Platform for Multi-Omics Integration (PlatOMICs) applied to skin diseases with alterations in Notch signaling pathway.

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ABSTRACT

Over the last years, a huge amount of information concerning Omics data have been produced and are of crucial significance for the understanding of the molecular mechanisms and for the identification of potential molecular targets associated to many diseases. Indeed, Omics approaches allowed to initially decipher several biological processes found to be critically involved in the context of various pathologies. Despite these remarkable scientific advances, the majority of obtained results are disconnected and divergent, making their use limited. Thus, our team started the deployment of PlatOMICs, a new Platform for multi-omics integration, carrying an user-friendly interface. Currently, PlatOMICs is under deployment in an international cooperation including Brazil, Qatar and Italy and has been divided into three phases. In the present work we report phase I in which multiple database/resource/repositories were interrogated to access data from skin diseases presenting alterations in Notch signaling pathway, as they constitute a cluster of disorders that were extensively studied during the Omics era, in order to perform biological syntactical analysis to be implemented in the next PlatOMICs phases.

KEYWORDS

Omics, genomics, transcriptomics, proteomics, network interaction, skin diseases.

1 INTRODUCTION

We developed a Platform for Multi-Omics Integration (PlatOMICs) that assembles a set of tools and bioinformatics applications that can allow the retrieval of scientific literature data (genomics, epigenomics, transcriptomics, proteomics and microbiomics) together with the analysis, deciphering, interpretation and integration of all these set of information automatically, therefore building networks of molecular interactions and Omics meta-analysis.
Our goal is to refine the data available in scientific literature and in Omics databases/resource/repositories relative to skin diseases that are characterized by defects in Notch signaling route, seeking to describe networks of molecular interactions in the epithelial tissue potentially involved in the loss of homeostasis in this district, event that may lead to the onset of different skin pathologies.

1.1 Multi-omics integration applied to skin diseases with Notch signaling alterations

An aberrant progression of Notch signaling, either due to altered regulation or direct mutations, can induce skin diseases [1,2]. To date, molecular alterations in Notch signaling pathway have been reported for five human skin diseases including: Hidradenitis Suppurativa (HS), Dowling Degos Disease (DDD), Adams–Oliver Syndrome (AOS), Psoriasis (PS) and Atopic Dermatitis (AD) [1,3]. Therefore, a deep characterization of this cellular route seems to be of

pivotal importance in order to clarify potential new pathogenic scenarios involved in these skin diseases. Indeed, considering this critical aspect, in order to further restrict the search, we decided to consider in this study only skin diseases possessing alterations in Notch pathway excluding malignancies.
These skin disorders have been thoroughly studied in the last five years; indeed, 1555 articles regarding these five diseases and OMICs (genomics, transcriptomics, proteomics and microbiomics) studies are available in PubMed [4].
Specifically, considering these five skin disorders possessing alterations in Notch signaling, 821 articles about genome, 225 about transcriptome, 143 about proteome and 602 about microbiome, were published.

1.2 Perspectives on multi-omics integration for skin diseases with alterations in Notch signaling pathway

Currently, PlatOMICs is under deployment in an international cooperation including Brazil, Qatar and Italy. PlatOMICs will be an online platform offering services to access and analyze scientific literature and Omics data automatically with great accuracy. The deployment was divided into three phases and in the present work, we report phase 1. Briefly, the various phases that constitute PlatOMICs multi-omics analysis are given by: phase I, step based on the interrogation and analysis of the whole available literature and Omics databases; phase II, stage regarding the analysis and questioning of previous and new Omics (or multi-omics) studies; phase III, part relative to the merge of findings deriving from phases I and II in order to finally compose the ultimate multi-omics integration in a meta-multi-omics analysis (Figure 1).

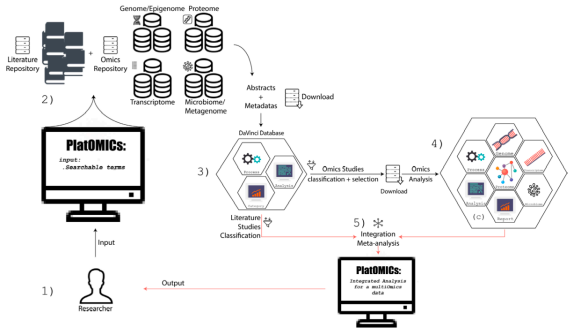

Figure 1. Workflow of OMICs Platform (PlatOMICs) for Omics integration. (1) The user informs the descriptors, categorical terms and keywords in PlatOMICs. (2-3) Through DaVinci tool, the literature and the OMICs databases will be evaluated. (4) Selected omics studies and new ones are (re)analyzed and integrated by standard pipelines. (5) PlatOMICs produces the final meta-analysis multi-omics integration results in a friendly interface.

The first analysis (phase I) outputted by PlatOMICs is performed by the new tool called *DaVinci Literature and Database Analysis* (under submission and not publicly available). Briefly, DaVinci is able to scan several databases, such as PubMed, SRA, GEODatabase and GWAS Catalog, extracting multiple information from summary, abstracts and other meta-data information to report a syntax analysis and molecular panels (genes, variants, tissues, cells and drugs). Next, following the study and sample selection from the previous researches, raw data might be downloaded. The analysis, including the new Omics (or multi-omics) studies, will be carried out by the same standard pipeline when performed, hence securing a more reliable and homogeneous investigation. Therefore, PlatOMICs will contain the results obtained from literature and their integration, databases and new Omics studies.

2 RESULTS

As a validation model, phase I of PlatOMICs was executed on skin diseases presenting alterations in Notch signaling pathway by examining the literature, thus providing molecular insights to multi-omics integration approaches.

2.1 Results deriving from literature analysis: molecular insights to multi-omics integration

The literature scan was accomplished by assessing the following term "(Hidradenitis Suppurativa OR Dowling Degos Disease OR Adams Oliver Syndrome OR Psoriasis OR Atopic Dermatitis) AND (Genome OR transcriptome OR proteome OR epigenome OR microbiome OR metagenome OR metabolome OR omic OR multi-omic) AND 'Homo sapiens'[orgn:__txid9606]" using the DaVinci tool.

A DaVinci literature database (DaVinci Lit) was created with 1252 articles retrieved from PubMed, and amongst all recovered papers 82 were excluded due to the absence of abstract/summary. Next, the remaining 1170 articles were analyzed, classified and categorized. The most cited words were 'skin' and 'patient'. The words ‘immune’, ‘inflammatory’ and ‘inflammation’ were common. 742 (63.4%) of articles cited, at least once, one of the indicated words. Next, we seeked the context of each of these terms, revealing that they were mainly used to explain the immune and inflammatory conditions of each disorder. 'Expression' was cited along 333 (28.4%) articles to demonstrate molecular expression on experimental works of transcriptome (48 articles), epigenome or methylome (36 articles) and proteome (12 articles). The last word worth commenting is 'gut'. Gut was present in 158 articles and refers to the existing relationship between gut dysbiosis and the onset of allergic, the latter also represents a term included in the top cited words, disbalance. The overview of word atomization enabled us to understand what was the main focus of Omics literature for skin diseases with alterations in Notch signaling pathway.
Next, we categorized the whole DaVinci Lit into five classes of Omics. Most of the articles were included as a genome or microbiome (metagenome) study, followed by transcriptome and multi-omics approaches (Table 1). Moreover, in the multi-omics category, the most commonly employed approaches included the combination between genome and transcriptome and genome and microbiome.

Category	Number of article
Genome	245
Microbiome	241
Transcriptome	97
Proteome	32
Metabolome	2
Multi-Omics	95

Table 1. Omic categorization of literature from Omics studies concerning skin diseases with alterations in Notch signaling pathway.

The next step in PlatOMICs is to extract genes and variants from the literature. The goal is to unravel genes/variants previously established as involved with skin disorders characterised by alterations in Notch signaling route. In this circumstance, the gene atomization process retrieved 546 genes. From obtained genes, we extracted each time the context in which the gene was cited. In total, 465 articles and 1308 gene contexts were analysed. Subsequently, four researchers classified, independently, the gene relations as associated or not associated with the disease. Of these, 80 genes were excluded, and 426 genes were associated.

Next, PlatOMICs outputted the top 10 pathways and gene ontology (GO) predicted by these genes (Table 2). Enrichment pathway and a GO analysis were conducted by reactomePA, limma and topGO Bioconductor package. The pathway reveals the role of interleukin (IL) signaling, mainly driven by IL-4, IL-13 and IL-10. GO adds the defense response and interspecies interactions between organisms. Collectively, both descriptions point out that inflammation and skin microbial host defense are to be considered as key outcomes from the global literature findings, suggesting that these pathways and GO should be included in future Omics studies.

PlatOMICs also performed a gene atomization on DaVinci Omics. This analysis was assessed on 158 genes, most of which were found to be similar to the DaVinci Lit output. Equals enriched pathways and GO from Table 2 were found, thereby ratifying the importance of these pathways and GO on multi-Omics integration.

3 CONCLUSION

The scientific goal of PlatOMICs is to promote the understanding of biological mechanisms and molecular networks, underlining both health and diseases states, using existing data. The presented platform for multi-omics integration constitutes a time-saving and cost-efficient approach that might surely guide researches in the advancement of more elaborate and articulated hypothesis. Indeed, PlatOMICs is able to refine, assemble and integrate thousands of information spread around multiple database/resource/repositories. In the future, PlatOMICs will present an intuitive and automated friendly web-end interface with accessible tables, graphs and images.

The accumulation of scientific texts and Omics data settled in various databases may have never been correlated and analysed in conjunction. In this perspective, it is presumable that significant scientific responses may have been generated but are still uncovered. In this critical context, PlatOMICs was developed in order to promote the analysis and integration of the available Omics data, and in the present study we applied PlatOMICs for the analysis of skin diseases as a validation model. Our approach allowed us to further emphasize that our integrated strategy seeks to identify a common link between skin diseases and deregulations in homeostatic processes in epithelial tissues.

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Reactome ID	Pathway Description	GO ID	GO Description
R-HSA-449147	Signaling by Interleukins	GO:0034097	Response to cytokine
R-HSA-6785807	Interleukin-4 and Interleukin-13 signaling	GO:0019221	Cytokine-mediated signaling pathway
R-HSA-6783783	Interleukin-10 signaling	GO:0071345	Cellular response to cytokine stimulus
R-HSA-877300	Interferon gamma signaling	GO:0002376	Immune system process
R-HSA-447115	Interleukin-12 family signaling	GO:0006952	Defense response
R-HSA-8854691	Interleukin-20 family signaling	GO:0009605	Response to external stimulus
R-HSA-913531	Interferon Signaling	GO:0044419	Interspecies interaction between organisms
R-HSA-380108	Chemokine receptors bind chemokines	GO:0070887	Cellular response to chemical stimulus
R-HSA-451927	Interleukin-2 family signaling	GO:0010033	Response to organic substance
R-HSA-1059683	Interleukin-6 signaling	GO:0051707	Response to other organism

Table 2: Top 10 Enriched pathway and a gene ontology of 426 genes associated with skin diseases with alterations in the Notch signaling pathway.

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