

ACADEMIC: ESSAY

The JAK/STAT signalling pathway: Tiny molecules transforming therapeutics

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Why is an understanding of the JAK/STAT signalling pathway important in common skin diseases and how will that knowledge transform therapeutics?

From genomes to vaccines, organ transplants to biotechnology, it is fair to say that modern medicine has seen magnificent breakthroughs in the last century. Fundamentally, what has enabled these advancements is an understanding of basic cellular and molecular biology. Among the pivotal discoveries in this field, the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway has emerged as a critical player in some of today's most debilitating and deadly human diseases, including various cancers, autoimmune disorders, and chronic inflammatory diseases.¹ Now, an understanding of the JAK/STAT pathway has become important in common skin diseases, from predictive biomarkers and disease prognosis to tiny molecules transforming therapeutics.

The JAK/STAT signalling pathway

The JAK/STAT pathway is a key orchestrator of the immune system, activating 57 out of the 200 cytokines known to date.² On a broader level, it regulates various immune-related functions, including cell differentiation and proliferation, inflammation, and apoptosis.³ On a molecular level, the JAK/STAT system transduces environmental cues at the cell surface to elicit gene expression in the nucleus.⁴ Overactivation and dysregulation of the pathway is now understood to be a key pathogenic basis for the development of autoimmunity, allergy, inflammation, and tumorigenesis.

The JAK/STAT signalling pathway initiates when a cytokine binds to its cell surface receptor. This binding event causes the cytoplasmic portions of the receptors to dimerize, bringing the JAKs into spatial proximity and enabling them to activate each other through autophosphorylation.⁵ The activated JAKs then phosphorylate tyrosine residues on the receptor, revealing binding sites for STAT proteins. A single STAT molecule then binds to a phosphorylated region of the receptor. After being phosphorylated by JAK, the STAT monomer dissociates from the receptor and dimerises with another STAT molecule in the cytoplasm. Finally, the dimerized STATs translocate to the nucleus through nuclear pore complexes and bind to DNA, inducing the transcription of target genes (Figure 1).

Many common skin diseases are attributed to dysregulated inflammatory cascades perpetrated by cytokines. Thus, mounting evidence now links the JAK/STAT pathway to the pathogenesis of common skin conditions pertaining to the distinct biological functions of individual members of the JAK/STAT family. For instance, STAT6 serves as a mediator for T_H2 cytokines, which play a dominant role in the pathogenesis of atopic dermatitis.⁶ In contrast, STAT3 promotes the development of T_H17 cells, and its overexpression has been strongly associated with psoriasis.⁷ IFN- γ and TFN- α signal through the STAT1 pathway to suppress melanocyte pigmentation, a critical pathway in vitiligo pathogenesis.⁸

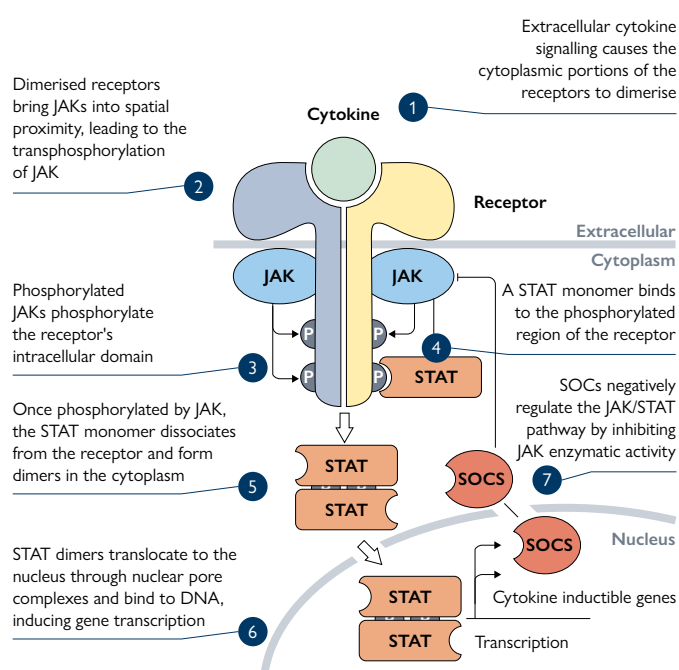


Figure 1: Essential mechanism of the JAK/STAT signalling pathway (adapted from Morris et al.)³

Cytokines have pleiotropic and redundant effects through the JAK/STAT system (Figure 2). Therefore, multiple cytokines and their downstream JAK/STAT signalling proteins are involved in a diverse range of skin diseases. In atopic dermatitis, the ingress of foreign antigens into the epidermis triggers the release of danger signals, activating T_H2 immune cells to produce a range of cytokines.⁹ For example, IL-4 activates the JAK1/JAK3/STAT6 pathway, which further promotes T_H2 cell differentiation and overregulation of T_H2 immune responses.¹⁰ This pathway also stimulates plasma cell class-switching to IgE antibodies, which binds to mast cells and stimulates histamine release.¹¹ IL-5 signals through the JAK2/STAT5 pathway to activate eosinophils, a key mediator overexpressed in atopy.¹² Furthermore, pruritus, a characteristic symptom of atopic dermatitis, is effected by IL-31 through the JAK1/2 and STAT1/3/5 pathway. Additionally, IL-22 signals through JAK1 and STAT1/3/5 to induce epidermal hyperplasia and lichenification.^{13,14}

JAK/STAT biomarkers

Why is understanding the JAK/STAT pathway important? Firstly, it has led to the discovery of prognostic biomarkers in important skin diseases. A pertinent setting is skin cancer prognosis. Numerous studies have shown that STAT1 expression is decreased in melanoma patients

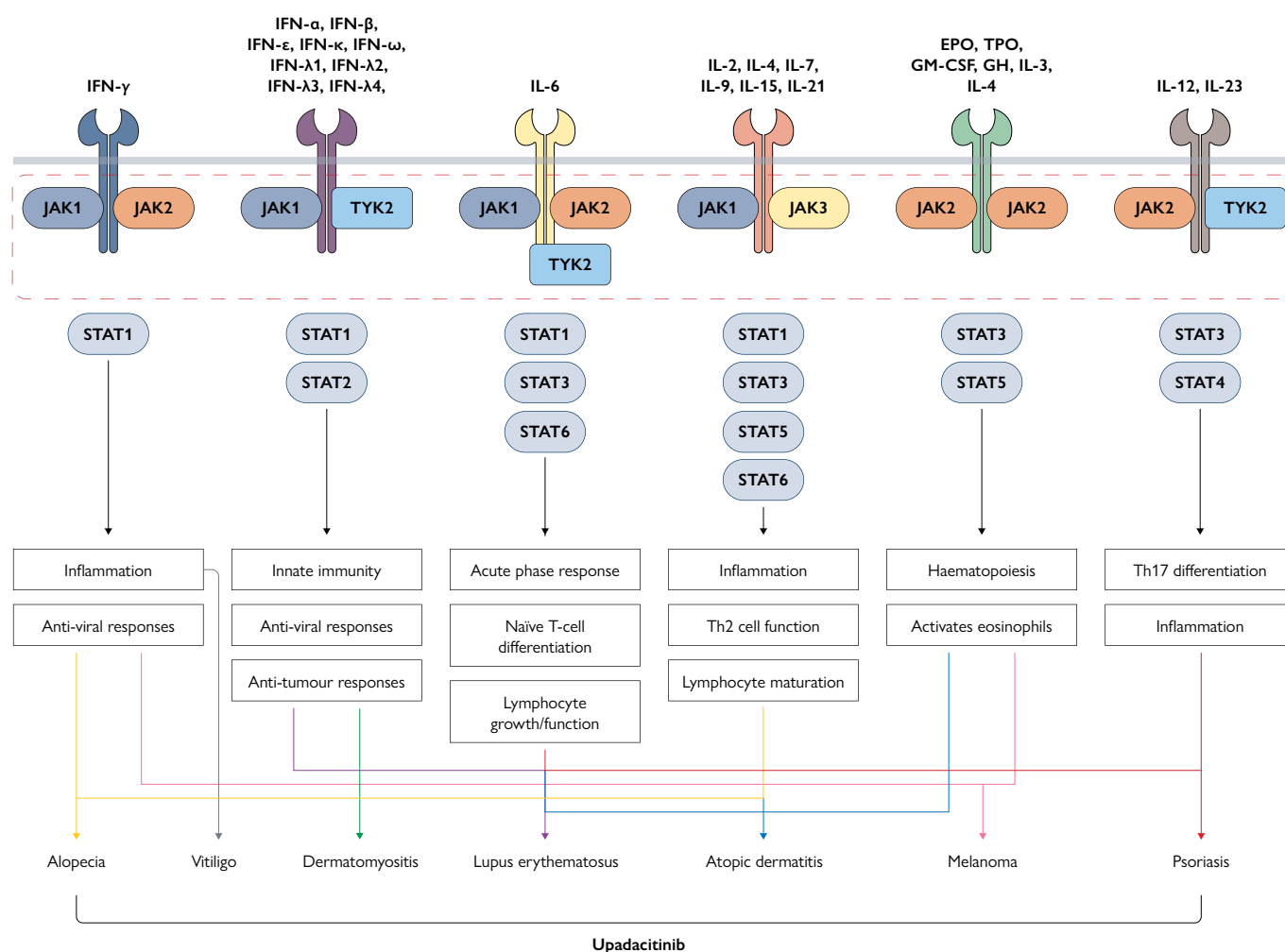


Figure 2: Ligands and biological functions of the JAK/STAT family and their role in the pathogenesis of common skin diseases

and STAT1 phosphorylation is non-inducible in a significant proportion of melanoma tumours.^{15, 16} STAT1 functions as a “tumour-suppressor” transcription factor, conveying the anti-tumour effects of interferons and mediating tumour cell sensitivity to pro-apoptotic signals. Thus, dysregulation of basal STAT1 expression is proposed as a mechanism by which melanoma cells evade immune cell recognition and destruction.¹⁷ Conversely, melanoma cells exhibit constitutional activation of STAT3, an “oncogenic” factor that promotes cell proliferation, angiogenesis, and metastasis.¹⁸ Not surprisingly therefore, elevated STAT3 expression has been associated with poorer prognosis not only in melanoma, but also in most solid tumours.¹⁹ Recent studies have further suggested that the ratio of STAT1 to STAT3 could serve as a strong predictor of melanoma progression.²⁰ Overall, JAK/STAT molecules offer promising prognostic significance; with more robust research, they may well become part of the future clinical practice of skin cancer.

Beyond cancer prognosis, genome-wide association studies have identified JAK/STAT molecules as susceptibility biomarkers in common skin diseases (Table 1). For instance, STAT3 has been recognised as a new at-risk genetic locus for atopic dermatitis and psoriasis.²¹ Biopsy studies of skin lesions in acne have also shown overexpression of JAK1 and JAK3.²² The potential applications of JAK/STAT biomarkers are broad, including identifying individuals susceptible to disease, monitoring treatment, and predicting therapeutic responses. But will predictive JAK/STAT biomarkers become part of future practice? Certainly, the cost-to-benefit ratio is important to consider. Ultimately, it is likely that the predictive prospects of JAK/STAT biomarkers remain an academic novelty: compelling in theory but impractical in reality. Nonetheless, they are a footprint for the underlying disease

mechanism, making them crucial to the discovery of new drug targets that could potentially transform therapeutics.

Transforming the future of therapeutics

The treatment of skin diseases poses a significant challenge for clinicians. Chronic skin diseases are often refractory to existing therapies, and long-term corticosteroid and immunosuppressant use can be problematic due to their adverse effects. In this context, there is substantial space for novel therapies that strike a better balance between efficacy and side effects to make a transformative impact. Understanding the JAK/STAT pathway has led to the development of JAK/STAT inhibitors (JAKis), small molecule immunotherapies that disrupt the fundamental intracellular transduction of overactive immune pathways in the pathogenesis of skin diseases. JAK is are, indeed, more than a theoretical ideal. In New Zealand, Medsafe approved upadacitinib, a second-generation JAK1 inhibitor, for the treatment of moderate to severe atopic dermatitis in 2021.³¹ Globally, numerous JAKis have been approved or are currently under trial for a wide range of common skin conditions (Table 2).

Could JAKis be the solution to treatment failure in skin diseases? It is possible. One of their strongest advantages is their superior efficacy compared to existing therapies. For example, in atopic dermatitis, a dose of 30 mg of upadacitinib leads to a 75% improvement in the Eczema Area and Severity Index (EASI75) for 73% of patients, compared to only 13% of patients on a placebo.⁴⁰ Similar benefits have also been seen with tofacitinib in psoriasis, with studies supporting a rapid effect onset within four weeks and sustained efficacy through to two years.^{41, 42} JAKis are also orally or topically administered, unlike injected biologic agents, allowing less hospital dependence and

Disease	Genetic Associations	Functional Biomarkers
Alopecia areata	IL-2/21, IL-2RA	Active STAT1 and STAT3 in human hair follicles
Atopic dermatitis	IL-6R, IL-2/21, IL-7R, IL-15RA, STAT3 ²⁴	IL-4, IFN, and IL-22 are expressed in the skin of patients with atopic dermatitis
Lupus erythematosus	IL-12A, IL-10, JAK2, TYK2, STAT4	STAT4 variants interfere with IFN sensitivity in patients with lupus erythematosus
Psoriasis	IL-23A, IL-12B, IL-23R, IL-4/13, TYK2, STAT3	IL-19, IL-20, IL-22, IL-23, and active STAT3 are expressed at high levels in the skin of patients with psoriasis
Melanoma	STAT1, STAT3, STAT4, STAT5B, STAT6 ¹⁰	Suppression of STAT1 is observed in vitro in melanoma tumour samples

Table 1: Genetic associations and functional biomarkers in common skin diseases

Drug	Selectivity	Approved Uses	Proven Benefits in Clinical Trials
Abrocitinib	JAK1	Refractory moderate-to-severe atopic dermatitis	Atopic dermatitis, psoriasis
Baricitinib	JAK1, JAK2	Severe alopecia areata	Psoriasis, alopecia areata, atopic dermatitis, lupus erythematosus
Delgocitinib	Non-selective	Atopic dermatitis	Atopic dermatitis, alopecia areata
Deucravacitinib	TYK2	Moderate-to-severe plaque psoriasis	Psoriasis
Ruxolitinib	JAK1, JAK2	Moderate atopic dermatitis	Psoriasis, alopecia areata, atopic dermatitis, dermatomyositis, cutaneous lupus, graft versus host disease, pyoderma gangrenosum
Tofacitinib	JAK1, JAK2, JAK3	No current skin diseases	Psoriasis, alopecia areata, atopic dermatitis, vitiligo, hidradenitis suppurativa, lichen planus, dermatomyositis, sarcoidosis
Upadacitinib	JAK1	Moderate-to-severe atopic dermatitis	Atopic dermatitis, psoriasis

Table 2: Approved JAK/STAT inhibitors in the treatment of skin diseases (data from Solimani et al.)³⁹

better suiting some patients' preferences. However, what sets JAKis apart is their broad applicability in dermatology. Many common skin diseases are influenced by multiple cytokines, making JAKis an attractive therapy compared to biologics and other agents that target only one cytokine.⁴³ Furthermore, JAKis block cytokines irrespective of the cell producing them, inhibiting various types of immune responses, such as both the T_H2 and T_H17 components in psoriasis. This versatility makes them more effective than therapies that specifically target one type of immune cell. Consequently, a single JAKi can also effectively treat patients with multiple coexisting autoimmune or inflammatory diseases, such as both rheumatological and dermatological conditions.

However, a caveat of their broad-spectrum activity is the risk of collateral damage. While common adverse effects of JAKis are generally mild, such as an increased risk of infection, headache, nausea, diarrhoea, and acne and pruritis with topical agents, there have been growing safety concerns regarding their use.⁴⁴ Serious reactivation infections such as tuberculosis and herpes zoster have been observed, along with increased risks of venous thromboembolism and reversible haematological abnormalities.⁴⁵ As a result, some approved JAKis now carry "black label" warnings in many countries. Nonetheless, safety data for JAKis are often derived from clinical trials in rheumatology using study populations comprising older patients with more co-morbidities that may not be generalizable to dermatology. Overall, JAKis have an acceptable safety profile with a low absolute risk of potentially serious adverse events compared to their benefits.⁴⁶ Moving forward, developing more selective JAKis may overcome their current safety concerns, albeit at the cost of their versatility.

Whether JAKis will transform future therapeutics also requires us to consider several practical limitations. In Aotearoa, accessibility is a considerable barrier. Aotearoa has a generally "low and slow" adoption of newer and more expensive therapeutics, resulting in far lower usage of biologics and other novel treatments than Australia and any of the Western European countries.^{47,48} Currently, PHARMAC only funds two JAKis, and the limited choice and potential to switch to alternative agents may lead to suboptimal treatment for non-responsive or intolerant patients. Why does Aotearoa face more barriers to

accessing the transformative potential of JAKis? Cost-effectiveness is one key factor. Aotearoa faces relatively higher prices for therapeutics, but healthcare spending per capita is lower compared to other Western European countries, leading to a higher affordability index and more difficulty affording innovative treatments.⁴³ JAKis must also compete for funding against other novel developments, but their relative cost-effectiveness is relatively low. For example, the incremental cost-effectiveness ratio of upadacitinib for the treatment of atopic dermatitis is £219,734 (approximately \$450,000 NZD) per quality-adjusted life year (QALY) compared to dupilumab.⁴⁹ Economic considerations also have an impact on clinical practice and guidelines. Newer treatments often fall under the PHARMAC special authority system, which entails more restrictive eligibility guidelines, longer approval processes, and administrative hurdles, further impeding the timeliness and ease of access.

If JAKis do gain a prominent role in future therapeutics for skin diseases, then equity must be considered. Disparities in healthcare provision are a significant concern for Māori and Pasifika. These communities suffer a higher prevalence of common skin conditions, are more likely to present with more advanced skin cancer, and experience the highest hospitalization rates for serious skin infections. Yet, they are less likely to receive biologic therapy or be referred to secondary specialist services like dermatologists compared to NZ Europeans.^{50,51} In this context, it is a hopeful vision that JAKis may help reduce unmet needs and future health inequities in skin disease. One potential solution to ensure access for disadvantaged populations is to include ethnicity as a special authority criterion for PHARMAC subsidisation of JAKis. Ultimately, improving health outcomes with novel therapies requires an inclusive healthcare system that provides equitable opportunities for innovative treatments.

Conclusion

Since their introduction in the 1990s, JAK/STAT inhibitors have transformed therapeutics in many medical fields. Decades of research on the JAK/STAT signalling pathway have now resulted in significant breakthroughs in the treatment of the most prevalent skin diseases

today. We now know of more molecular biomarkers that can predict and offer prognoses for skin conditions both common and malignant. More significantly, the emergence of JAK/STAT inhibitors as a novel drug class holds immense potential in addressing the current treatment challenges in dermatology. However, the transformative potential of JAK/STAT inhibitors may be constrained by certain factors. Safety concerns, cost-effectiveness, access barriers, and local feasibility are among the considerations that need to be addressed. As a novel development, further studies are required to clarify the long-term efficacy and safety of these inhibitors and to determine the generalizability of research findings in real-world settings and specific population subgroups, such as children, elderly, or ethnically diverse populations. Nonetheless, knowledge of the JAK/STAT pathway has seen promising potential. It will be exciting to see how the story unfolds as more opportunities and challenges unveil and, ultimately, whether these tiny molecules will truly transform the future of therapeutics.

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