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REVIEW ARTICLE

Molecular analysis of inflammatory diseases

Aya Hamad Almughrbi | Sergio Crovella

Biological Science Program, Department of Biological and Environmental Sciences, College of Arts and Sciences, Qatar University, Doha, Qatar

Correspondence
Sergio Crovella, Department of Biological and Environmental Sciences, College of Arts and Sciences, Qatar University, P.O. Box 2713, Doha, Qatar.
Email: sgrovella@qu.edu.qa

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Abstract

If we try to describe the search for molecular actors involved in inflammatory diseases, the picture best representing this task is a mission to unexplored worlds. However, researchers nowadays have powerful tools to support this journey to the complexity of the unknown: Next generation Sequencing technologies have provided a plethora of data describing the different OMICs possibly involved in the different inflammatory diseases. Here, we focused on autoinflammatory skin diseases showing the progress of OMICs-related findings in the understanding of Syndromic HS pathogenesis. We described the studies reporting possible genotype/phenotype correlation in PASH and PAPASH patients (both unrelated or familial cases), highlighting those just genetic variations associated with the diseases have been observed, but the information on common pathways shared by PASH and PAPASH patients were lacking, thus rendering difficult to decipher the common molecular basis of these autoinflammatory conditions. Aimed at filling this gap of knowledge, we proposed an integrated OMICs approach able to identify common pathways shared by subjects suffering from PASH and PAPASH: pathway-based whole sequencing analysis allowed the identification of 4 pathways, keratinization, formation of the cornified envelope steroid metabolism and Vitamin D metabolism, disrupted in PASH and PAPASH patients. Finally, we mentioned the novel bioinformatic platform, named PlatOMICs, capable of integrating OMICs experimental findings also with the ones already reported in public repositories supporting the efforts of the researchers and clinicians to discover molecular pathways shared by individuals suffering of a disease, confronting and integrating the bench findings with the in-silico ones.

KEYWORDS
bioinformatics, data integration, inflammation, OMICs, skin autoinflammatory diseases

1 | BACKGROUND

The search for molecular mechanisms involved in inflammatory diseases is a task of giant proportion due to the numerous inflammatory disorders and to the rising role of inflammation in diseases not previously considered as inflammatory (i.e. Alzheimer, Parkinson). Moreover, inflammation is a hallmark of cancer and is considered as a possible target for drug intervention.[1]

Inflammation is a natural complex body defense reaction to biological, chemical or physical stimuli that is strongly bounded with innate immunity, its inflammatory mediators that are regulated by both innate and adaptive immune cells and molecular mechanisms.[2] Inflammation is primarily active in defense mechanisms against pathogenic and infectious agents; however, it also participates in the pathophysiology of many chronic conditions.[3]

According to Ilya Mechnikov's discovery of phagocytosis, the recruitment of leukocytes in inflamed tissue represents the basic characteristic of inflammatory diseases after having observed the ingestion of foreign bodies by blood leukocytes. Acute and chronic inflammation have been distinguished by the mere manifestation of the cardinal signs of inflammation elucidated in the past: redness (rubor), pain (dolor), heat (calor) and swelling (tumour). In the presence of them all, it is announced as an acute inflammation, but the absence of some might indicate chronic inflammation.[2] Physiologically, the acute stage of inflammation involves the migration of immune cells to the site of injury in a cascade of reactions induced by mediators such as chemokines, cytokines and acute-phase proteins. Nevertheless, if the acute stage was insufficient to heal the damaged tissues, persistent inflammation will contribute to the chronic phase, which as a result, leads to the rise of consequential pathological conditions; some of which include arthritis, asthma, atherosclerosis, autoimmune diseases, diabetes and cancer.[4]

Despite the fact that inflammation is not the primary cause of such pathologies, it plays a pivotal role in their progression.[2] As a matter of fact, cancer-related inflammation denotes the seventh hallmark of cancer in addition to six other hallmarks including selective growth and proliferative advantage, invasion and metastasis and vascularization, which makes it increase the risk factor of cancer.[5]

It has been found that inflammation is accompanied by an overall decline in immune competency, which leads to the proliferation, endurance and metastasis of malignant cells while additionally reducing the hormonal and chemotherapeutic responses due to subversion of adaptive immunity. Moreover, research has pointed out the presence of another molecular mechanism in relation to cancer, which has been known as the eighth hallmark, where inflammatory mediators induce genetic instability by accumulating random alterations of the genetic composition of tumour cells.[6] On the contrary, neurodegenerative diseases such as Alzheimer's, Parkinson's, multiple sclerosis and amyotrophic lateral sclerosis have been recently found in close association with inflammation in onset or progression, as inflammatory components were present in nervous tissue even though they have not been identified as inflammatory diseases priorly.[7] Furthermore, chronic inflammation is also proposed as an underlying mechanism of aging that would contribute to a gradual transformation from normal aging into age-related diseases. Published data imply a clear connection between persistent upregulated pro-inflammatory mediators for example, TNF-alpha, IL-1beta, IL-6, COX-2, iNOS and aging because of an age-related redox imbalance that triggers the activation of several pro-inflammatory signalling pathways. This recent finding may postulate improved treatments, which can directly target the process of aging and lower the severity of age-related pathologies, inevitably boosting healthy life expectancy.[8]

All considered, inflammation has been perceived as an imperative therapeutic target for the development of new pharmacological interventions for numerous pathological conditions. As such, more innovative drug designs were approached that can control the multi-factorial biological systems and propose new implications of already existing clinical medications.[9]

2 | INFLAMMATION AND INFLAMMATORY DISEASES

In this complex inflammation universe, the search for molecular biomarkers and mechanisms involved in this trait is a typical needle in a haystack mission. Just to have an idea of the current literature, if we perform and NCBI PubMed query including the key words "Molecular Inflammation," more than 121000 entries are found. (https://pubmed.ncbi.nlm.nih.gov/?term=Molecualr+inflammation).

Even a broader number of articles (more than 449000) https://pubmed.ncbi.nlm.nih.gov/?term=inflammation+diseases.

Thus, with such great numbers, even when considering studies focused on only one disease or a disease category, the PubMed search shows a great the numerosity of findings. As an example, using the key words, inflammation and cancer, we retrieve almost 111000 articles (https://pubmed.ncbi.nlm.nih.gov/?term=inflammation+cancer); if we look at cardiovascular diseases, interrogating PubMed with cardiovascular and inflammation key words, more than 93000 hits are found.

(https://pubmed.ncbi.nlm.nih.gov/?term=cardiovascular++inflammation&sort=date).

Moreover, the search for inflammation and neurologic disorders results in more than 81000 articles when using the key words "neurologic diseases inflammation".

(https://pubmed.ncbi.nlm.nih.gov/?term=neurologic+diseases+inflammation&sort=date),

If we restrict the search focusing on skin diseases, using the key words "molecular inflammation in skin diseases", more than 5400 entries are found in PubMed.

(https://pubmed.ncbi.nlm.nih.gov/?term=molecular+inflammation+in+skin+diseases&sort=date). When the search is further specified, focusing just on one category of inflammatory diseases, namely the autoinflammatory skin diseases, PubMed provides 811 entries using the keywords "inflammation in autoinflammatory skin diseases".

(https://pubmed.ncbi.nlm.nih.gov/?term=inflammation+in+autoinflammatory+skin+diseases&sort=date).

3 | SKIN AUTOINFLAMMATORY DISEASES

In this section, the focus will be on autoinflammatory diseases with emphasis on those involving the skin. Autoinflammatory diseases are disorders of a wide spectrum of genetic and non-genetic inflammatory diseases of the innate immunity and they are characterized by recurrent fever, rash and systemic inflammation damaging skin, joints and serosal surfaces. Therefore, it has also been confirmed that such diseases are a result of innate immunity dysfunction through most of

their responsiveness to IL-1β blockade, which indicates the key pro-inflammatory cytokine of innate immune reactions.[10] In contrast to autoimmune diseases, which are activated by adaptive immune cells, no specific autoantibodies or autoreactive immune cells are located in autoinflammatory diseases.[11] The pathogenesis of autoinflammatory diseases largely involves the dysregulation of inflammasomes that leads to excessive production of interleukin 1β. The diagnosis of such diseases requires recognition of the trends in presentation and differential diagnosis.[12] In many cases, the genetic study of autoinflammatory diseases links them all to mutations taking place in a single gene, which are called monogenic autoinflammatory diseases. Typically, autoinflammatory diseases are caused by genetic alterations, which in turn dysregulate the functions of many proteins participating in innate immune responses; however, there are some diseases that remain of unknown cause.[13] The four initial autoinflammatory diseases to be discovered were familial Mediterranean fever (FMF), hyper IgD syndrome (HIDS), cryopyrin-associated periodic fever syndrome (CAPS) or NLRP3-associated autoinflammatory disease and tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS). Common symptoms observed in all the aforementioned syndromes include fever, arthritis, chest pain and swelling of bone tissue.[14] In addition, such diseases are accompanied with the risk of developing amyloidosis, a lethal accumulation of blood protein in visceral organs.[15] Ever since these syndromes were described, many new disorders have been found; some of which present with predominant cutaneous symptoms that are known as autoinflammatory skin diseases.[16]

The skin is one of the main organs associated with classic autoinflammatory diseases of the innate immune system, where most pathological manifestations are represented by cutaneous lesions. In addition to the previously named 4 syndromes, IL-1β is also responsible for the production of other cytokines and chemokines that trigger the recruitment of neutrophils, the key players in autoinflammation, to initiate the deficiencies of IL-1 and IL-36 receptor antagonists (DIRA) and (DITRA). Both syndromes feature pustular lesions as one of the most common symptoms of autoinflammation.[17] There are many other skin disorders hallmarked by a build-up of neutrophils in the skin and internal organs. Such conditions that are distinguished by mature neutrophil infiltration in the absence of infection are called neutrophilic dermatoses. Pyoderma gangernosum (PG), for instance, is a neutrophilic dermatosis that may manifested isolated or in syndromic autoinflammatory forms with other neutrophilic dermatoses including pyogenic arthritis, acne and hidradenitis suppurativa. Consequently, (PAPA) involves pyogenic arthritis, PG and acne, (PASH) PG, acne and suppurative hidradenitis and (PAPASH) combines pyogenic arthritis, PG, acne and suppurative hidradenitis.[18] Two of which are syndromes of hidradenitis suppurativa (HS), a chronic autoinflammatory skin disease that is found predominantly in body skin folds and is characterized by a wide range of clinical manifestations and multifactorial pathogenesis. Hidradenitis suppurativa, as proposed, may exist with other comorbidities in the form of complex syndromes in some patients, making it additionally challenging for new diagnostics and therapeutic approaches.[19] Follicular hyperkeratinization, plugging and activation of autoinflammatory pathways are the main aetiological contributors to HS pathogenesis. The classification of syndromic HS comprises 3 categories: genetic, follicular and autoinflammatory diseases, where PASH and PAPASH are displayed.[20]

PASH and PAPASH are autoinflammatory syndromes found in the disorder spectrum of PAPA. Although PG and HS present with different clinical features, PASH and PAPASH share a similar pathogenesis; a mutation in the promoter region of proline-serine-threonine phosphatase interacting protein 1 (PSTPIP1) gene.[21] This mutation is followed by a molecular autoinflammatory process through the activation of an inflammasome, which, in turn, activates caspase-1 that is responsible for the cleavage of pro-interleukin IL-1β into its active form. The excessive production of IL-1β causes an over secretion of inflammatory cytokines, specifically, IL-17 that is directly controlling the recruitment of neutrophils. As a result, an inflammatory response will be mediated in the clinical form of PG, acne and HS.[22] In the case of isolated PG, the overexpression of the IL-17 in the lesional skin supports its hypothetical role as an innate immunity-related cytokine in the pathophysiology of PASH and PAPASH.[23] PG, particularly, is characterized by skin ulcers with impaired erythematous-violaceous borders while HS is featured with debilitating nodules, abscesses, sinus tracts and fistulas. PASH differs from PAPASH by the absence of pyogenic arthritis whereas PG and HS symptoms are presented in both. Even though PASH was thought to be a monogenic syndrome of pleiotropic involvement, recent research has suggested a polygenic autoinflammatory nature. It was found that the presence of alleles of high numbers of CCTG repeats similar to that of *PSTPIP1* promoter dysregulated the expression of *PSTPIP1* promoter, which made patients disposed to neutrophilic dermatoses like PASH and PAPASH.[24] Since the overexpression of IL-17 is the main pathogenetic signalling pathway of such autoinflammatory syndromes, IL-17 antagonists might indicate a possible therapeutic approach in the future.[18]

4 | MOLECULAR TOOLS FOR STUDYING INFLAMMATORY DISEASES

As reported above, the role of inflammation in several diseases is well recognized. However, analysis of the molecular component of the different multifactorial inflammatory diseases is a task in need of technological solutions, allowing researchers to have a wider and more detailed vision on all the actors involved in the disease onset, clinical progression and drugs' response. This, in turn, will provide answers to the challenges of the modern medicine endeavouring patients' tailored diagnosis and follow-up.

Currently, we are in the post-genomic era and recent advances in technology, such as the Next Generation Sequencing, provided the scientists with novel, robust and powerful tools to study the molecular mechanisms at the basis of inflammatory diseases.

Nowadays, many OMICs data, mostly, genomics and transcriptomics, are available in public repositories and are consultable.

Therefore, researchers can take advantage of already published data to create hypotheses on the aetiopathogenesis of diseases. Nevertheless, even if many studies widely analysing the genome, such as Genome Wide Association Studies (GWAS), have been performed, due to the high statistical pressure characterizing the GWAS findings, a relatively small contribution has been obtained to mechanistically unravel most of the oligogenic, polygenic and multifactorial diseases. Besides, transcriptome studies are sometimes difficult to be used and compared within them due to the different conditions, tissues, analysis methods and depth (Chips vs. RNASeq) in which they have been performed.

Hence, being aware of the heterogeneity of the methods, samples and platforms used to obtain genomics and transcriptomics results, the findings that could have an impact on improving the understanding of how a disease initiates and develops are those related to the identification of biological pathways associated with a pathological condition. To identify these pathways, there is no choice other than integrating OMICs findings to achieve information possibly translatable to the clinical practice; both diagnosis or patients' follow-up.

To visualize the volume of published articles dealing with inflammation, NGS and OMICs, we performed a quick search on PubMed. If we interrogate PubMed using the keywords "next generation sequencing inflammatory diseases," we obtain more than 1300 published articles on this topic, showing how many OMICs data have been produced and are still being currently produced (https://pubmed.ncbi.nlm.nih.gov/?term=next+generation+sequencing+inflammatory+diseases&sort=date). When restricting the search to "next generation sequencing inflammatory skin diseases," 182 results are found in PubMed. (https://pubmed.ncbi.nlm.nih.gov/?term=next+generation+sequencing+inflammatory+skin+diseases&sort=date). Finally, 61 entries can be retrieved from PubMed by narrowing the search to "next generation sequencing autoinflammatory skin diseases."

(https://pubmed.ncbi.nlm.nih.gov/?term=next+generation+sequencing+autoinflammatory+skin+diseases&sort=date).

Most studies are focused on genome and transcriptome while a smaller number of articles describe proteomics findings. When considering the genome results, several GWAS are present in the literature, many of them considering a high number of patients interrogated with high density SNV chips or whole exome sequencing (WES). As a recent example, we report the extensive review of Calender et al.[25] on the impact of the immune mediated autoinflammatory disorder named sarcoidosis. The authors critically discuss the findings obtained by GWAS, showing an association with DRB1*1101 and DRB1*1501 HLA class II alleles with the disease, highlighting the contribution of this approach in understanding such a complex disorder. In addition, the limitations due the high statistical pressure characterizing GWAS studies have been cited. Furthermore, the WES approach in both familiar cases as well as in sporadic patients is extensively described. Novel findings reported that within all genes in which rare variants have been found, 10 genes, involved in pathways related to autophagy impairment, namely Sec16A, AP5B1 and RREB1, regulation of G protein, namely OBSCN, CTTND2 and DNAH11 and activation of T-cell response, namely IDO2 and IGSF3, mitotic cell division and immunologic synapsis have been observed.

After having attempted to retrieve and describe the main pathways playing a possible role in the disease onset and its management, the authors are strongly recommending an integration of genetic findings with transcriptome results aimed at obtaining a more comprehensive and detailed picture of the aetiopathological mechanisms at the basic of the highly heterogeneous, both genetically and clinically, disease as sarcoidosis. At the end of their elegant review, the authors were wondering how to translate such heterogeneous findings in the clinical practice to be able to possibly provide a personalized patients' treatment.

5 | MOLECULAR GENETICS AND PATHWAYS DISCOVERY IN SINDROMICS HS PATIENTS: THE EXAMPLES OF PASH AND PAPASH

In this section, we will describe OMICs findings in autoinflammatory skin diseases focusing on Hidradenitis suppurativa and its syndromic forms as PASH and PAPASH and novel bioinformatic pipelines will be proposed to analyse NGS results.

Several articles have been published on genetics of PASH and PAPASH; however, most of them just focused on gene variations findings, which is well worth of attention, but not always useful in fully understanding the pathogenesis of the diseases. Mutation-based NGS analysis provided interesting findings, discovering novel genes and actors involved in these complex pathologies, yet not always has it been possible to integrate the results, thus not being able to define shared pathological or impaired pathways common to the majority of PASH and PAPASH patients. The identification of common pathways is the major challenge and can shed supplementary light on the mechanisms involved in these autoinflammatory diseases. Aimed at showing examples of the state of the arts concerning genetic studies in PASH and PAPASH using a gene/variation based approach, we are now citing some recent interesting studies.

Zhang et al.[26] described 5 PASH patients from a Chinese Han family whose affected members were carrying a novel mutation (c.228_229insCACC) in heterozygosis occurring in one of the genes, namely PSENEN, involved in the gamma-secretase pathway already known to be genetically impaired in some familiar cases of HS. While this finding is interesting, it is just supporting a possible involvement of a HS specific pathway (gamma-secretase) in the PASH, without identifying others able to explain the entire pathological complex phenotype, not only characterized by HS but also by Pyoderma gangrenosum contributing to PASH.

Although it is not recently published, the study of Marzano and collaborators performed on 5 unrelated Italian PASH patients is giving a very useful lesson related to the genetic heterogeneity of the disease, showing mutations in genes involved in autoinflammatory

disease, namely *NLRP3*, *IL1RN*, *PSPTIP1*, *MEFV*, *NOD2* and *PSMB8*, each with variants specific for a PASH patient.[27] Therefore, it suggests that the 5 enrolled patients did not share any common pathways able to explain the disease.

In a successive case report the genetic heterogeneity of PASH has been confirmed by Sonbol et al.[28] who have not found previously known mutations in *PSTPIP1*, *NCSTN*, *PSENEN and PSEN1* of a 42-year-old PASH patient. In this case, targeted gene analysis did not provide any useful result.

Another case study by Dushastelet et al.[29] reports a novel Nicastrin mutation (p. Thr115Asn*20 at *NCTSN* gene) in a PASH patient. Once again, this information is just useful to include the impaired gamma secretase pathway, a feature of HS, in the molecular patient's description, which only provides a partial picture of the pathogenesis.

Calderón-Castrat et al.,[30] again, in a simple case study reported the presence of a PSTPIP1 heterozygous missense mutation c.1213 C>T (p. Arg405Cys) in a PASH patient. Thereby, adding another genetic variant associated with the disease without any shared pathways analysis to contribute to a better understanding if and how PASH patients, despite of the genetic heterogeneity, do share some common molecular characteristics.

In their interesting study, Marzano et al.[27] analysed the genetic characteristics of 13 patients with pyoderma gangrenosum (PG) and 7 patients with PASH. The authors observed genetic variations in *MEFV*, *NLRP3*, *NLRP12*, *NOD2*, *LPIN2* and P*STPIP*, suggesting a common genetic background shared by PG and PASH patients related to autoinflammation. Despite this hypothesis, the authors failed in discovering any pathway specific to the diseases, and, eventually, comparable with the ones, if any, already described in the literature for PASH patients.

A very recent research from Marzano and colleagues succeeded in deciphering, at least partially, the genotype/phenotype correlation in 10 unrelated PASH patients by using Whole-Exome Sequencing.[31] Mutations have been identified in *MEFV*, *PSTPIP1*, *NLRC4*, *WDR1*, *NOD2* and *OTULIN* genes as well as in two genes regulating the keratinization process, including *NCSTN* and *GJB2*. This study confirmed known mutations typical of PASH patients and discovered new variants in genes possibly involved in the complex mechanisms at the basis of skin autoinflammatory diseases. However, in this case too, no pathway has been observed as a common base of the disease.

Consequently, when considering the examples reported above, we can easily observe that in most of the studies few patients were available; some described one single patient, clinical heterogeneity was present, and there was a lack in the identification of common pathways in all cases.

Here, we report a recent study also performed on a small number of Italian unrelated PASH ($n = 4$) and PAPASH ($N = 1$) patients, showing clinical heterogeneity.[32] A common pathway approach has been used based on pathways enrichment analysis obtained by computing the functional variants density in genes involved in the Reactome Pathways (https://reactome.org/). By doing so, 4 disrupted pathways, shared by all patients, have been identified, namely keratinization, formation of the cornified envelope steroid metabolism and Vitamin D metabolism. Interestingly, all patients showed Vitamin D deficiency, thus confirming the results obtained, and opening an easy feasible possibility of intervention aimed at diminishing Vitamin D avitaminosis. Lack of Vitamin D is a well-known fact in HS patients mostly associated with disease severity.[33] This common feature has been also identified in the 5 syndromic HS patients, together with other disrupted pathways, thus providing novel mechanistic insights on the syndromic HS pathogenesis, simply using an alternative strategy, considering not only the genotype/phenotype correlation, but also the disrupted pathways shared by all patients.

When considering transcriptome studies, as stated before, few of them are present in the scientific literature and no integration with other OMICS findings has been reported so far. As an example, we cite the work of Mariottoni et al.[34] who analysed the expression signature of monocytes and macrophages in Hidradenitis suppurativa using Single Cell RNASeq, which was aimed at identifying differentially expressed genes acting during the transition from monocytes to macrophages and their polarization. The authors suggested the STAT1/IFN-signalling axis as possible drug targets for future therapeutic intervention.

Finally, we found an additional interesting study on the microbiome of skin and gut in HS patients.[35] The authors succeeded to identify in the stools, the Ruminococcus gnavus, while Finegoldia magna has been detected enriched in the skin from HS subjects when compared with the skin of healthy controls.

6 | OMICS INTEGRATION IS AN URGENT NEED TO UNRAVEL THE AETIO-PATHOGENETIC MECHANISMS OCCURRING IN INFLAMMATORY DISEASE: FOCUSED ON SKIN AUTOINFLAMMATORY DISEASES

As conclusive remarks of this article, we highlight the great heterogeneity of OMICs application in inflammatory diseases, including the tools used (i.e. GWAS vs. WES; Expression Arrays vs. RNA Sequencing), and the analyses performed using different bioinformatic platforms (Figure 1).

Throughout the article, we considered a narrow category of inflammatory diseases, the Syndromic HS, namely PASH and PAPASH, showing how most of the studies identified genetic variants useful for a tentative genotype/phenotype correlation, but unable to detect pathways shared by all patients. Hence, no matter which NGS tool is used, the results provided are still far away from the identification of a common mechanism at the basis of the complex and heterogeneous clinical phenotype of syndromic HS patients.

OMICs data integration is mandatory, so as to allow clinicians to better understand how molecularly the diseases are functioning. Moreover, they should as well understand how to take advantage of the molecular pathways knowledge to diagnose the diseases earlier

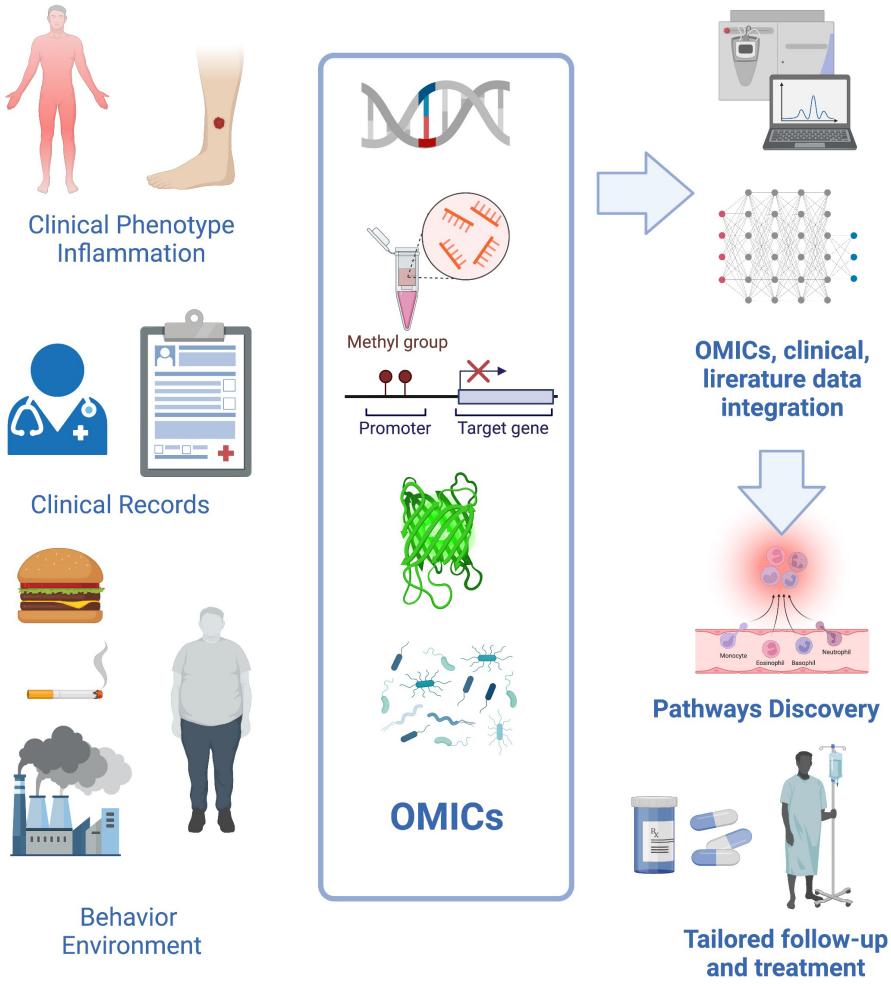

FIGURE 1 Heterogeneity of complex inflammatory diseases is depicted, showing the different types of data that need to be considered as a whole. Examples of different OMICs are shown as well as the need of data integration, including literature and public repositories findings, to achieve the objective of a personalized diagnosis and a tailored patients' follow-up. Images have been created using Licenced Biorender Software (https://biorender.com)

to enhance patients' follow-up and try a tailored treatment based on the molecular background.

A simple, however, useful example has been already cited.[32] The impairment of Vitamin D has been molecularly observed by using a WES approach, this, though looks simple and obvious, allows clinicians to supplement this Vitamin in the attempt to ameliorate the quality of life of patients. In addition, in attempt of increasing the possibility of integrating OMICs experimental findings with the ones already reported in public repositories, we recently developed a bioinformatic platform named PlatOMICs.[36] It is aimed at supporting the efforts of the researchers and clinicians to discover molecular pathways shared by individuals suffering of a disease, confronting and integrating the bench findings with the in-silico ones.

Finally, two initiatives are worth to be mentioned; the first one is brightly described in the article of Zouboulis et al.[37] It revises through an extensive Metaanalysis, the integrated relationships between Hidradenitis suppurativa related genes, transcriptomes and the available drugs including the most recent and advanced ones. The second one is the very recent bioinformatic pipeline, employing variant enrichment analysis (VEA) to identify common disrupted pathways in PASH and PAPASH patients, simply using WES data.[32] It proposes, in absence of transcriptomic findings, an in-silico method to compare the newly discovered pathways with the expression repositories (both transcriptome and proteome findings) related to health and lesional skin tissues. This, is the last model of integration that we have developed, which allowed us to identify autophagy and neutrophils-invasion disrupted pathways as the common mechanical background in PASH and PAPASH patients.

In conclusion, OMICS data integration with clinical and exposome findings represents the novel frontier, in continuous growth improvement that will endeavour the next discoveries in the field of inflammatory diseases.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

SC conceived the article and drafted the manuscript, HAH performed extensive literature review and revised the manuscript contributing to image drawing.

DATA AVAILABILITY STATEMENT

All links cited in the article are from NCBI PubMed and are freely available.

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