Dia 2. Otras enfermedades inflamatorias

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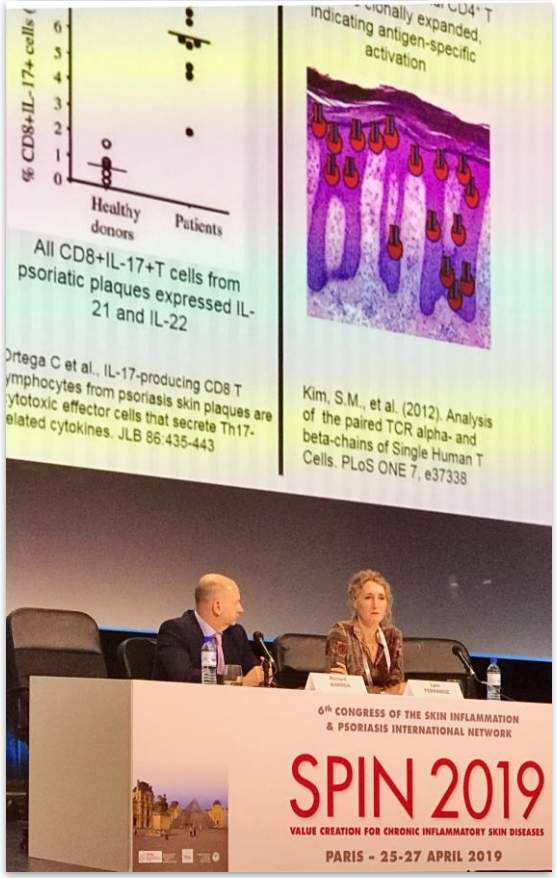
Iniciativa científica de:

New insights in HS
New technologies in basic medicin



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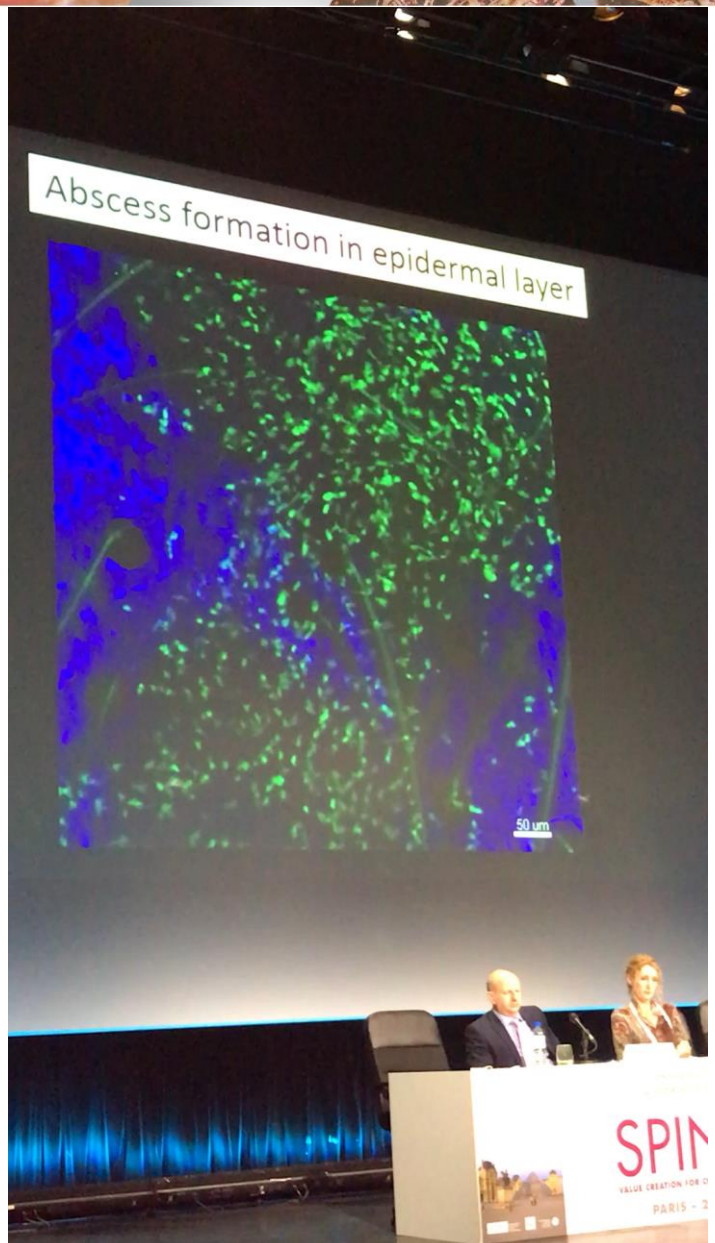
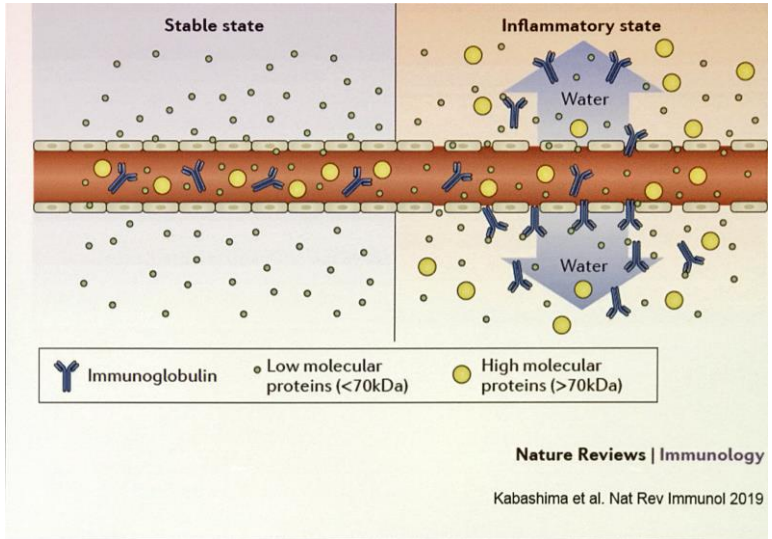
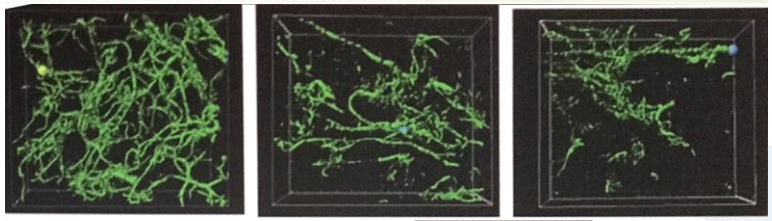
ACADEMIA ESPAÑOLA DE DERMATOLOGÍA Y VENEREOLOGÍA AEDV 1909

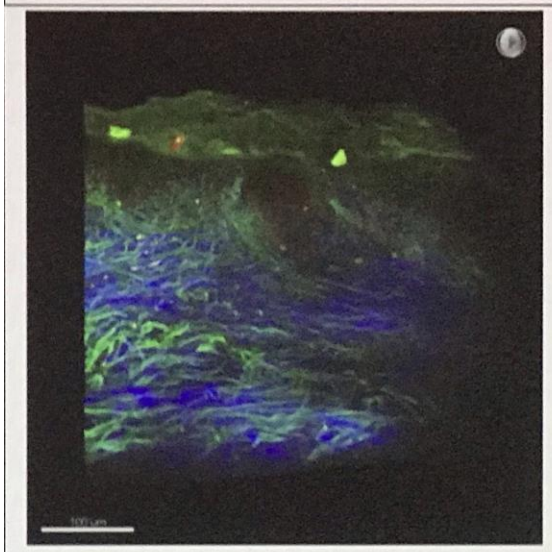


Two Photon/Confocal microsopy

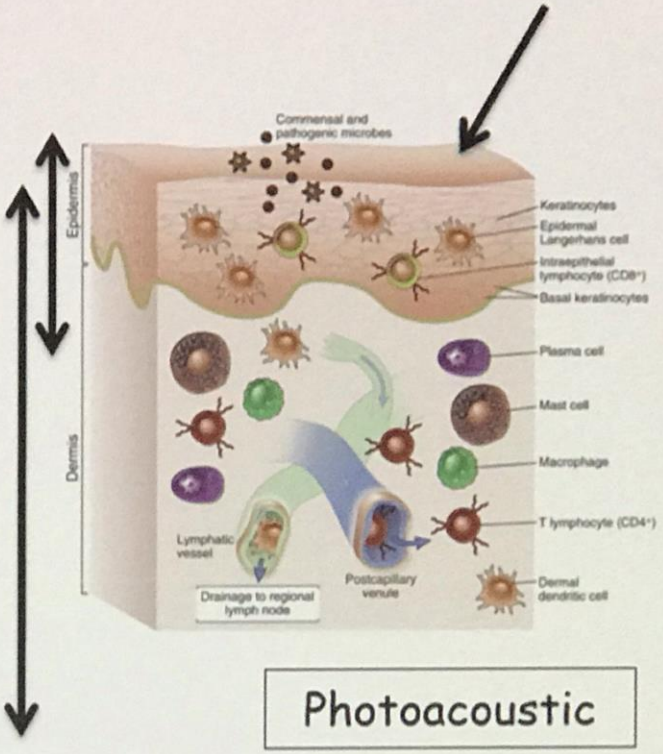




Two photon/confocal microscopy



Raman spectroscopy



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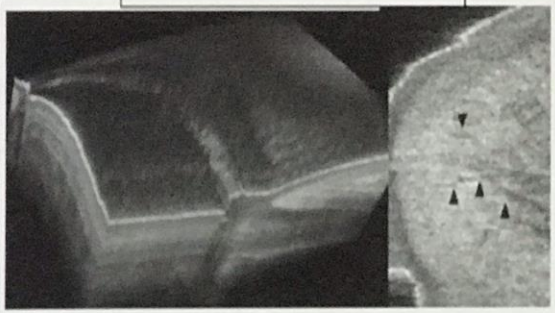
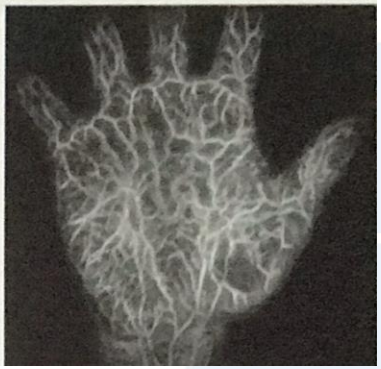
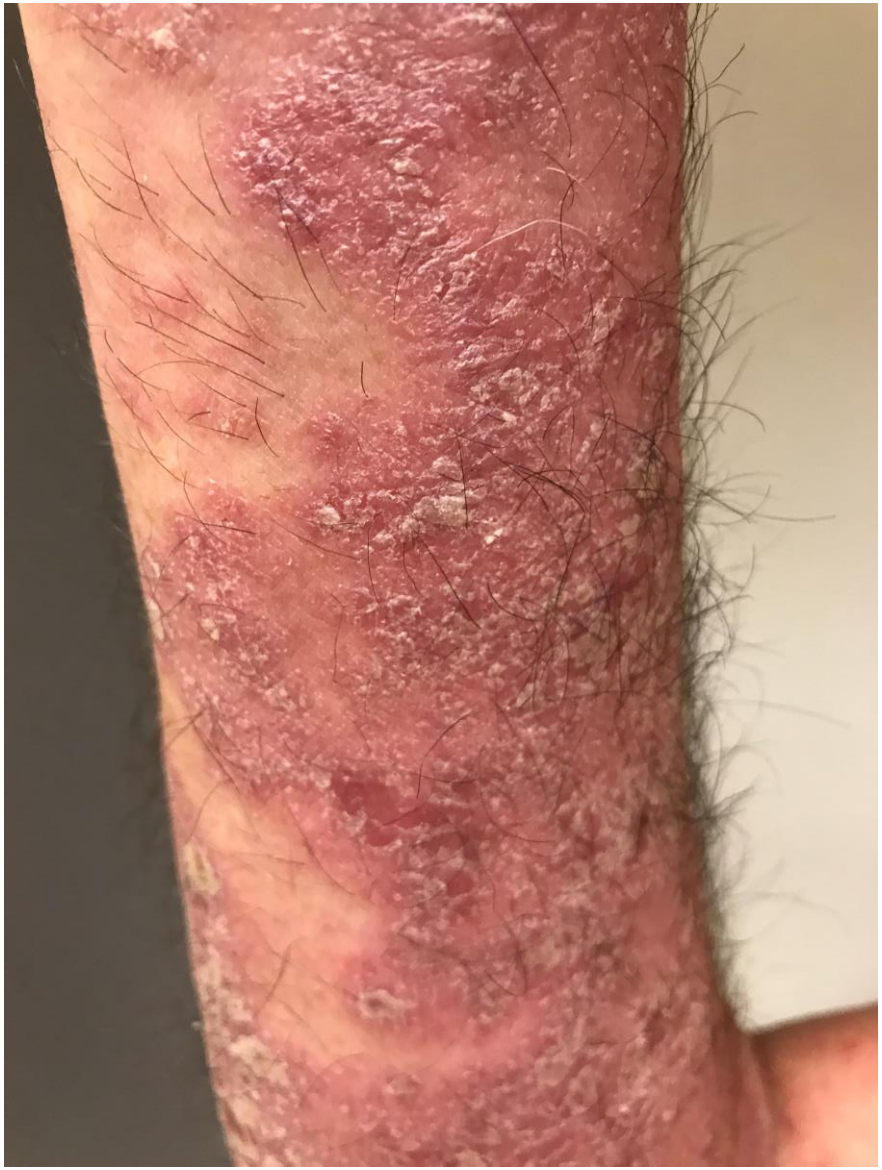
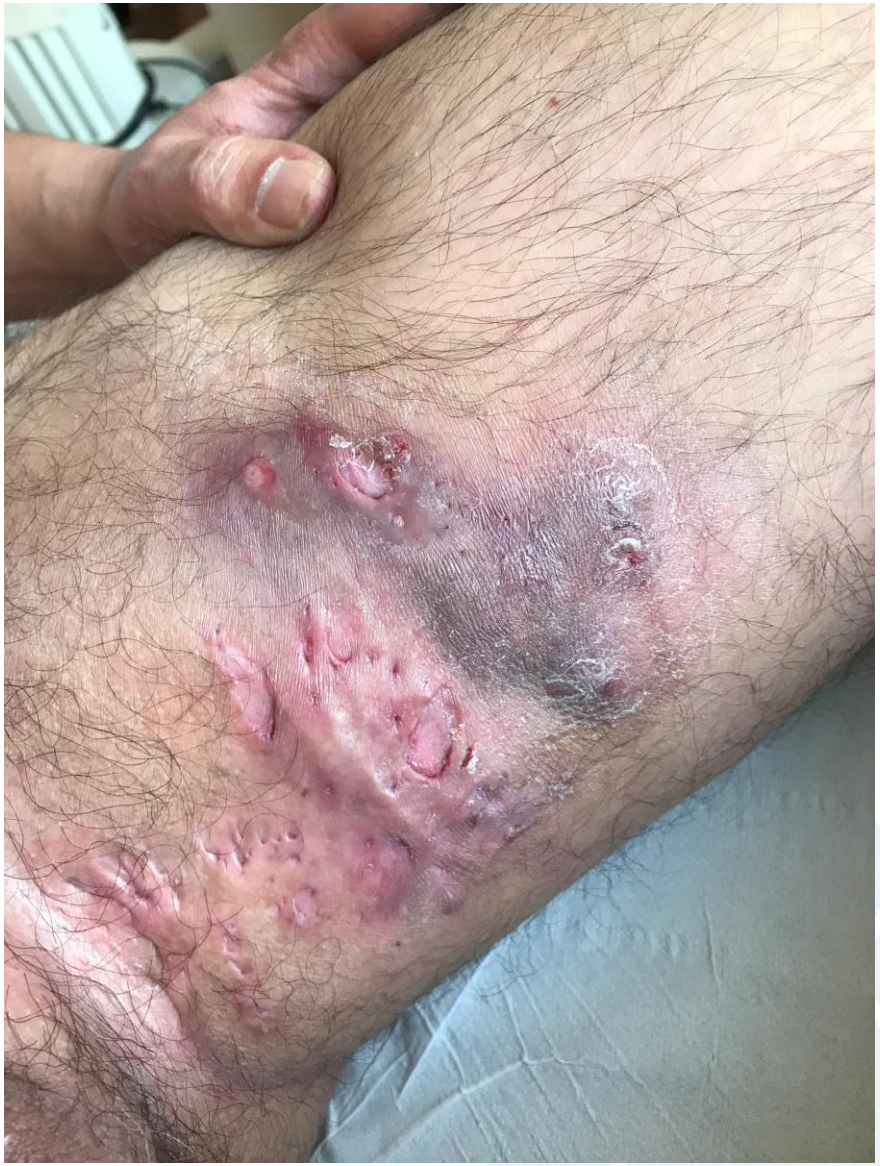


Photoacoustic







IS THERE ANY ASSOCIATION BETWEEN PSORIASIS AND HS?

- A total of 68,836 patients with **psoriasis** and 68,836 controls were included in the study
- The prevalence of HS was increased in patients with **psoriasis** as compared to the control group (0.3% vs. 0.2%, respectively; OR, 1.8; 95% CI, 1.5-2.3; P<0.001)
- In a multivariate analysis adjusting for smoking, obesity, and other comorbidities, **psoriasis** was still associated with HS (OR, 1.8; 95% CI, 1.4-2.2; P<0.001)
- Patients with coexistent **psoriasis and HS were significantly younger** (39.0±15.7 vs. 42.6±21.2 years; P=0.015) and had a **higher prevalence of obesity** (35.1% vs. 25.3%; P=0.001) **and smoking** (58.5% vs. 37.3%; P<0.001) as compared to patients with psoriasis alone

Kridin K, et al. J Am Acad Dermatol 2018 Nov 28

International Journal of Molecular Sciences

MDPI

Review

Advances in Understanding the Immunological Pathways in Psoriasis

Simona-Roxana Georgescu [1,2], Mircea Tampa [1,2,*], Constantin Caruntu [3,4,*], Maria-Isabela Sarbu [1], Cristina-Iulia Mitran [5], Madalina-Irina Mitran [5], Clara Matei [1], Carolina Constantin [6,7] and Monica Neagu [6,7,8]

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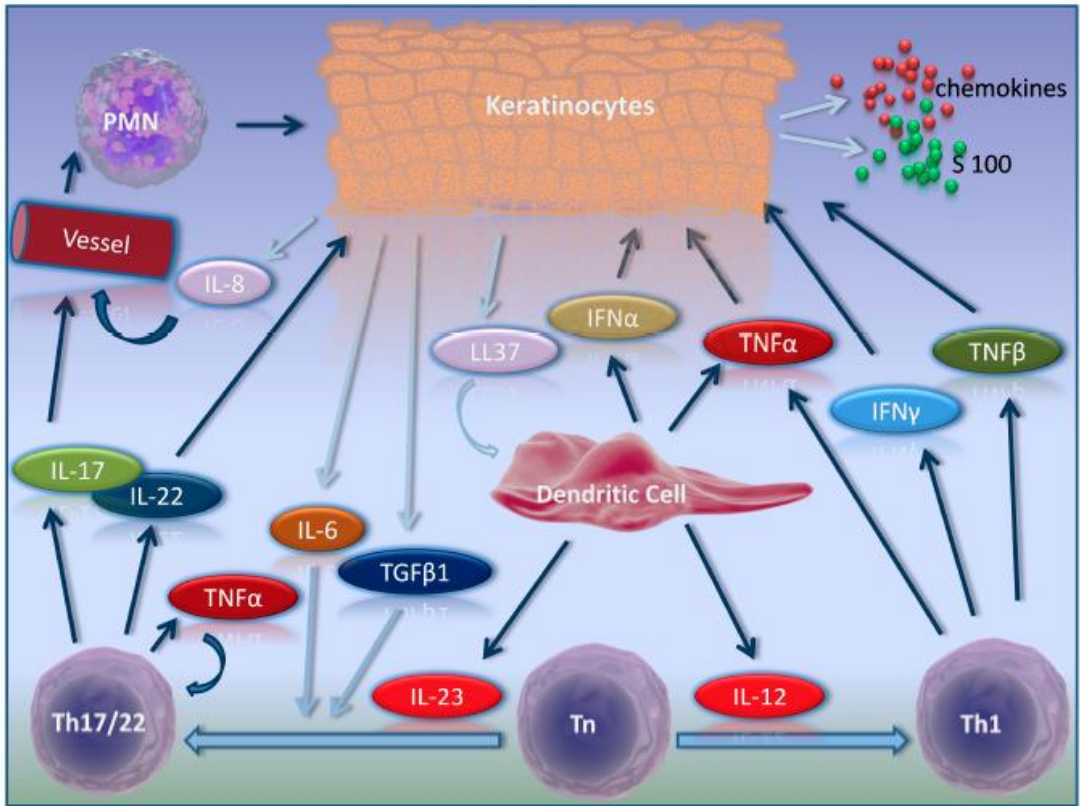
Abstract: Psoriasis vulgaris is a chronic, immune-mediated, inflammatory, polygenic skin disorder affecting approximately 2% of the population. It has a great impact on quality of life; patients often experience depression, anxiety, stigma as well as suicidal behavior. Even though psoriasis is one of the most studied dermatological conditions, the pathogenesis of the disease is still not completely elucidated. The complex interactions between keratinocytes, dendritic cells, T-lymphocytes, neutrophils and mast cells are responsible for the histopathological changes seen in psoriasis. The pathogenic model leading to the formation of psoriatic plaques has however evolved a lot over the years. There is now enough evidence to support the role of interleukin (IL)-23, IL-17, IL-22, T helper (Th)-17 cells, Th-22 cells, T regulatory cells, transforming growth factor (TGF)-β1 and IL-10 in the pathogenesis of the disease. Moreover, several inflammatory and anti-inflammatory molecules are currently being investigated, some of them showing promising results. The aim of this paper is to look over the most recent advances in the immunological pathways involved in the pathogenesis of psoriasis vulgaris.

Keywords: psoriasis; inflammation; immunology; Th-17; IL-17; T regulatory cells

1. Introduction

Psoriasis vulgaris is a chronic, immune-mediated, inflammatory, polygenic skin disorder affecting approximately 2% of the population. It has a universal occurrence; males and females being equally affected [1–4]. It can appear at any age, but two peaks in age of onset have been described: the first between 20 and 30 years and the second between 50 and 60 years [4,5]. Plaque-type psoriasis accounts for approximately 90% of cases and clinically manifests as well-demarcated erythematous plaques covered by silvery-white scales with a predilection for the extensor surfaces of the extremities, scalp,



Could these molecules be involved in the pathogenesis of psoriatic arthritis?

DR. TIANFU WU (Orcid ID : 0000-0003-4406-1449)

Article type : Full Length

Identification of Novel Autoantibodies Associated with Psoriatic Arthritis

Yulin Yuan (MD, PhD)[1,2], Jingyi Qiu (MSc)[2], Zuan-Tao Lin (PhD)[2], Wen Li (PhD)[3], Christopher Haley (MD)[4], Uyen Ngoc Mui (MD)[4], Jing Ning (PhD)[3], Stephen K. Tyring (MD, PhD)[4,5], Tianfu Wu (PhD)[2]*

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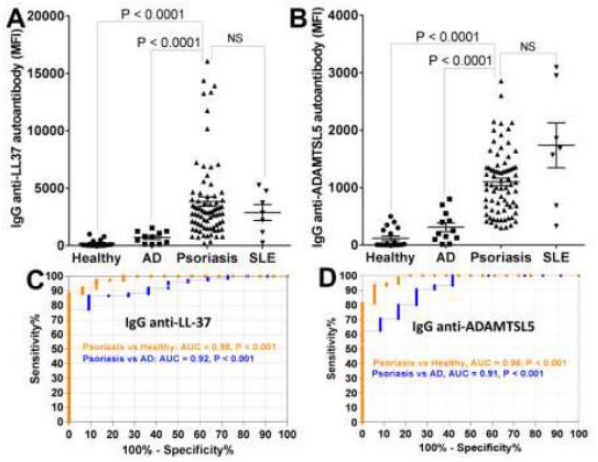
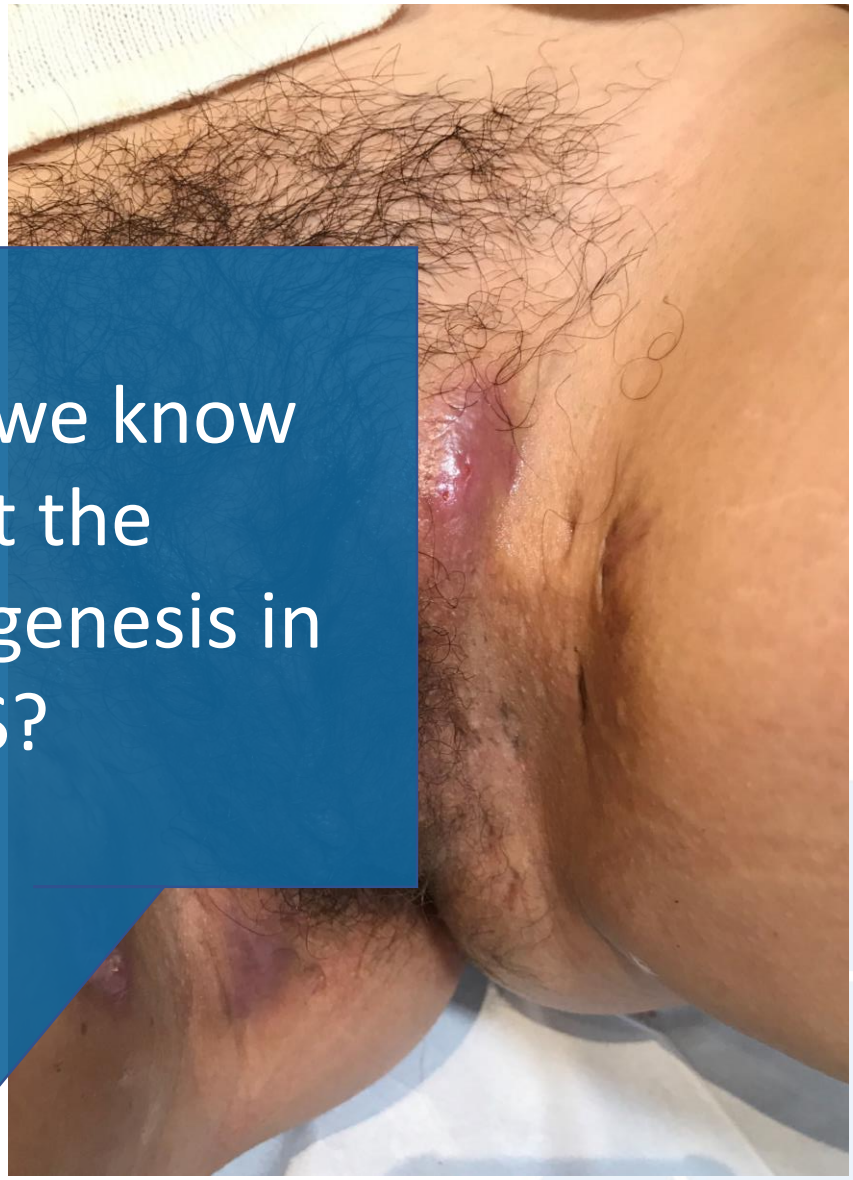
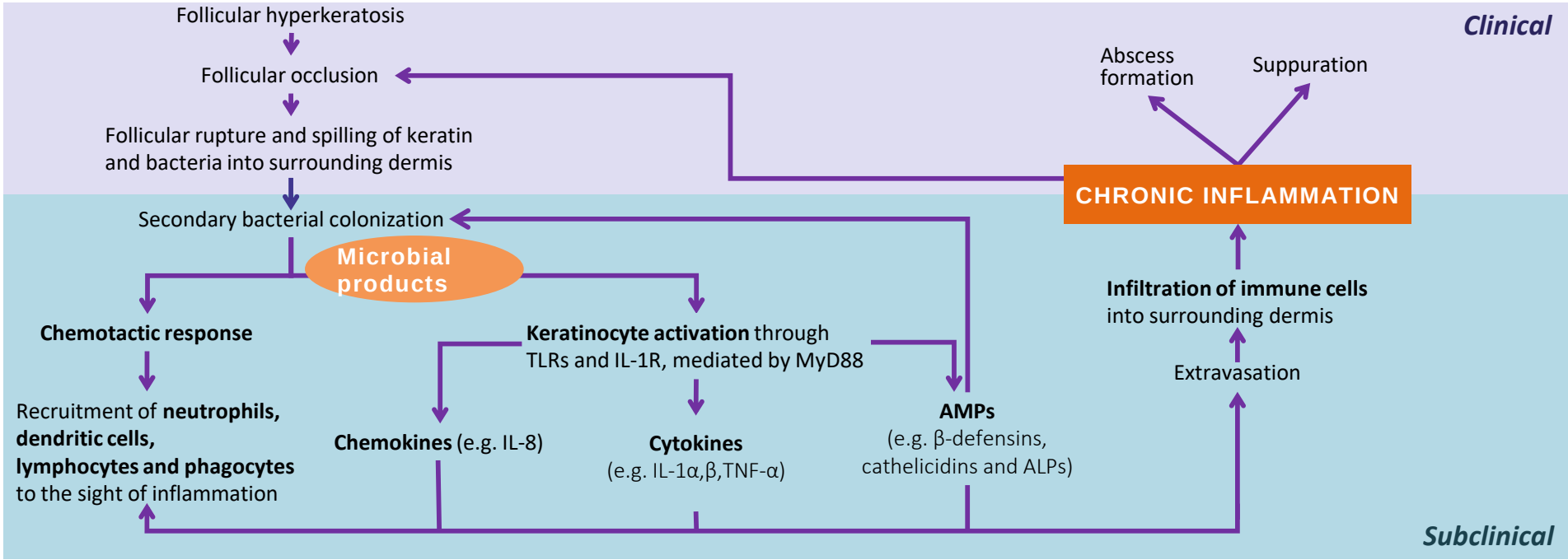


- Several serum autoantibodies were elevated in psoriasis patients compared to healthy controls
- Particularly, **IgG autoantibodies** against two novel antigens, **LL37** and **ADAMTSL5.**
  - Correlated with Psoriasis Area and Severity Index (PASI), and reflected disease progression
  - Significantly elevated in psoriatic arthritis (PsA)compared to Non-PsA,



What do we know about the etiopathogenesis in HS?

IMMUNOPATHOGENESIS OF HS



•ALPs, aerolysin-like proteins; NFκB, nuclear factor kappa B; PAMPs, pathogen-associated molecular pathogens; TLRs, toll-like receptors
Nazary M, et al. Eur J Pharmacol. 2011;672:1–8

GENETICS OF HS: ABERRANT NOTCH PATHWAY SIGNALLING

- These mutations are mainly seen in **familial HS with autosomal dominant inheritance**, as well as in some sporadic cases.
- The gamma-secretase complex study with the largest cohort included both familial (n=57 unrelated) and sporadic (n=38) patients revealed **mutations in 2.1%**
- **Recent studies point out that variations in the gamma-secretase gene complex can explain minority of the HS cases**

Does the autoinflammation play a prominent role in HS pathogenesis?

NCSTN, nicastrin; PSEN1, presenilin; PSENEN, presenilin enhancer.

1. Andersson ER, *et al. Nat Rev Drug Discov.* 2014;13:357–378; 2. Pink AE, *et al. J Invest Dermatol*. 2013;133:601-607

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Article type : Original Article

Association of Pyrin mutations and Autoinflammation with Complex Phenotype Hidradenitis Suppurativa: A Case Control Study

Running Head: Pyrin mutations in Complex Hidradenitis Suppurativa

S. Vural[1,2], M. Gündoğdu[1], E. Gökpınar[3], C.D. Durmaz[3], A. Vural[4], L. Steinmüller-Magin[5], A. Kleinhempel[6], L.M. Holdt[6], T. Ruzicka[7], K.A. Giehl[7], H.I. Ruhi[3], A. Boyvat[1]

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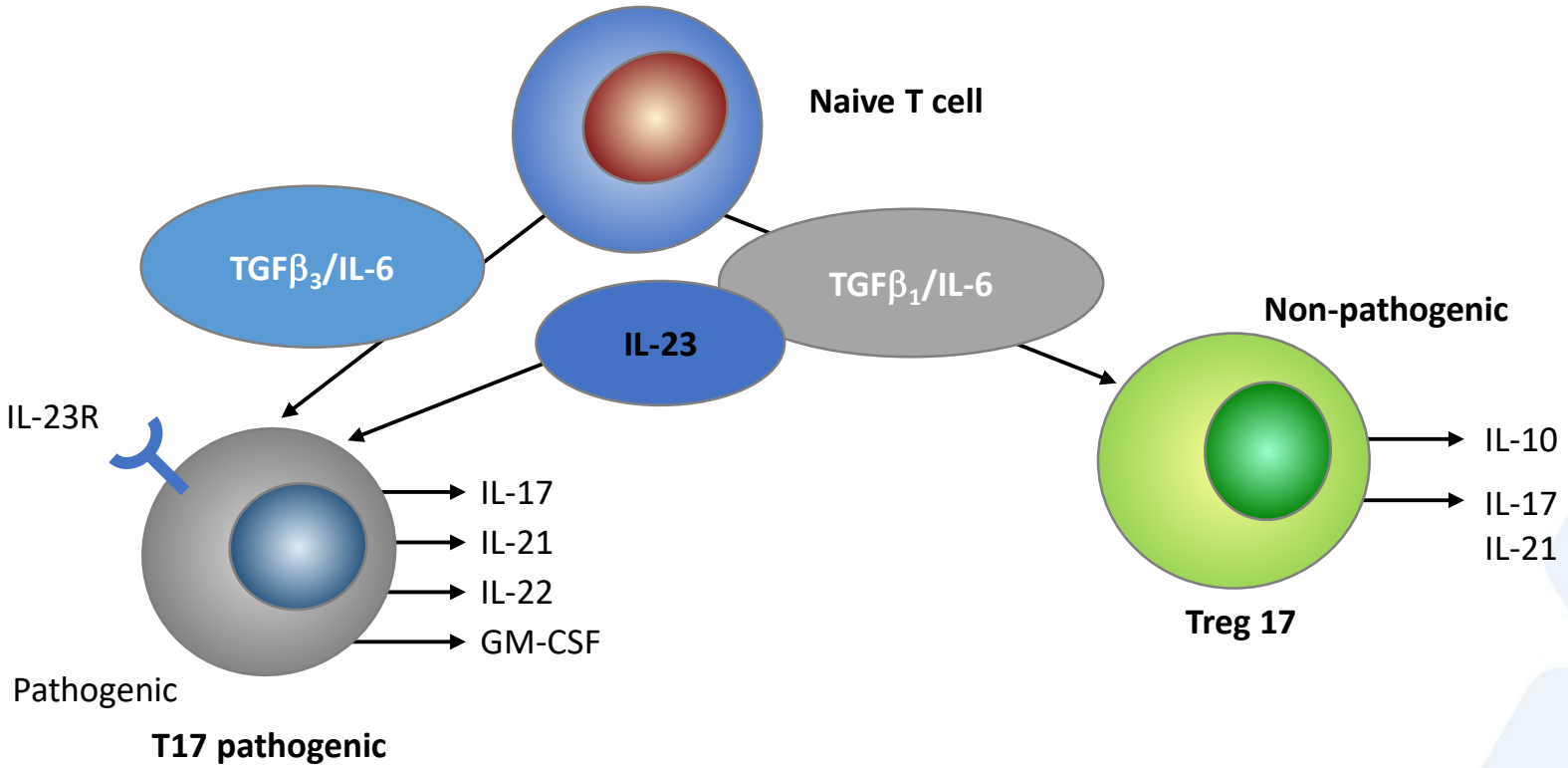
6-Ludwig Maximilian University of Munich, Institute of Laboratory Medicine, Munich, Germany

7-Ludwig Maximilian University of Munich, Department of Dermatology and Allergy, Munich, Germany

- **Complex phenotype**= (Hurley stage III disease and/or additional inflammatory symptoms)
- Of the patients with complex HS**, 38% were positive for pathogenic variants of *MEFV***
- **The odds ratio** for carrying a pathogenic *MEFV* allele was **2.80** (CI: 1.31-5.97, p<0.001).
- **Not only HS in syndromic forms (PASH, PAPASH) but also severe HS and HS with additional inflammatory symptoms** belong to autoinflammatory spectrum neutrophilic skin diseases

IS THERE ANY COMMON INFLAMMATORY PATHWAY IN HS AND PSORIASIS?

- Role of Th17/Treg axis in psoriasis and HS



Dermatology Online Journal || Review

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The role of interleukin-17 in the pathogenesis of hidradenitis suppurativa

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Corresponding Author: Simon Francis Thomsen, Professor, MD, PhD, Department of Dermatology, Bispebjerg Hospital, DK-2400 Copenhagen NV, Denmark, Tel: 45 2613 9838, Email: simonfrancisthomsen@gmail.com

Abstract:

Hidradenitis suppurativa is a chronic inflammatory skin condition affecting primarily the axillary, perianal, and inguinal areas. Patients with hidradenitis suppurativa present with occlusion and subsequent rupture of follicular ducts, profound abscesses, fistulae, odorous discharge, fibrosis, and scar formation, causing significant morbidity. Knowledge of the pathogenesis of hidradenitis suppurativa is limited and treatment with antimicrobial drugs, immunosuppressants, and surgical procedures have shown varying results. The pathogenic role of the interleukin-17 cytokine family in chronic inflammatory skin conditions has been described. Interleukin-17A and interleukin-17F have similar properties and induce the production of cytokines, chemokines, antimicrobial peptides, and metalloproteinases, all of which take part in the inflammatory response. The efficacy of anti-interleukin-17A therapy in psoriasis has also been proven and anti- interleukin-17A drugs are already in use for this condition. There is currently no consensus on the role of interleukin-17 in the pathogenesis of hidradenitis suppurativa. Studies have demonstrated increased interleukin-17 mRNA expression in lesional hidradenitis suppurativa skin, whereas the protein concentrations of interleukin-17 were found to be normal compared to healthy control skin in one other study. A phase II clinical trial on anti- interleukin-17 therapy in hidradenitis suppurativa is ongoing.

Keywords: hidradenitis suppurativa, interleukin-17

Introduction:

Hidradenitis suppurativa is a chronic inflammatory skin condition affecting primarily the axillary, perianal, and inguinal areas of the body. Hidradenitis suppurativa is characterized by initial occlusion and subsequent rupture of follicular ducts leading to formation of profound abscesses (**Figure 1**). Fistulae, odorous discharge, fibrosis, and scar formation are seen in later and more severe stages of hidradenitis suppurativa (**Figures 2, 3**). Onset of hidradenitis suppurativa is typically post pubertal, in the second to third decades of life.

The prevalence of hidradenitis suppurativa in the French population is estimated to be around 1%, although other studies have estimated prevalence rates ranging from as low as 0.0033% to as high

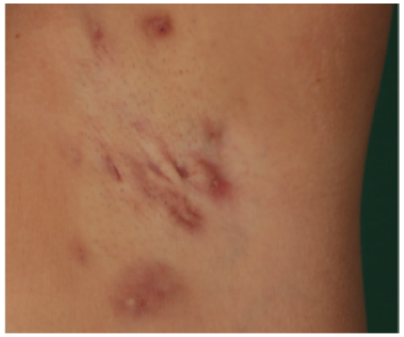
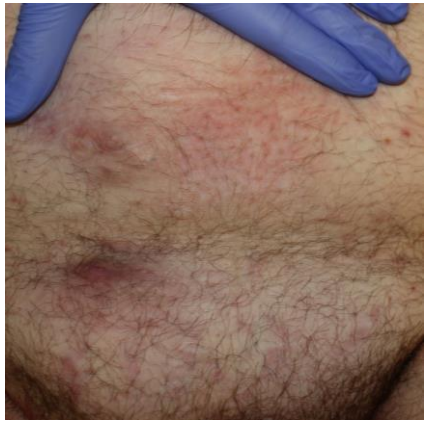


Figure 1. *Abscess formation and inflammatory nodules in hidradenitis suppurativa.*

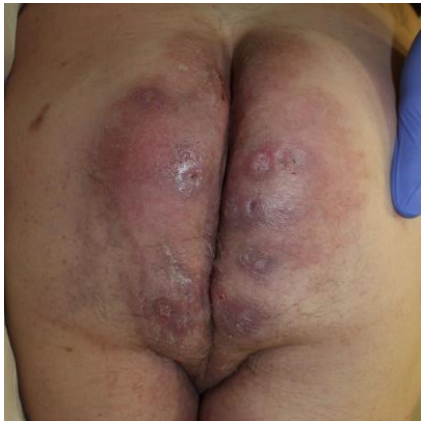
Table 2. Interleukin mRNA expression and protein concentration data results from lesional hidradenitis suppurativa skin from different studies.

Study	Interleukin-17 mRNA expression	Interleukin-17 protein concentration
Wolk et al., 2010 [1]	Elevated	Not tested
Schlapbach et al., 2011 [20]	Elevated	Not tested
Kelly et al., 2015 [21]	Elevated	Not tested
Blok et al., 2016 [24]	Not tested	Not elevated

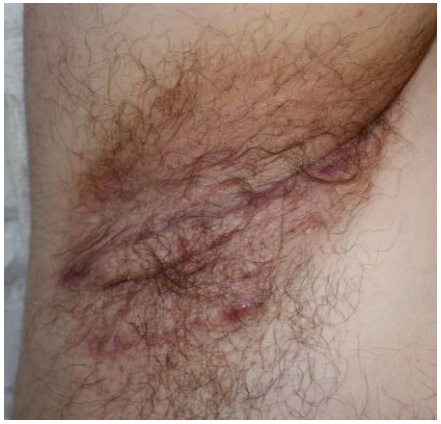
Protein concentrations were analyzed by enzyme linked immunosorbent assay, while mRNA expressions were analyzed by polymerase chain reaction.



IL-1B
TNF-alfa



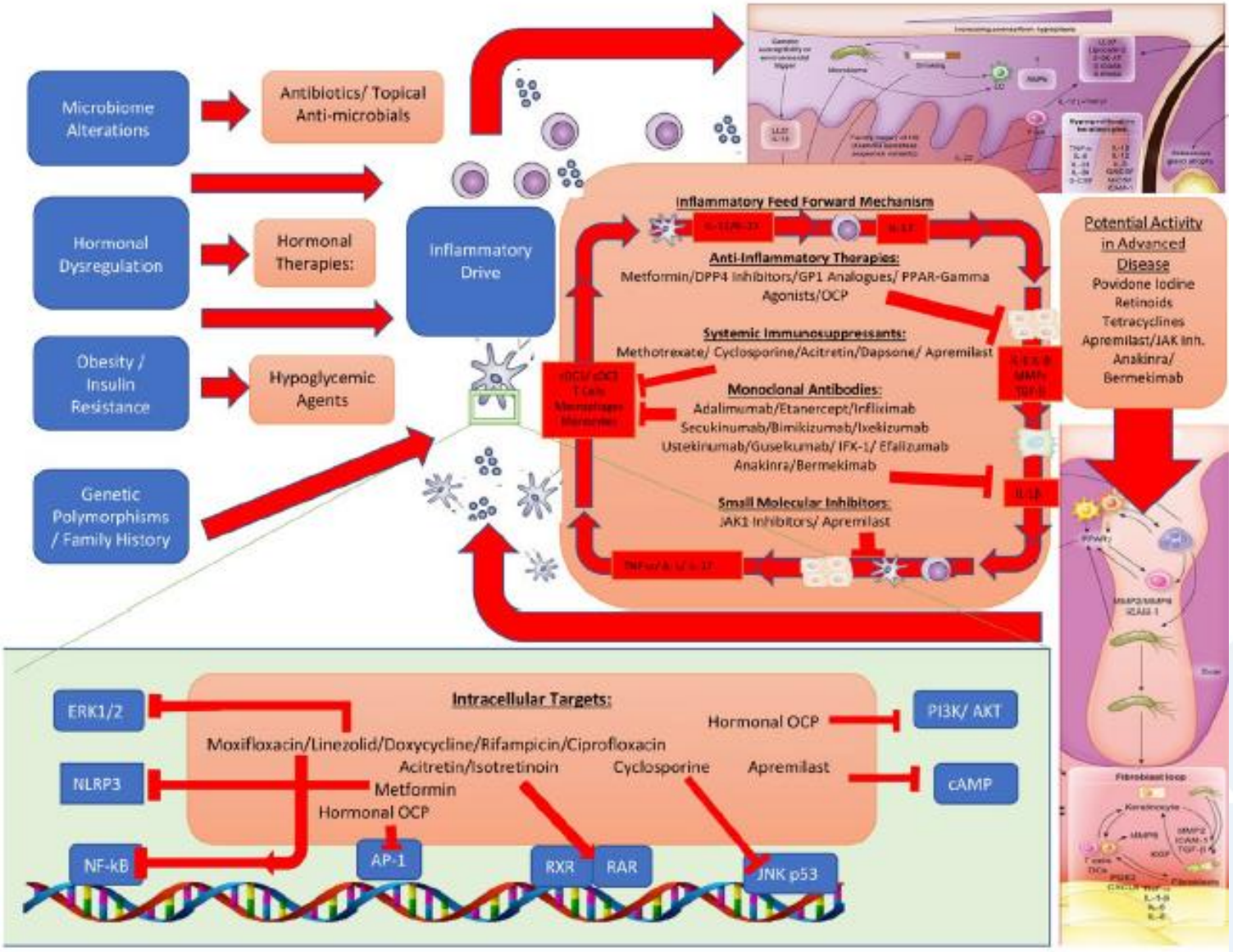
IL-17
TNF-alfa
IL-1B



MMP
IL1alfa
TNF-alfa

Superinfections

Different severity stages, different inflammatory cytokines in the skin: An hypothetical explanation


Microbiome Alterations
Antibiotics/ Topical Anti-microbials
Hormonal Dysregulation
Hormonal Therapies:
Obesity / Insulin Resistance
Hypoglycemic Agents
Genetic Polymorphisms / Family History
Inflammatory Drive
Inflammatory Feed Forward Mechanism
Anti-Inflammatory Therapies:
Metformin/DPP4 Inhibitors/GP1 Analogues/ PPAR-Gamma Agonists/OCP
Systemic Immunosuppressants:
Methotrexate/ Cyclosporine/Acitretin/Dapsone/ Apremilast
Monoclonal Antibodies:
Adalimumab/Etanercept/Infliximab
Secukinumab/Bimikizumab/Ixekizumab
Ustekinumab/Guselkumab/ IFX-1/ Efalizumab
Anakinra/Bermekimab
Small Molecular Inhibitors:
JAK1 Inhibitors/ Apremilast
Potential Activity in Advanced Disease
Povidone Iodine
Retinoids
Tetracyclines
Apremilast/JAK Inh.
Anakinra/
Bermekimab
Intracellular Targets:
ERK1/2
NLRP3
NF-kB
AP-1
RXR
RAR
JNK p53
Moxifloxacin/Linezolid/Doxycycline/Rifampicin/Ciprofloxacin
Acitretin/Isotretinoin
Metformin
Hormonal OCP
Cyclosporine
Apremilast
Hormonal OCP
PI3K/ AKT
cAMP

CONCLUSIONS

- HS is a **complex chronic inflammatory disease**
- In a multivariate analysis adjusting for smoking, obesity, and other comorbidities, **psoriasis was still associated with HS** (OR, 1.8; 95% CI, 1.4-2.2; P<0.001)
- **Few cases related with mutations in Notch genes**
- **Autoinflammatory pathways**, such as the FMF, **can explain some of HS cases**
- Sufficient evidence exists to support the role of **Th17/Treg axis in the inflammatory mechanisms of HS, but not the sole pathogenic pathway**

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