocytes and FB proliferation, inflammation
TNFα	Macrophages, mDC, pDC keratinocytes, FB, Th17	TNFαR1/TNFαR2	mDc, macrophages, keratinocytes, FLS	Proinflammatory, DC activation, immune cells recruitment, angiogenesis Keratinocyte proliferation, osteoclastogenesis, Th17 amplification
IFNα	pDC	IFNαR	mDC	Initation of immune response
IFNγ	Macrophages, mDC, Th1, Th17	IFNγR	mDC, macrophages	Th1 differentiation, inflammation
TGFβ	Macrophages, mDC	TGFβR1/TGFβR2	Keratinocytes, FLS, T cells	Keratinocyte proliferation, inflammation, Th17 differentiation, angiogenesis
RANKL	T cells, FB, FLS, OB	RANK	Synovial lining layer	Osteoclastogenesis
OPG	OB, FLS	RANKL decoy R	EC below synovial lining	Osteoclastogenesis inhibition

Figure 2: Cytokines involved in Pso and PsA

(Source: Mylonas, and Conrad 2018)

Histopathological and molecular similarities

According to Marinoni *et al*.2014, The author has stated that cytokines play a vital role in the development of psoriatic disease especially the cytokines in the Th17 axis. It is an established fact that, IL-23 is involved in the determination and survival of Th17 cells, and in turn, Th17 secretes IL-17, which is seen as having a major role in keratinocyte activation meditations and joint inflammation. Thus, it is rather more convenient to talk about Th1/Th2 skewing concerning certain cytokines and report that both IFN-g and IL-12, produced in obscene amounts by the sources in

the chronic inflammation setting, are Th1-related cytokines. Another pro-inflammatory cytokine familiar with psoriasis and PsA is TNF-α which also interacts with IL-17 and IL-23 to enhance inflammation reactions (Marinoni *et al*.2014). This constant interaction enhances the inflammatory cycle in skin and joint tissues which in turn feedback on the other two cytokines resulting in the continuous perpetration of this process. This cytokine network does not only mark the disease advancement but also offers a therapeutic intercession point and numerous biologics against TNF-α, IL-17, and IL-23 illustrate effectiveness.

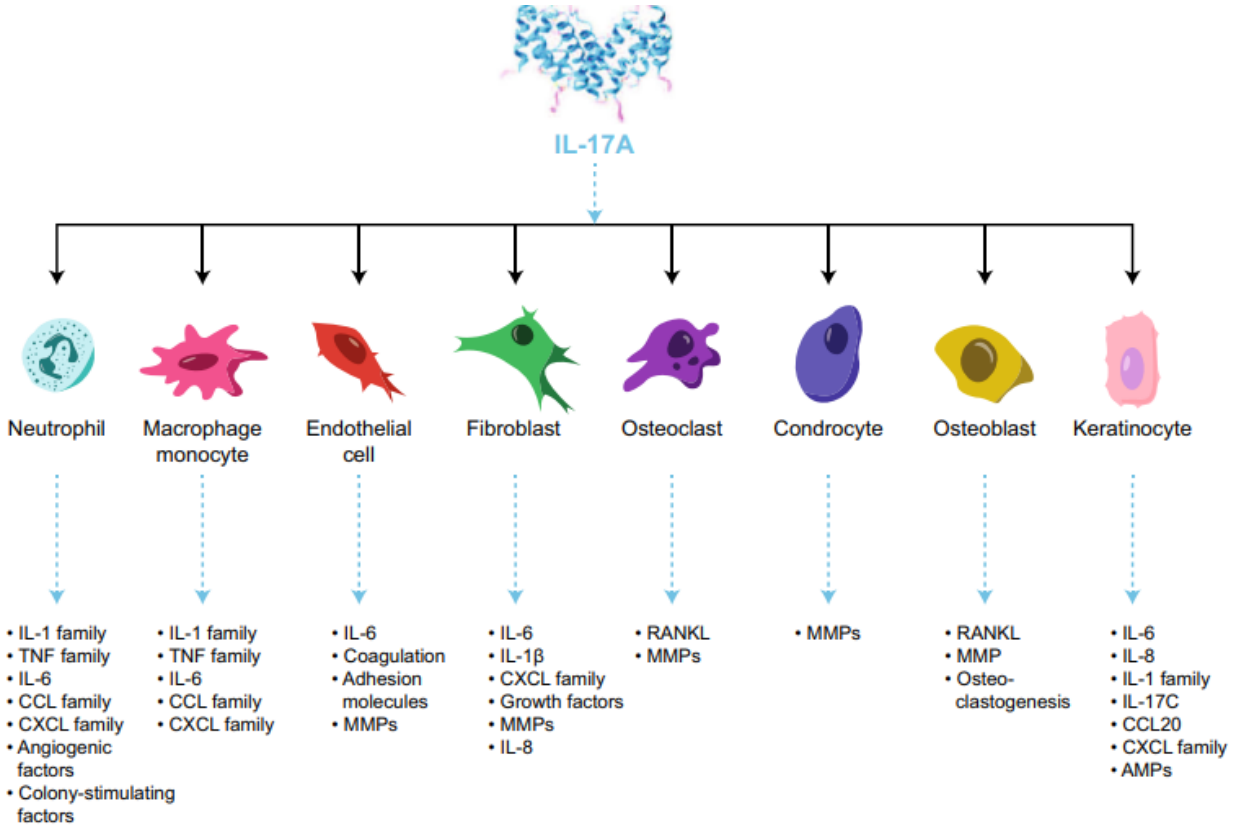

Figure 3: Effects of IL-17 on different cellular targets

(Source: Marinoni *et al*.2014)

Diagnostic challenges and overlap syndromes

According to Blauvelt, and Chiricozzi 2018, the author of this research has mainly focused on the pressure on the histopathological and molecular similarity of psoriasis and PsA focusing on the IL-17-dependent inflammation. Both conditions are associated with increased T cells that produce IL-17, mainly Th17 and Tc17 cells and therefore evoking chronic inflammation in skin

and joint tissue. In psoriasis, IL-17 stimulates the process of hyper-proliferation of keratinocytes and neutrophil infiltration in the skin, while in PsA, it leads to synovial proliferation and activation of osteoclasts (Blauvelt, and Chiricozzi 2018). Depending on the type of lesion, the histological differences between these diseases could be minimal: the tissues appear to infiltrated with immune cells and cytokines. Therefore, from the skin and joint lesions point of view IL-17 and its related pathways are involved consistently and suggest a similar immunopathogenetic process. These shared molecular profiles provide evidence for the idea of psoriatic disease as a systemic inflammatory process across skin and joint disease; and considerations for IL-17 inhibition, including cutaneous and arthritis.

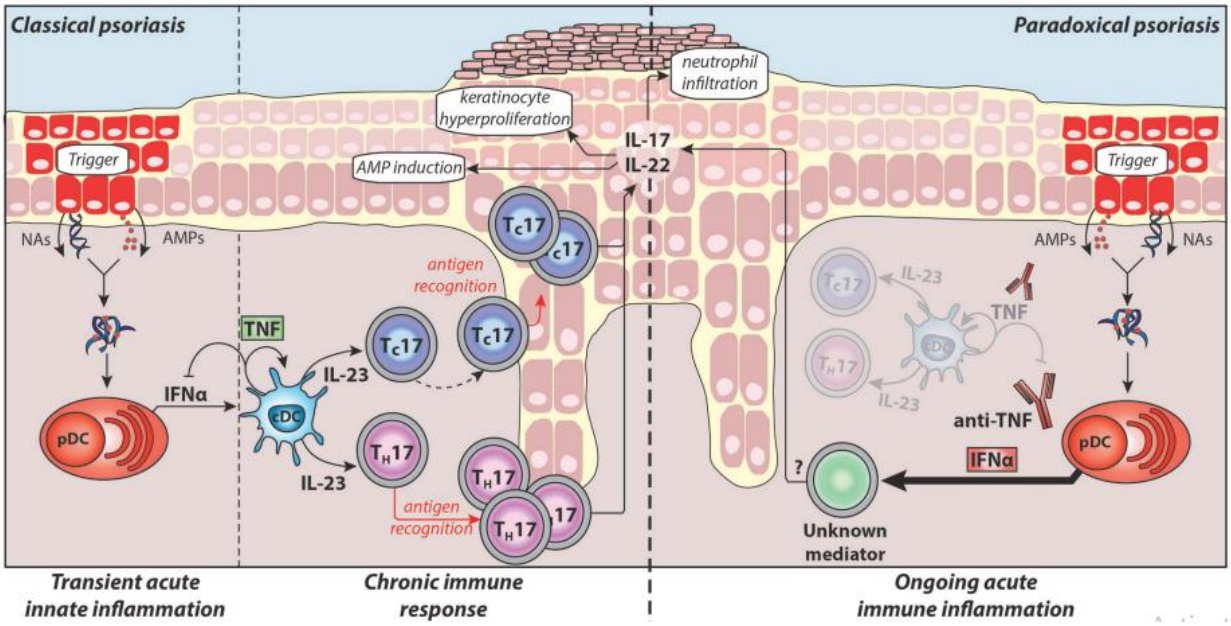

Figure 4: Pathogenesis of classical plaque psoriasis and paradoxical psoriasis

(Source: Blauvelt, and Chiricozzi 2018)

Methods

Research design

The research study followed a qualitative research approach, which utilized secondary data analysis to examine the relationship between molecules and pathophysiology of psoriasis and psoriatic arthritis. When analyzing data collect from currently available scholarly publications, both dermatological and orthopedically perspectives is employ. The study meant that it collected only peer-reviewed articles, clinical reviews, and research papers to identify specific themes to address in the study (PLAN, 2010). A qualitative method of study is use to capture and describe

the immunological, genetic, and clinical relationships that may exist. This structure accords with an interdisciplinary perspective of psoriatic disease rather than using first-hand experiential or quantitative findings.

Data collection

Secondary data was collect from the scientific articles and journals which were published from 2010 through 2018 using databases such as PubMed, Science Direct, MDPI, and Google Scholar using relevant keywords like ‘psoriasis’, ‘psoriatic arthritis’, ‘IL-17’, ‘TNF-α’, ‘HLA-Cw6’, and ‘pathogenesis’. Identifying the most relevant papers is done in the following way, only articles in English were in the list, the availability of the full text and the papers dealing with dermatological or orthopedic aspects of the psoriatic disease were consider. Preferably, the studies to review were systematic reviews, meta-analyses, trials, and molecular studies that provide specific details about immunological responses and genetic variations (Costanzo, and Spinelli 2016). The data collection is done purposively to capture the most appropriate data that reflected to the thematic areas and methodological quality with reasonable qualitative research practices.

Data analysis

The information collected is subjected to thematic analysis to derive themes most common in the immunologic, genetic, and clinical connection between psoriasis and psoriatic arthritis. The summary of the manuscript was develop based on particular sections of select literature, which were addressed under headings like cytokines, genetic factors, the process of skin Joint transition, and diagnosis. Particular focus was made to make cross-references between dermatological and orthopedic views (Kolliker Frers *et al*.2017). If there is an existence of multiple sources and findings, they were triangulate to ensure rigor. It was possible to construct a proper storyline of psoriatic disease based on the qualitative synthesis of data while admitting the weaknesses and limitations of the research.

Results

The key molecule pathways linking skin and joint inflammation

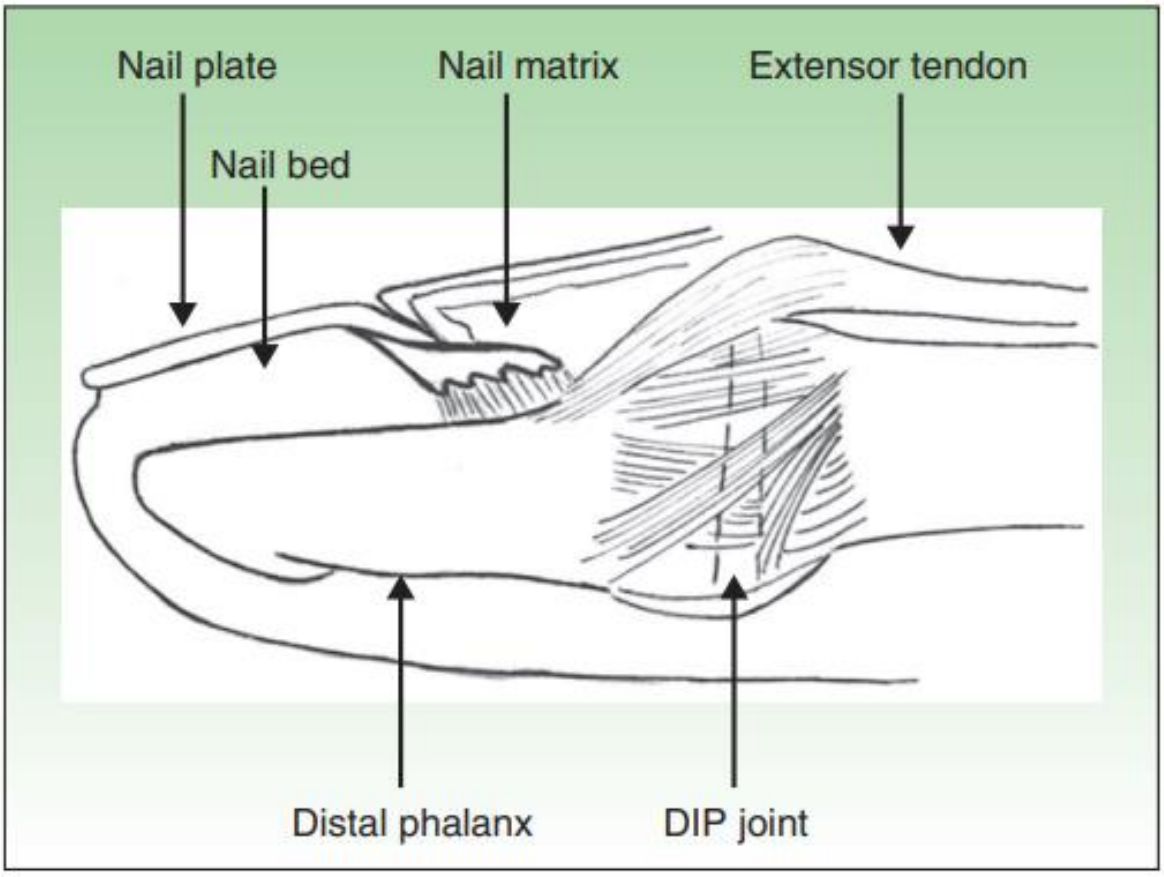

Figure 5: Anatomical relationship between the nail and distal Interphalangeal extensor tender enthuses

(Source: Smith, and Colbert 2014)

The study indicates that the involvement of the IL-23/IL-17 axis plays a crucial role in the communication between the skin and joint involvement in the pathogenesis of psoriatic disease. IL-23 is involved in the development of Th17 cells that produce IL-17 cytokine that induces the proliferation of keratinocytes in the skin and synovial fibroblast and osteoclast in joints. This common path in concert promotes chronic inflammation in both tissues with suggestions of molecular link between the two conditions: psoriasis and psoriatic arthritis. This study also acknowledges the involvement of IL-22 and GM-CSF as other factors that enhance joint and ethereal inflammation (Smith, and Colbert 2014). The studies highlighted in this article illustrate

a systemic process of psoriatic disease and draw attention to early and specific pathways in intervention.

Shared biomarkers

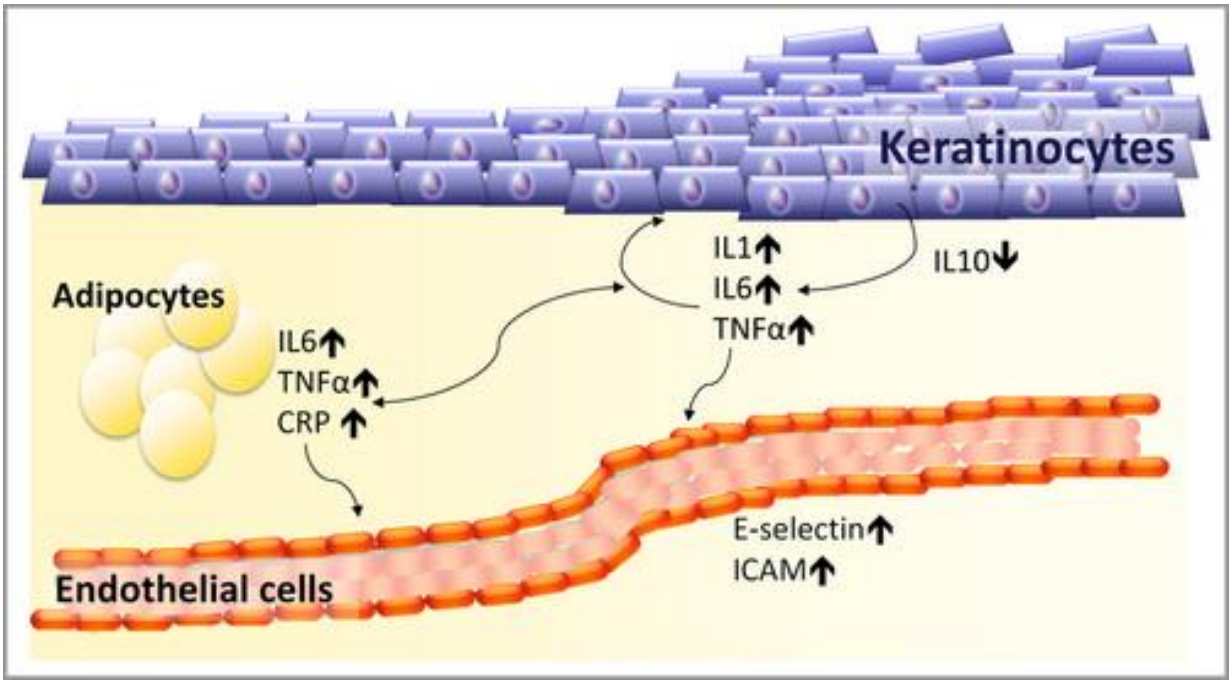

Figure 6: The role of the inflammatory markers

(Source: Dowlatshahi *et al*.2013)

According to the study, also a published systematic review and meta-analysis found a significant increase in the level of systemic inflammation in patients with psoriasis most specifically high sensitivity C - reactive protein, interleukin 6 and tumor necrosis factor-alpha. All of these biomarkers was raised significantly in the psoriasis group compared to the control group, and this suggested a chronic low grade of inflammation in persons with the skin condition (Dowlatshahi *et al*.2013). The study confirms the opinion that psoriasis is not just a skin disease rather there is immune activation in almost every organ including the one that leads to psoriatic arthritis. These biomarkers are useful for diagnostics as well as for assessment of the psoriatic disease severity and progression, therefore their use in the context of diagnosis and disease tracking is justified.

Dermatological signs predictive of PsA development

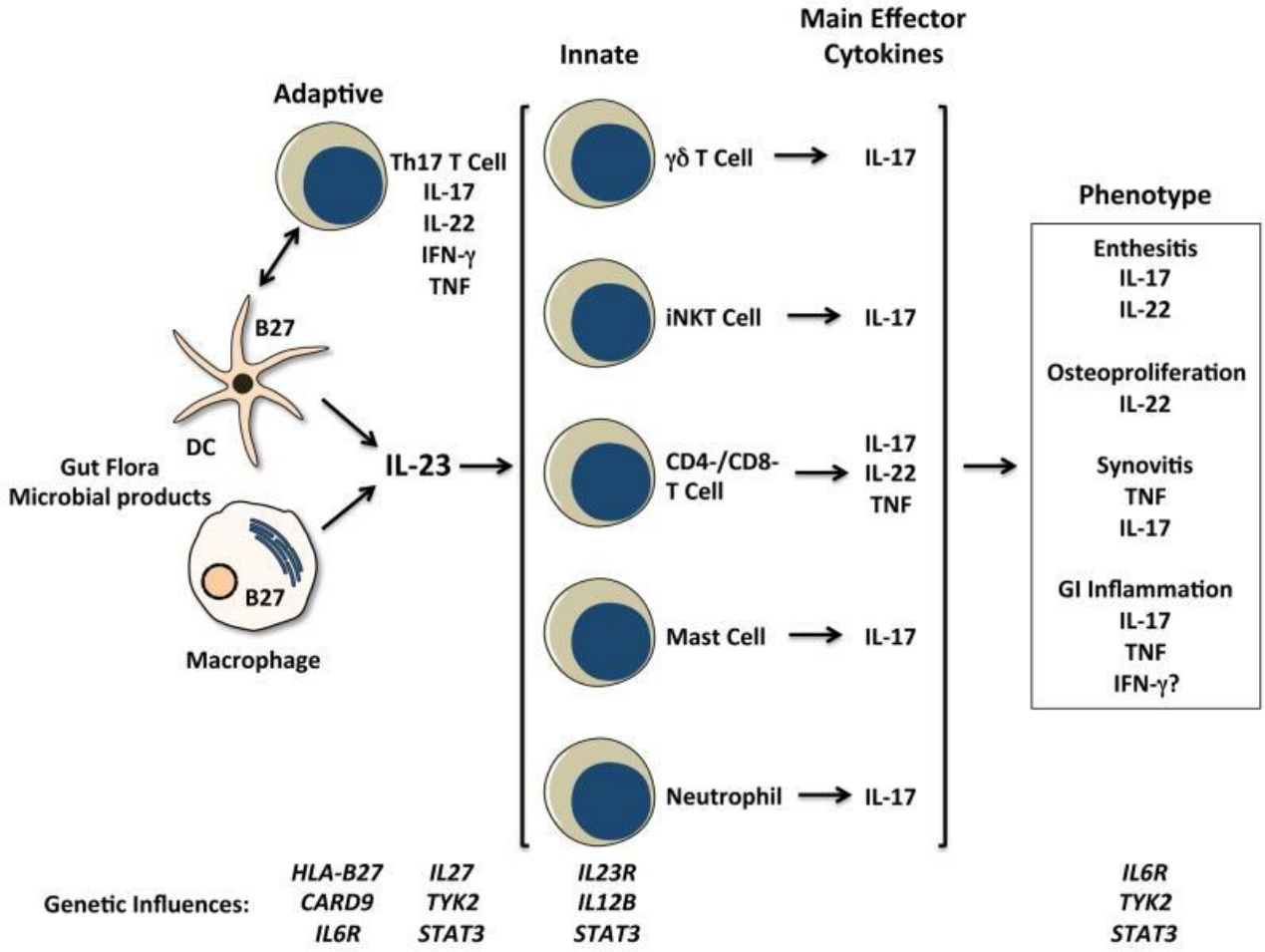

Figure 7: Depicting cells, effector cytokines and possible contributions to SpA pathogenesis

(Source: Raposo, and Torres 2015)

The author represents nail psoriasis as such a dermatological factor that can anticipate the emergence of PsA. They concluded that nail lesions from any of the diseases with pitting, onycholysis, and subungual hyperkeratosis have an increased risk of developing PsA. These nail changes are associated with inflammation that happens at the enthuses, which are areas in the body where the ligaments and tendons of the joint connect with bone; it is established that this is one of the primary locations of PsA (Raposo, and Torres 2015). This study recommends dermatosis in nail lesions in psoriasis patients in a way that will allow for early detection of musculoskeletal affection so that early intervention will consider preventing further joint disability.

Discussion

The data focuses on the multifactorial and interdependent nature of the relationship between psoriasis and psoriatic arthritis and mainly focuses on the role of the IL-23/IL-17 axis. On the molecular level, we have common biomarkers such as TNF-α and CRP, which help in assessing systemic inflammation on the clinical level, nail involvement, is consider to a major contributing factor in the prediction of the disease. This is especially so when giving general scenarios that also show a molecular and histological match in structure. It means that early diagnosis is still rather problematic because symptoms may vary (Chang *et al*.2011). The identification of immunological and genetic markers is beneficial for the diagnostic and therapeutic regime strengthening the concept of psoriatic disease as an autoimmune and inflammatory disease.

Future Directions

Future research should use detailed studies to confirm dermatological markers particularly the individual filaments on the nails, and scalp as predictors for psoriatic arthritis. There is a need to expand biomarker signatures to include IL-22 and GM-CSF to help detect the condition at an early stage and offer a more targeted approach. There must also be extensive research done to establish the effect of environmental factors, changes in the microbiome and human behavior on the progression of the disease (Lories, 2015). More research is necessary to further establish the effectiveness of using a multidisciplinary care approach for patients with lupus skin conditions that include dermatology, rheumatology and immunology. In the end, it will be helpful to take preventive and therapeutic actions in psoriatic disease when understanding the complex changes of the skin-joint immunological transition.

Conclusion

This research paper focuses on the immunological and clinical relationship between cutaneous psoriasis and PsA, with the central role played by the IL-23/IL-17 immune response. Psoriatic disease is no longer considered a skin or joint disease alone, but the study focus that there are molecular similarities overall. The awareness of dermatological manifestations especially involving nails is very important in the diagnosis of PsA. It is necessary for an accurate diagnosis and then to address the case, an integrative connotative approach is relevant. Further developments in the molecular field and identifying new biomarkers in systematic approaches to psoriatic disease

will, however, contribute to early intervention that will go a long way in improving the patient's quality of life.

Reference List

Journal

Blauvelt, A. and Chiricozzi, A., 2018. The immunologic role of IL-17 in psoriasis and psoriatic arthritis pathogenesis. Clinical reviews in allergy & immunology, 55(3), pp.379-390.

Boutet, M.A., Nerviani, A., Gallo Afflitto, G. and Pitzalis, C., 2018. Role of the IL-23/IL-17 axis in psoriasis and psoriatic arthritis: the clinical importance of its divergence in skin and joints. International journal of molecular sciences, 19(2), p.530.

Chang, C.A., Gottlieb, A.B. and Lizzul, P.F., 2011. Management of psoriatic arthritis from the view of the dermatologist. Nature Reviews Rheumatology, 7(10), pp.588-598.

Costanzo, A. and Spinelli, F.R., 2016. Foreword: Seminars in Research 2014 Joint Experiences in Rheumatology and Dermatology. Journal of International Medical Research, 44(1_suppl), pp.3-5.

Dowlatshahi, E.A., Van Der Voort, E.A.M., Arends, L.R. and Nijsten, T., 2013. Markers of systemic inflammation in psoriasis: a systematic review and meta-analysis. British Journal of Dermatology, 169(2), pp.266-282.

Kolliker Frers, R.A., Otero-losada, M.E., Kersberg, E., Cosentino, V. and Capani, F., 2017. Immune System Links Psoriasis-Mediated Inflammation to Cardiovascular Diseases via Traditional and Non-Traditional Cardiovascular Risk Factors. IntechOpen.

Lories, R., 2015. SP0135 What is New in Psoriatic Arthritis. Annals of the Rheumatic Diseases, 74, pp.33-34.

Marinoni, B., Ceribelli, A., Massarotti, M.S. and Selmi, C., 2014. The Th17 axis in psoriatic disease: pathogenetic and therapeutic implications. Autoimmunity highlights, 5, pp.9-19.

Mylonas, A. and Conrad, C., 2018. Psoriasis: classical vs. paradoxical. The Yin-Yang of TNF and type I interferon. Frontiers in immunology, 9, p.2746.

PLAN, L.R., 2010. National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

Raposo, I. and Torres, T., 2015. Nail psoriasis as a predictor of the development of psoriatic arthritis. Actas dermo-sifiliograficas, 106(6), pp.452-457.

Smith, J.A. and Colbert, R.A., 2014. The IL-23/IL-17 axis in spondyloarthritis pathogenesis: Th17 and beyond. Arthritis & Rheumatology (Hoboken, NJ), 66(2), p.231.

Suzuki, E., Mellins, E.D., Gershwin, M.E., Nestle, F.O. and Adamopoulos, I.E., 2014. The IL-23/IL-17 axis in psoriatic arthritis. Autoimmunity reviews, 13(4-5), pp.496-502.