Elucidating new drug targets in psoriasis by gene profiling: an opportunity to be seized

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Psoriasis vulgaris (psoriasis) is an autoimmune disease of the skin that affects ~3% of the world's population (1). It is easily diagnosed by characteristic red colored plaques most often located on the elbows, knees, and scalp. Importantly, psoriasis patients (PP) have shorter lifespans and higher risk of cardiovascular disease, obesity, and diabetes (2). The development of biologics for the treatment of psoriasis is a remarkable success story of translational medicine, which arguably started with the identification of T cell infiltrates in psoriatic lesions ~30 years ago (3,4). The molecular basis of psoriasis continues to be refined and therapeutic approaches in humans now provide critical data to improve our understanding of the disease. For example, the confirmation that psoriasis was a T cell-mediated disease was ultimately established using monoclonal antibodies (mAbs) that broadly eliminated T cells by various mechanisms. Subsequently, IL-23 was found to regulate T_H17 and T_H22 cell production (IL-23/T_H17 axis) and the main cytokines produced by these cells (IL-17 and IL-22) were found in high levels in human psoriatic plaques (4-6). This work and many others led to the development of anti-IL-23p19, anti-IL-17, and anti-IL-17R therapies that successfully reverse clinically features of psoriasis in 80-90% of patients (4). Notably, blocking T_H1 cell-produced interferon-γ or dendritic cell-produced interferon-α was not effective in reducing clinical symptoms of psoriasis, emphasizing the important role of the IL-23/T_H17 axis in psoriasis pathology (7,8). In regards to the interferon studies, kudos to these investigators and their institutions for publishing this important data that fails to validate these molecular targets, but is essential to further understand the molecular mechanisms underlying human psoriasis (7,8).

Despite great promise, genetic studies (transcriptional profiling or GWAS) have played a limited role in the development of psoriasis biologics, rather than driving the drug discovery process. The focus of this editorial is the recent work of Perera *et al*., who attempt to address this issue by identifying key IL-22-mediated gene targets involved in psoriasis (9). IL-22 is an IL-10 family cytokine (10) that is highly expressed in human psoriasis (11). IL-22 induces keratinocyte proliferation and differentiation, stimulates the production of antimicrobial peptides, and induces acanthosis in mouse psoriasis models and in reconstituted human epidermis (12,13). A human clinical trial to evaluate an anti-IL-22 mAb in psoriasis has been performed, but the outcome of the study has not been published at this time (14). Whether anti-IL-22 therapy will improve on the already impressive results obtained with anti-IL-17 or anti-IL23 biologics remains to be determined. However, since the study was completed in 2010, the delay in reporting suggests anti-IL-22 may not be an optimal therapy option for psoriasis. As discussed above for the interferons, it is hoped that the clinical study on anti-IL-22 will be published soon.

The significance of the work by Perera *et al*. does not lie in the importance of IL-22 as the best therapeutic for psoriasis. Rather, this study demonstrates the potential of using global transcriptional profiling to identify novel drug targets that directly contribute to human psoriasis. IL-22, like any cytokine, induces thousands of genes. But what gene, or genes, among the thousands are "the ones" contributing to the disease phenotype? To address this question, transcriptional profiling was performed on normal human skin (NN) and skin from PP. Human skin samples used in the study were grafted onto immunosuppressed AGR mice to allow the investigators to monitor lesional PP skin at baseline (PP0) and 21 days later (PP21), where PP skin grafts exhibit an increase in disease severity. This xenotransplantation (XT) mouse model is arguably the

best mimic of human psoriasis at this time (15). Using the XT model, an IL-22 gene signature was established by measuring differential gene expression in NN skin and NN skin injected with recombinant IL-22. Second, differences in gene expression were measured between PP0 and PP21 skin. Finally, gene expression differences were measured in PP0 and PP21 skin treated with an anti-IL-22 mAb. Comparing the transcriptional profiles of these three experiments revealed a surprisingly small list of 19 genes that were upregulated in NN skin injected with IL-22 and in PP skin transitioning to the severe PP phenotype (PP21 *vs*. PP0), but were suppressed in the PP21 *vs*. PP0 experiments performed in the presence of an anti-IL22 mAb. The combination of appropriate molecular tools (cytokines and mAbs), the XT mouse model, and clever experimental design, provide convincing evidence that these genes are regulated by IL-22 and important in psoriasis.

Notably, one of the 19 genes identified, PIM1, was also found to be upregulated in a gene coexpression network the authors derived from genes differentially expressed in skin samples obtained from healthy individuals and PP. Data for assembling the gene coexpression network was obtained from the Genetic Association Information Network (GAIN) archived in the database of Genotypes and Phenotypes (dbGaP) (16). PIM1 is a serine-threonine kinase that was originally found to be overexpressed in cancers of hematological and epithelial origin and more recently has been linked to pulmonary artery hypertension (17,18). This later association is particularly interesting as psoriasis is associated with an increased risk of cardiovascular disease (2). Importantly, Perera *et al*. confirmed PIM1 is overexpressed in blood vessels from human psoriatic skin. To establish functional relevance, PIM1 knockout mice, anti-IL22 mAb, and a small molecule inhibitor of PIM1 (SFI1776), were used to demonstrate partial reduction in vascularization and/or epidermal thickening in mouse psoriasis models. This suggests IL-22-mediated induction of STAT3 may be at least partially responsible for PIM1-mediated vascularization of psoriatic skin and could play a role in the increased incidence of cardiovascular disease in PP (2,18). Other studies suggest PIM1 might impact other signaling pathways relevant to psoriasis. For example, Shen *et al*. have demonstrated PIM1 inhibitors reduce the expression of IFNγ and IL-17 in a dextran sodium sulfate (DSS) model of colitis in mice (19). This is consistent with studies by Fox *et al*. that have shown PIM1 is responsible for T cell growth and proliferation (20). Based on the outcome of future studies, PIM1 inhibitors, which are under development for cancer, might be repurposed as therapeutics for psoriasis (17).

Of course, no study is perfect and several questions come to mind. First, more information on the criteria used for establishing the definition of "significant" gene expression would be helpful. Statistics are important, but additional studies demonstrating the sensitivity of the final results to different significance criteria would really validate the study. This is important as the authors are quick to point out that IL-20 cytokines (10), which are upregulated by IL-22 in numerous studies, do not meet the expression significance criteria. There might be other reasons, besides data processing, that contribute to the weak expression of IL-20 cytokines. For example, large variations in IL-22-induced genes were observed in normal human epidermal keratinocytes [NHEKs, (131 genes)], reconstituted human epithelium [RHE, (1,712 genes)], and NN skin from the XT model (4,251 genes). These data suggest cell heterogeneity may contribute to significant variability in the gene expression data, or lack of significance of expected IL-22-induced genes. Ultimately, evaluating the expression profile of individual cell types, possibly using laser capture microdissection, within psoriatic tissues will determine if different cell types exhibit different gene expression profiles that confound the current analyses. Thus, exciting studies lie ahead for the Nestle group and others to extend the findings of the current manuscript.

In summary, this proof-of-principle study suggests we may be getting closer to a time when gene profiling experiments can drive our understanding of the mechanisms of psoriasis and other autoimmune diseases. The integrative approach taken by Perera *et al*., clearly depends on access to human gene expression data, a robust animal model (e.g., the XT mouse model), and a rigorous and transparent computational analysis. The results reported here further validate the establishment of dbGaP repository for genome-based studies. However, the gene expression data collected during multiple clinical trials of anti-cytokine biologics for psoriasis are not available for study (14). If they were, the scientific community would have access to an unprecedented collection of human gene expression datasets with specific perturbations of different cytokines in the context of human psoriasis, possibly replacing or reducing the need for optimal animal models. Additional studies evaluating small molecule inhibitors (e.g., JAK inhibitors) will continue to generate even more gene expression data in humans to supplement the anti-cytokine data (14). Access to all of this data, combined with analyses similar to those described by Perera *et al*. (9), could potentially uncover other essential

initiators and/or drivers of human psoriasis. At some point very soon, this data integration will be required to move the field forward. There are obvious complications in establishing a mechanism for such data sharing. However, the benefits of a longer and higher quality life for patients that suffer from the disease make the effort worth it.

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