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A Report from the 2024 IPC Think Tank Symposium – Psoriasis: The Multiple Facets of a Global Disease

Bryan Guevara, MD, FPDS, FDSP, 2024 IPC Fellow

SUMMARIZING SESSIONS WITH A FOCUS ON PSORIASIS

2024 THINK TANK
LONDON

INTRODUCTION

The 2024 IPC Think Tank Meeting was held in London on Wednesday, December 4. This annual meeting brought together over 100 participants, including IPC Board Members, Councilors, Fellows, and Corporate Members, to discuss emerging trends and insights in psoriasis research and treatment. This year's meeting was particularly significant as IPC celebrated its 20th anniversary. The symposium, **Psoriasis: The Multiple Facets of a Global Disease**, included nine lectures covering epidemiology, clinical features, genetics of psoriasis and related diseases, mechanistic scenarios, and treatment advances. This report summarizes the key discussions and presentations from the meeting.

TABLE OF CONTENTS

Epidemiology and Comorbidities of Psoriasis Across the Ages

Luigi Naldi, MD, IPC Councilor
Centro Studi GISED, Bergamo, Vicenza and Bergamo, Italy

The global prevalence of psoriasis is 2-3 % of the population, with a higher prevalence in Western countries while lower in Asian and African regions.[1] Psoriasis incidence showed a strong bimodal distribution in Italy, peaking at 35-44 (3.42 per 1,000 person-years) and 65-74 (4.20 per 10,000 person-years) years of age.[2] The initial peak corresponds with the early-onset (Type 1) psoriasis, while the second peak constitutes the late-onset psoriasis. HLA-C*06:02 is the primary genetic susceptibility allele of psoriasis, especially for Type I psoriasis. Dr. Luigi Naldi discussed other factors that affect the incidence of psoriasis, such as:

- Nutrition: The importance of early nutrition in the development of psoriasis in Sweden was discussed, and various factors, such as breastfeeding duration, the timing of the infant formula introduced, the amount of milk consumed, and the consumption frequency of fish from the Baltic Sea, were analyzed.[3] The study with a cohort of 16,415 individuals underscores that exclusive breastfeeding for four months appeared protective.
- Pollution: Long-term exposure to air pollutants, such as particulate matter with a diameter less than 2.5 µm ($PM_{2.5}$), particulate matter with a diameter less than 10 µm (PM_{10}), nitrogen dioxide (NO_2), and nitrogen oxides (NO_x) was associated with increased psoriasis risk-based from the UK Biobank.[4]

Comorbidity is defined as an occurrence of disorders with higher frequency than expected by chance alone. The association and progression of comorbidities in psoriasis favors the concept of "Psoriasis March." Important genetic and environmental triggers associate psoriasis with several comorbidities, such as obesity, metabolic syndrome, diabetes, and cardiovascular disease. Children with psoriasis have twice the rate of comorbidities, with an increased rate of obesity, hyperlipidemia, hypertension, diabetes mellitus, rheumatoid arthritis, and Crohn's disease. Obesity may also be viewed as a form of socioeconomic disadvantage.[6] Screening comorbidities and interventions on behavioral factors are key to holistic psoriasis management.

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Pigmentation Abnormalities in Patients with Psoriasis

Mauro Picardo, MD, PhD
UNICAMILLUS International University, Rome, Italy

Dr. Mauro Picardo highlighted the importance of pigmentary disorders among patients with psoriasis and elaborated on its pathogenesis. Firstly, the proliferation of keratinocytes disrupts epidermal melanin unit homeostasis due to severe disproportion between the numbers of keratinocytes and melanocytes in psoriatic lesions. Next, the proliferation of cultured melanocytes is observed through TNF-alpha and IL-17A stimulation.[1] Melanin content, melanocyte number, and hBD3 and IL8 expression were increased in psoriatic lesions compared to normal human skin.[1]

The interaction of inflammatory cells plays a significant role in melanogenesis. Hypopigmentation of lesions accompanies active inflammation, but these patients risk developing hyperpigmentation upon improvement or clearance of inflammation. Wang et al. proposed a model of IL-17 and TNF-mediated interactions between T cells, dendritic cells, keratinocytes, and melanocytic cells during skin inflammation.[3] A significant decrease in tyrosinase levels and cellular melanin content was detected in melanocytes after 48h exposure to IL-17 and TNF. The group was able to prove that IL-17 can dramatically amplify the inhibitory effect of TNF on melanogenesis. Also, it has been shown that pigmentation genes are rapidly recovered in psoriatic lesions after therapeutic neutralization of TNF and Il-17. The recovery of pigmentation signaling in psoriasis lesions at week 2 of treatment was noticed.

In conclusion, keratinocytic proliferation and inflammatory mediators mainly contribute to the pigmentary abnormalities among patients with psoriasis. After the lecture, there was a discussion on the possible prevention of pigmentary disorders through inhibiting TNF-alpha and IL-17, and proposed further research on the possibility of predicting hyper- or hypo-pigmentation among our patients.

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Deciphering of *CARD14*-related Disease(s): 15 Years On

Anne Bowcock, PhD, IPC Councilor
Icahn School of Medicine at Mount Sinai, New York, New York, United States

Dr. Anne Bowcock started the talk by discussing the importance of understanding the genetic basis of psoriasis, which will lead to better treatment options and possibly a cure. PSORS2 at chromosome 17q25 harbors a gene for a highly penetrant, dominantly inherited form of psoriasis and psoriatic arthritis – a gain of function mutations in *CARD14*.[1,2]

Inflammatory skin diseases with *CARD14* mutations have been reported in familial pityriasis rubra pilaris and *CARD14*-associated papulosquamous eruption.[3,4] Other rare gains of function mutations with *CARD14* are associated with classic psoriasis generalized pustular psoriasis, while hypomorphic mutations are seen in atopic dermatitis.

CARD14^{E138A} forms a constitutive CBM complex to activate NF-κB in keratinocytes.[5] The proposed model of psoriasis pathogenesis with the mutant/activated *CARD14* leads to the formation of the CBM complex (CARD14-BCL10-MALT1), leading to the activation of NF-κB and MAPK signaling in the keratinocytes and endothelial cells. Furthermore, knocked out *CARD14* in mice with the introduction of imiquimod did not have developed psoriasiform features.

A novel approach that can lead to the degradation of *CARD14* and subsequent dissolution of the CBM complex is through bridged PROteolysis Targeting Chimera (PROTAC), which may be applied to treat psoriasis and psoriatic arthritis in patients with *CARD14* mutations.

After the lecture, questions focused on the mechanism of CARD14 degradation as a treatment target that may lead to a possible shift to or flare-up of atopic dermatitis. However, Dr. Bowcock suggests the potential use of a small molecule targeting the CBM complex, which has the advantage of titrating the dose.

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Genetics of Pustular Psoriasis: Where Are We Now?

Francesca Capon, PhD, IPC Councilor
University of British Columbia, Vancouver, Canada

Dr. Francesca Capon briefly described the different pustular forms of psoriasis, categorized as acute (generalized pustular psoriasis) and chronic/localized (palmoplantar pustulosis).

Generalized Pustular Psoriasis (GPP)

GPP is caused by abnormal IL-36 signaling, where recessive IL36RN mutations are found in ~25% of GPP cases.[1,2] IL36RN mutations have been reported among Japanese, Chinese, Malay, North-African, and European populations. Recently, recessive MPO mutations have also been described among patients with GPP.[3] The loss-of-function myeloperoxidase mutations are associated with increased neutrophil counts and pustular skin disease.[4]

Palmoplantar Pustulosis (PPP)

IL36RN and MPO mutations are found in only <5% of PPP cases, which may partially explain the inefficacy of IL-36 inhibitors with this subtype of pustular psoriasis.[5] Recent evidence supports genetic evidence for Th2 involvement among PPP patients based on GWAS data.[6] Furthermore, smoking status is strongly associated with disease severity based on Palmoplantar Area and Severity Index.[7]

The clinical implication of this genetic difference between GPP and PPP is the potential treatment options, especially for PPP. Clinical data shown by Dr Capon on dupilumab and upadacitinib as treatment of PPP strongly supports the role of Th2 inflammation in this condition.

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Lessons from Transcriptomic, Single-cell, and Spatial Analyses in Psoriasis

Johann Gudjonsson, MD, PhD, IPC Board Member
University of Michigan, Department of Dermatology, Ann Arbor, Michigan, United States

Transcriptomics through bulk, single-cell, and spatial sequencing has helped explore a more profound understanding of the immunopathogenesis of psoriasis and identify the differences in the gene expression in a tissue. Integrating genetics with single-cell transcriptomics provides a better understanding of what is happening in psoriatic skin. This identifies psoriatic genetic susceptibility genes among cytokine-regulated genes in varying cells in a psoriatic lesion, such as keratinocytes, T-cells, fibroblasts, and dendritic cells. Transcriptomics can integrate cytokine responses with disease biology or lesional severity. Furthermore, single-cell sequencing has been utilized to dissect the molecular pathology of GPP (e.g., Higher myeloid cells in generalized pustular psoriasis vs control). All the data presented by Prof. Gudjonsson will be soon published. The combination of single cell and spatial RNA sequencing has also emphasizes the differences in immune cells and inflammatory markers particularly keratinocytes and fibroblasts.[1] This integrated data has identified keratinocytes and keratinocyte responses within the epidermis, and immune and endothelial cells in the dermis.

According to Prof. Gudjonsson, single-cell and spatial technologies are set to transform our view of biological processes in psoriatic disease. Some major limitations include the cost and infrastructure for data generation and data processing/analyses. The further integration of multi-omic data (bulk, single-cell, and spatial sequencing) will fill in current gaps, and provide novel resource for future investigations into psoriasis immunopathogenesis and accelerate the path toward a cure.

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Trained Immunity in Psoriasis: Where Does it Lie?

Curdin Conrad, MD, IPC Councilor
University Hospital of Lausanne, Lausanne, Switzerland

Professor Curdin Conrad highlighted that the skin is the largest organ, which makes up 12-16% of our body weight and is the most exposed surface to the environment while constantly exposed to potential hazards.

Innate Immunity of the Skin

The skin is more than a physical barrier, as it is part of our innate immunity that provides immediate response to pathogens passing the epithelial layer (e.g., complement system, antimicrobial protein, etc.).[1]

The innate immune cells do not express specific antigen recognition receptors. These cells distinguish "self" and "non-self" by recognizing pathogen-associated molecular patterns (PAMPs) through pattern recognition receptors (PRR). PRR can be activated by self-derived damage-associated molecular patterns (DAMP) released in the context of sterile inflammation. The processes are rapid but nonspecific (e.g., phagocytosis)

Adaptive Immunity in the Skin

The adaptive immune system is interestingly found only in vertebrates. This consists of T and B cells, which have slower processes but generate a potent antigen-specific response. Adaptive immunity generates highly differentiated immune cells, memory T and B cells.

Trained Immunity (Innate Memory)

Long-term functional reprogramming of innate immune cells and epithelial stem cells (and stromal cells), evoked by exogenous or endogenous insults, leads to an altered response to a nonspecific second challenge after the return to a non-activated state. Epigenetic memory is a fundamental characteristic of host defense that can play a significant role in chronic and recurrent inflammatory disease.

Prof. Conrad recapped that therapeutic reversal of trained immunity or inhibition of its induction are promising approaches for immune-related diseases. Early intervention in psoriasis can potentially reverse/ prevent an epigenetic scar, leading to disease modification (and cure?) in some patients.

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Metabolomics and Psoriasis Inflammation: What is the Connection?

Nicole Ward, PhD, IPC Councilor
Vanderbilt University Medical Center, Nashville, Tennessee, United States

There has been an increasing trend on psoriasis and metabolism, and metabolomics may provide new insights into the immunometabolism, outcome, and treatment of psoriasis. Professor Nicole Ward focused on metabolomics, which can reveal the various effects of exogenous factors, particularly diet and the microbiome. She summarized the metabolomics workflow, which starts with any biological sample that can be analyzed through targeted or untargeted methods. The progress in understanding metabolomics in psoriasis has significantly provided new links in the pathogenesis of psoriasis.

A clinical implication of metabolomics includes metabolomic profiling supporting interleukin-17 monoclonal antibody treatment that can ameliorate lipid metabolism and potentially reduce cardiovascular risk among patients with psoriasis.[1]

Metabolomics also explored the linkage of inflammation in mouse skin with keratinocyte glucose metabolism. The inhibition of glucose transport may affect these metabolic pathways, identifying possible therapeutic targets for psoriasis.[2] The topical application of a Glut1 inhibitor also effectively protected mice from imiquimod-induced psoriasiform hyperplasia.

Another pathway is the L-type amino acid transporter (LAT) 1 (SLC7A5), which is critical for T cells.[3] LAT1 expression is increased in keratinocytes and lymphocytes in psoriatic lesions. This has been linked to IL-23 and IL-1B-induced PI3/AKT/mTOR pathways to promote lymphocyte proliferation and IL-17 release in psoriasis. Polyunsaturated fatty acids (PUFA) metabolism is decreased in T cells, which correlates with inflammatory T cell pathways.[4] Finally, Prof. Ward shared their experience supplementing PUFA through fish oil, which improves psoriasis-like skin inflammation in their KC-Tie2 mice. The future direction of metabolomics is to combine omics to attribute metabolomic changes to disease pathogenesis and treatment.

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What's New in the Definition and Treatment of Pustular Psoriasis and Related Diseases?

Siew Eng Choon, MBBS, FRCP, IPC Board Member
Hospital Sultanah Aminah Johor Bahru, School of Medicine and Health Services, Monash University Malaysia, Johor, Malaysia

Generalized pustular psoriasis (GPP) previously lacked an internationally accepted definition and diagnostic criteria that hampered the timely diagnosis and treatment of this debilitating rare condition. Therefore, the International Psoriasis Council (IPC) developed an international consensus definition and diagnostic criteria based on expert reviews of 69 challenging GPP cases submitted online.

IPC definition of GPP[1]:

- GPP is a systemic inflammatory disease characterized by cutaneous erythema and macroscopically visible sterile pustules
- It may manifest:
    - With or without systemic inflammation
    - With or without laboratory abnormalities
    - With or without other types of psoriasis
- GPP can present as an acute form with widespread pustular eruption or a subacute variant with an annular phenotype

Psoriasis with pustulosis (psoriasis cum pustulatione) should not be recognized as GPP. Other important differential diagnoses to rule out are acute generalized exanthematous pustulosis, pemphigus foliaceus, IgA pemphigus, and subcorneal pustular dermatosis. Finally, pustular lesions on the acral regions can occur during flare-up and should not rule out the diagnosis of GPP.

Effective therapies targeting IL-36, such as spesolimab, have been approved for treating and preventing GPP flare. Meanwhile, Imsidolimab, HB0034 (Recibokibart), and IMG008 are new IL-36 inhibitors that have been recently developed and studied.

Palmoplantar pustulosis (PPP) occurs more in males (3.5:1), and 90% are smokers. *AP1S3*, *IL36RN,* and *CARD14* mutations occur with frequency of 6.6%, 5.1%, and 2.1%, respectively.[2-4] Anakinra and spesolimab have not shown significantly superior efficacy to placebo; hence, targeting IL-1 or IL-36 pathways is ineffective.[5,6] Recent data implicates the role of Th2 dysregulation in PPP; thus, dupilumab and Janus kinase inhibitors have been successfully used for PPP.

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Stratified Approaches in Psoriasis: Why Search for Biomarkers?

Hervé Bachelez, MD, PhD, IPC President
Hôpital Saint-Louis, Imagine Institute for Human Genetic Diseases, Paris Cité University, Paris, France

Professor Hervé Bachelez highlighted that psoriasis vulgaris (PV) and generalized pustular psoriasis (GPP) are genetically and functionally distinct yet are epidemiologically connected. Adaptive immunity is considered the main driver for PV, while innate immunity for GPP.[1]

Biomarkers may be beneficial, especially for unclear diagnosis of psoriasis (e.g., infancy/childhood psoriasis, palmoplantar psoriasis, or nail psoriasis). However, no biological biomarker has been validated for routine clinic practice at present.

Five applications of transcriptomics for the clinic (Figure 1):[2]

1. Disease diagnosis
2. Disease molecular stratification
3. Disease prognosis
4. Treatment response monitoring
5. Treatment response prediction

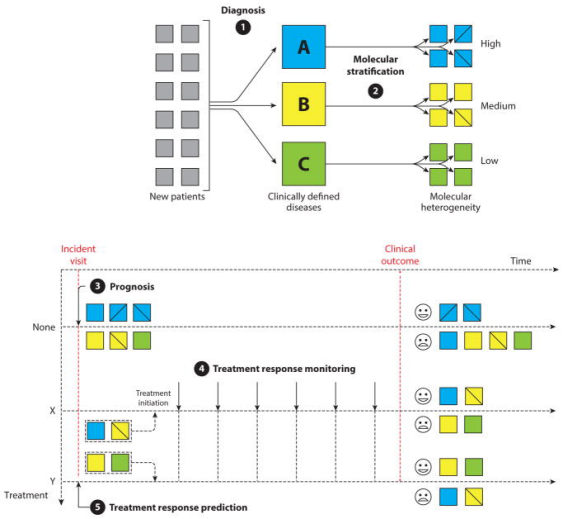

Figure 1. Five applications of transcriptomics for the clinic.[2]

Skin transcriptome studies' advantages include identifying dominant/canonical pathways and new therapeutic targets. However, this may not provide a hierarchy of pathways and an in-depth understanding of in vivo scenarios; hence, it may risk prioritizing by standard players.[3]

Stronger IL1 and IL36 signatures are seen in GPP in contrast with PV.[4] However, Top 20 upregulated genes (transcriptome using microarrays) in GPP (without PV) and in PV (vs healthy volunteers) are identical, but the magnitudes of upregulation differ (IL1B, IL36A, 1L19, CXCL8, CXCL1, CCL20, SERPINB3, SERPIN4, etc.).[5]

Single gene or oligogenic models greatly help identify the mechanistic scenario operating in vivo, paving the way for precision medicine approaches. Single gene models lead to stratification based on genetic architecture and their mechanistic consequences, such as CARD14-associated diseases, deficiency of the interleukin 1 (IL-1) receptor antagonist (DIRA), and deficiency of interleukin-36 receptor antagonist (DITRA).[6] Interestingly, Dr. Bachelez shared that psoriasis is a prevalent component of Singleton-Merten syndrome that is a rare interferonopathy has a gain-of-function mutation in *IFIH1* (MDA5) or *DDX58* (RIG-1).[7] Indeed, type I interferon overlaps rare and more frequent immune-mediated inflammatory diseases.

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