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Integrative clinical transcriptomics analyses for new therapeutic intervention strategies: a psoriasis case study

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Psoriasis is a chronic inflammatory skin disease with complex pathological features and unmet pharmacotherapy needs. Here, we present a framework for developing new therapeutic intervention strategies for psoriasis by utilizing publicly available clinical transcriptomics data sets. By exploring the underlying molecular mechanisms of psoriasis, the effects of subsequent perturbation of these mechanisms by drugs and an integrative analysis, we propose a psoriasis disease signature, identify potential drug repurposing opportunities and present novel target selection methodologies. We anticipate that the outlined methodology or similar approaches will further support biomarker discovery and the development of new drugs for psoriasis.

In this review, we propose an integrative analysis of clinical transcriptomic data associated with psoriasis to gain understanding of disease mechanisms and, more importantly, derive novel strategies for therapeutic development. As an example, we share the computational biology meta-analysis of publicly available clinical transcriptomic data derived from psoriasis, induced psoriasis-like and drug intervention samples. We propose a strategy to identify drug repositioning and new target identification opportunities for further prosecution by drug discovery programs for psoriasis. Specifically, we: (i) identify a high confidence disease signature that potentially forms the core of disease resolution; (ii) show reversal of the signature by therapeutic intervention; (iii) provide enhanced understanding of core pathways modulated by the therapeutics associated with disease resolution; and (vi) propose potential new therapeutic intervention strategies based on repurposing and target identification approaches.

Pathophysiology of psoriasis

Psoriasis is a chronic inflammatory skin disease, affecting approximately 2–3% of the population in the USA and over 125 million people worldwide [1,2]. The disease is characterized by scaly, erythematous and inflammatory skin plaques, resulting from hyperproliferation of the epidermis with incomplete differentiation of keratinocytes and abnormal formation of horn cells of the epidermis with persistence of nuclei. Lesions often display inflammatory cell infiltration and neovascularization. The pathophysiology of psoriasis remains largely unclear [3]. The notion of psoriasis being a local skin disease has been challenged by several large epidemiological studies and it is now recognized as a systemic disease. It has been estimated that between 7% and 40% of patients with psoriasis eventually go on to develop psoriatic arthritis [4]. Population and genome-wide association studies (GWAS) suggest a genetic component that predisposes individuals to the disease [5,6]. A complex interaction between genetic, environmental and systemic factors then leads to a wide spectrum of psoriasis disease in these genetically predisposed individuals [5]. These complex interactions involve the immune system, leading to a cascade of events, including activation of dendritic cells, generation of effector T cells and interactions of immune cells with skin epithelium. This contributes to the initiation and perpetuation of the inflammatory response in the skin, leading to psoriasis [7]. Additionally, multiple cytokines released from immune cells, such as interferon alpha (IFNα), tumor necrosis factor (TNFα), interleukins IL-23, IL-17, IL-6, IL-1β and IL-12, have been reported to contribute to the initiation and exacerbation of psoriasis through modulation of the innate as well as the adaptive immune responses [8].

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Pharmacotherapy challenges for psoriasis

None of the currently available therapies offers a potential cure for psoriasis; thus, treatment is mainly aimed at reducing the disease burden and symptoms. The choice of using topical therapies, phototherapy or systemic agents, is influenced by: (i) the type and severity of psoriasis; (ii) extent of involvement of various regions of the body; (iii) symptoms; and (iv) additional co-morbid conditions [9]. Available therapeutic options for psoriasis continue to expand with the development of biologic agents aimed at modulating immune-mediated functions (e.g. TNFα) and anticytokine approaches (e.g. IL-12, IL-23, IL-17 and IL-22) [8]. Combination therapy is frequently used and is often aimed at individualization of treatment to patient needs [10]. Furthermore, several therapeutic agents have been associated with the risk of severe adverse reactions and, occasionally, significant morbidities, such as skin cancers, serious infections, lymphomas and hepatic conditions [11–13]. Given the risk of adverse treatment outcomes and the considerable variability in response to current treatments, there is an urgent need for new therapies for, and an effective disease management of, psoriasis.

Psoriasis clinical transcriptomics: disease, induced and intervention data sets

Elucidating underlying molecular mechanisms associated with the disease is a first key step in developing new psoriasis treatment strategies. Among the various 'omics' technologies, global transcriptomic profiling has been widely used to generate hypotheses on molecular mechanisms associated with disease and interventions [14]. To date, several transcriptomics studies have investigated the molecular mechanisms of psoriasis, including comparing lesional skin to nonlesional (NL) skin in patients with psoriasis or to normal skin in healthy volunteers [15–21] and defining the response to alternative treatments [22,23]. Integrating multiple transcriptomics studies across diverging platforms, laboratories, patient populations and experimental conditions can be a challenge [24]. However, when successfully applied, it has proven to be a valuable approach in discerning disease-specific expression patterns from different sources of variation and promises to define robust and generalizable transcriptional disease signatures [25,26].

In attempts to understand psoriasis at the molecular level, several genomics studies have been conducted in humans. We reviewed and selected gene expression data sets from the NCBI Gene Expression Omnibus (GEO) [27] that were derived from skin biopsy samples as the following sets: (i) psoriasis disease set; (ii) psoriasis induced set; and (iii) psoriasis intervention set (Table 1). The psoriasis disease set comprises a total of 564 samples from psoriasis lesional (LS) and NL or healthy control (NN) skin, from eight data sets. The psoriasis induced set comprises 60 samples from either placebo-controlled psoriasis NL or healthy subjects, along with psoriasis subjects given an intradermal interferon gamma (IFNγ) injection to NL skin, from a single clinical study [28]. The psoriasis intervention set comprises 78 samples from subjects treated with either one of two drugs: (i) etanercept (a biologic TNFα inhibitor used to treat psoriasis): including 48 skin biopsies derived from patients with psoriasis pre- and post-treatment who were treated with etanercept 50 mg biweekly for 12 weeks [22]; and (ii) ixekizumab (an anti-IL-17 monoclonal antibody developed to treat psoriasis): including 30 skin biopsies derived from patients with psoriasis pre- and post-treatment who were treated with either ixekizumab 150 mg or placebo for 2 weeks [23].

Integrative analysis of psoriasis transcriptomics

For each data set listed in Table 1, we obtained the raw mRNA expression data from GEO [27] and processed the data using the robust multi-array average (RMA) algorithm in combination with a method that accounts for evolving transcript definitions by remapping microarray probes to the most current gene annotations [29], as previously described [30]. Expression changes (i.e. disease versus normal or treated versus untreated) were determined by linear model fit taking into account paired study designs where applicable. Variance estimates were derived by applying an empirical Bayes methodology [31]. The data sets were then merged by matching Entrez gene identifiers corresponding to the respective custom probe sets, covering a total of 19,006 unique human genes.

Highly concordant gene expression changes in psoriatic skin lesions

Our meta-analysis of the selected psoriasis data sets resulted in ten disease comparisons, three IFNγ-induced to uninduced comparisons, and six psoriasis treated-to-untreated comparisons (Fig. 1a–d). Consistent with prior findings [21], our analysis suggested a high degree of concordance among various data sets, despite the fact that they were derived from different patient populations and

TABLE 1

Microarray gene expression studies included in the meta-analysis

Category	GEO accession	Condition	Sample size	Platform	Refs
Psoriasis disease set	GSE2737	LS versus NL	8	HG_U95A	[15]
	GSE6710	LS versus NL	26	HG-U133A	[16]
	GSE14905	LS versus NL (or NN)	82	HG_U133 Plus 2.0	[17]
	GSE13355	LS versus NL (or NN)	180	HG_U133 Plus 2.0	[18,19]
	GSE30999	LS versus NL	170	HG_U133 Plus 2.0	[20]
	GSE34248	LS versus NL	28	HG_U133 Plus 2.0	[21]
	GSE41662	LS versus NL	48	HG_U133 Plus 2.0	
	GSE41663	LS versus NL	22	HG_U133 Plus 2.0	
Psoriasis induced set	GSE32407	IFNγ-induced versus NL (or placebo)	60	HG_U133 Plus 2.0	[28]
Psoriasis intervention set	GSE11903	Etanercept	48	HG_U133 Plus 2.0	[22]
	GSE31652	Ixekizumab	30	HG_U133 Plus 2.0	[23]