Dermatology

Brief Report

Dermatology
DOI: 10.1159/000531496

Received: March 22, 2023
Accepted: June 5, 2023
Published online: June 10, 2023

Clinical and Molecular Characterization of Hidradenitis Suppurativa: A Practical Framework for Novel Therapeutic Targets

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Keywords
Hidradenitis suppurativa · Syndromic forms · Autoinflammatory skin diseases · Causative genetic variants and disrupted pathways · 2D-3D cells and organoids models · Biomarkers discovery · Genotype-phenotype correlation · Tailored treatment

Abstract

Background: The pathophysiological picture underlying hidradenitis suppurativa (HS) and its syndromic forms is still patchy, thus presenting a great challenge for dermatologists and researchers since just by better understanding the pathogenesis of disease we could identify novel therapeutic targets. ***Methods:*** We propose a practical framework to improve subcategorization of HS patients and support the genotype-phenotype correlation, useful for endotype-directed therapies development. ***Results:*** This framework includes (i) clinical work-up that involves the collection of demographic, lifestyle, and clinical data as well as the collection of different biological samples; (ii) genetic-molecular work-up, based on multi-omics analysis in combination with bioinformatics pipelines to unravel the complex etiology of HS and its syndromic forms; (iii) functional studies, – represented by skin fibroblast cell cultures, reconstructed epidermal models (both 2D and 3D) and organoids –, of candidate biomarkers and genetic findings necessary to validate novel potential molecular mechanisms possibly involved and druggable in HS; (iv) genotype-phenotype correlation and clinical translation in tailored targeted therapies. ***Conclusion:*** Omic findings should be merged and integrated with clinical data; moreover, the skin-omic profiles from each HS patient should be matched and integrated with the ones already reported in public repositories, supporting the efforts of the researchers and clinicians to discover novel biomarkers and molecular pathways with the ultimate goal of providing faster development of novel patient-tailored therapeutic approaches.

Introduction

Hidradenitis suppurativa (HS) is a chronic autoinflammatory skin disease of the pilosebaceous unit presenting pseudocystic and inflammatory nodules, abscesses, fistulas, and/or fibrotic scars on apocrine sweat gland-bearing skin

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[1], which may occur as single disorder or with associated diseases [2]. Syndrome-like presentation of HS consisting of several immune-mediated inflammatory disorders or inherited conditions has been also reported in few patients, a setting termed "syndromic" HS [3].

A prospective multinational survey of HS patients identified several critical unmet needs that will require multidisciplinary collaboration: (i) disease awareness, (ii) delay in diagnosis, (iii) quality and cost of care, (iv) control of symptoms, (v) assessment of life impact, (vi) mental wellness, (vii) associated diseases, and (viii) safe and effective treatments [4]. Treatment of HS patients is challenging as each patient has a particular phenotype and response to available treatments [3]. This could be also due to the genetic and immunological background of each patient; a range of genetic variants shared among other autoinflammatory diseases have been reported in these patients that point to HS as an inborn error of the immune response characterized by an increased secretion of pro-inflammatory molecules in both lesional skin and serum [5]. Despite this, the pathophysiological picture underlying HS and its syndromic forms is still jagged; this represents an important challenge since just by unravelling the disease's pathogenesis we will be able to recognize novel therapeutic targets.

Materials and Methods

Based on our expertise, we propose a practical framework to improve the management of HS patients, with an integrated clinical and molecular pipeline to expand subcategorization of HS patients and to support the genotype-phenotype correlation, useful for endotype-directed therapies development.

Results

An optimized framework for HS patients as well as for patients with related complex phenotypes includes the following steps: (1) deep clinical investigation; (2) genetic-molecular work-up; (3) functional studies; (4) genotype-phenotype correlation and clinical translation in tailored targeted therapies (shown in Fig. 1).

1. Clinical work-up of HS and its complex syndromic forms involves the collection of demographic, lifestyle, and clinical data as well as the collection of different biological samples. An accurate clinical phenotyping requires full-skin examination through objective assessment and in-vivo noninvasive skin imaging such as high-frequency ultrasound, thermography, and three-dimensional (3D) skin topography. The production of holistic health records through a smartphone application, already available for patients on Android platform [6], represents an innovative way to complement medical observations and remotely monitor the patient's psychophysical condition, thus enhancing integration of clinical and lifestyle data [7]. Histology of HS lesional skin, while not recommended by current HS guidelines, is important for the differential diagnosis of complex phenotypes and for marking the disease development. In addition, biobanking is a critical step involving an accurate sampling strategy of lesional, perilesional, and healthy control skin – from cutaneous biopsies and/or resected tissues specimens – and other biological samples such as saliva, plasma, serum, and peripheral blood mononuclear cells [7]. These samples could reveal biomarkers useful for stratifying HS patients into therapeutic subcategories related to clinical response, thus reserving great potential for advancing knowledge of HS pathophysiology and improving clinical management of HS patients through the identification of novel therapeutic targets.
2. Genetic-molecular work-up is principally based on genetic counseling. Next-generation sequencing analyses (e.g., genomics and transcriptomic profiling of skin biopsies and/or peripheral blood mononuclear cells) in combination with bioinformatics pipelines are enabling researchers to employ a more comprehensive approach to unravelling the complex etiology of HS and its syndromic forms, thus translating the omic findings into functional models to validate/identify novel potential therapeutic targets. In our current experience, these approaches allowed us to describe common biological pathways shared by syndromic HS patients [8] as well as to draft a preliminary genotype/phenotype correlation [9].
3. Functional studies of candidate molecular biomarkers and genetic findings are necessary to validate novel potential molecular mechanisms underlying the complex HS phenotypes. These studies involve immunostaining techniques on patients' skin biopsies as well as on ex vivo models represented by skin fibroblast cell cultures, reconstructed epidermal models (both 2D and 3D), and organoids – tissue-engineered cell-based in vitro models that sum up different aspects of both the structure and function of the corresponding in vivo tissue – able to recapitulate the complex pathogenetic scenario of HS and its syndromic forms. Cultivation of outer root sheath-derived keratinocytes from HS patients, carrying genetic variations associated with the disease, represents a useful strategy for in vitro studies on molecular markers, candidate genes, and biological signaling pathways possibly involved and druggable in HS [7].

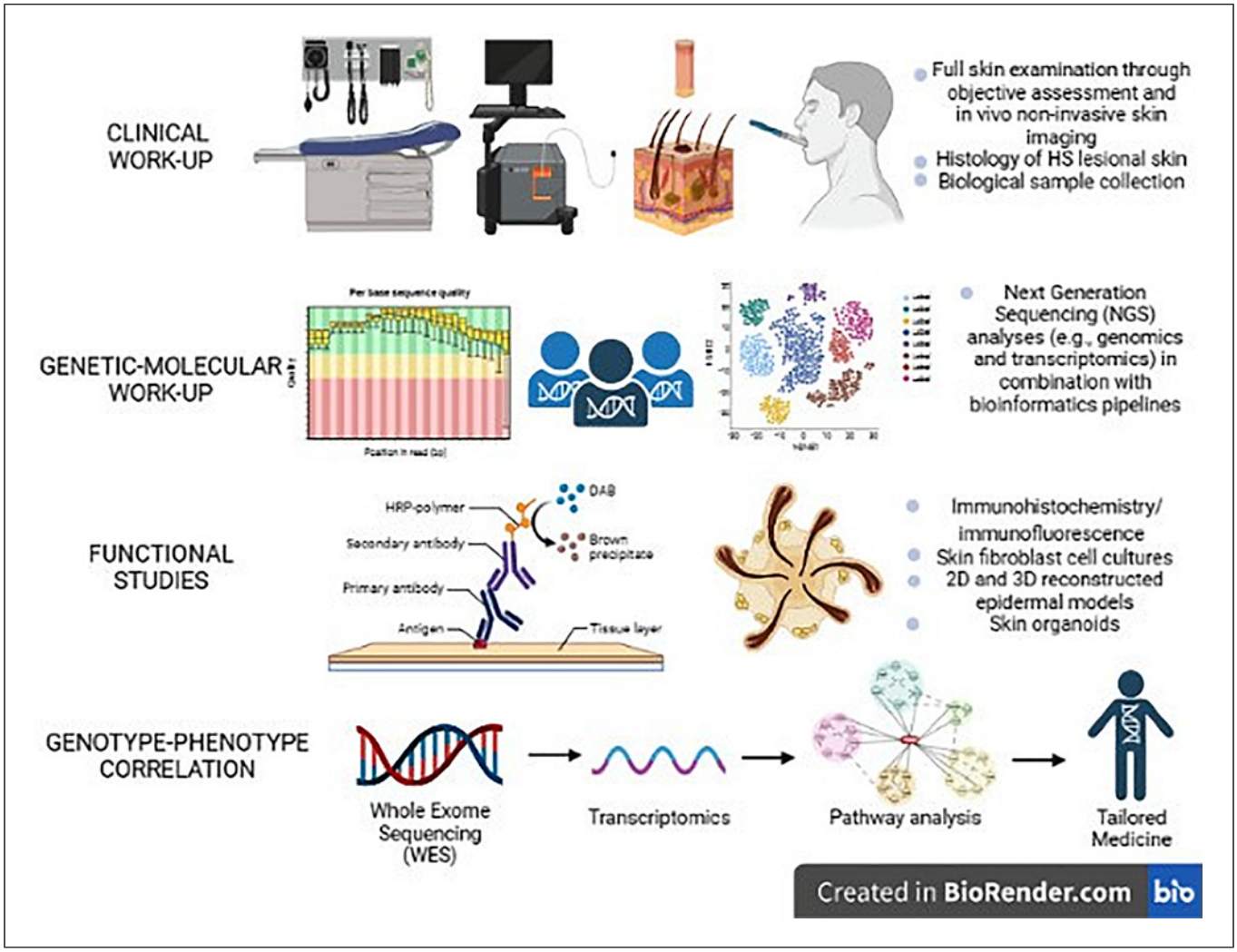

Fig. 1. Schematic representation of the proposed framework for HS patients, including a thorough clinical and genetic-molecular work-up, functional studies, genotype-phenotype correlation, and clinical translation into tailored targeted therapies (created with BioRender.com).

4. Genotype-phenotype correlation represents the crucial step aimed at integrating clinical, genetic, and molecular data in a cohesive model based on each individual patient, carrying the hope and the potential to develop personalized therapy for each patient.

Conclusion

In our proposed pipeline, genomics and transcriptomics data are merged and integrated with clinical and histopathological findings; furthermore, the skin-omic profiles from each HS patient are matched and integrated with the ones already reported in public repositories, supporting the efforts of the researchers and clinicians to discover novel biomarkers and molecular pathways with the ultimate goal of providing faster development of novel patient-tailored therapeutic approaches.

Key Message

Discovery of biomarkers will provide a faster development of novel patient-tailored therapeutic approaches.

Statement of Ethics

This study was reviewed and approved by the Area B Milan Ethics Committee, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan (protocol No. 487_2020).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This work was supported by a Biomolecular Analyses for Tailored Medicine in AcneiNversa (BATMAN) project, funded by ERA-PerMed, by Starting Grant (SG-2019-12369421) funded by the Italian Ministry of Health, by Grant (RC16/2018) from the Institute for Maternal and Child Health IRCCS "Burlo Garofolo" funded by the Italian Ministry of Health, and by a grant from Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan (protocol No. 487_2020). This work was also partially supported by Italian Ministry of Health (Ricerca Corrente 2023)/Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Italy.

Author Contributions

Chiara Moltrasio: conceptualization. Chiara Moltrasio and Sergio Crovella: writing – original draft preparation. Paola Maura Tricarico, Ronald Rodrigues Moura, Lucas Brandao, and Angelo Valerio Marzano: writing – reviewing and editing.

Data Availability Statement

All data presented in this study are included in this article. Further inquiries can be directed to the corresponding author.

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