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?"

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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 cell biology. Since its discovery in 1990, the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway has been recognized as a critical player in the most debilitating and deadly human diseases today, including cancer, autoimmune, and chronic inflammatory diseases[i]. Now, an understanding of the JAK/STAT pathway has become important in common skin diseases: from predictive biomarkers, 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 recognized to date[ii]. On a broader level, it regulates various immune-related functions, including cell differentiation and proliferation, inflammation, and apoptosis[iii]. On a molecular level, the JAK/STAT system has three constituents: receptors, Janus tyrosine kinases, and signal transducer and activator of transcription proteins which transduce environmental cues at the cell surface to gene expression in the nucleus[iv]. Overactivation and dysregulation of the JAK/STAT pathway is now understood to be a key pathogenic basis for autoimmunity, allergy, inflammation, and tumorigenesis.

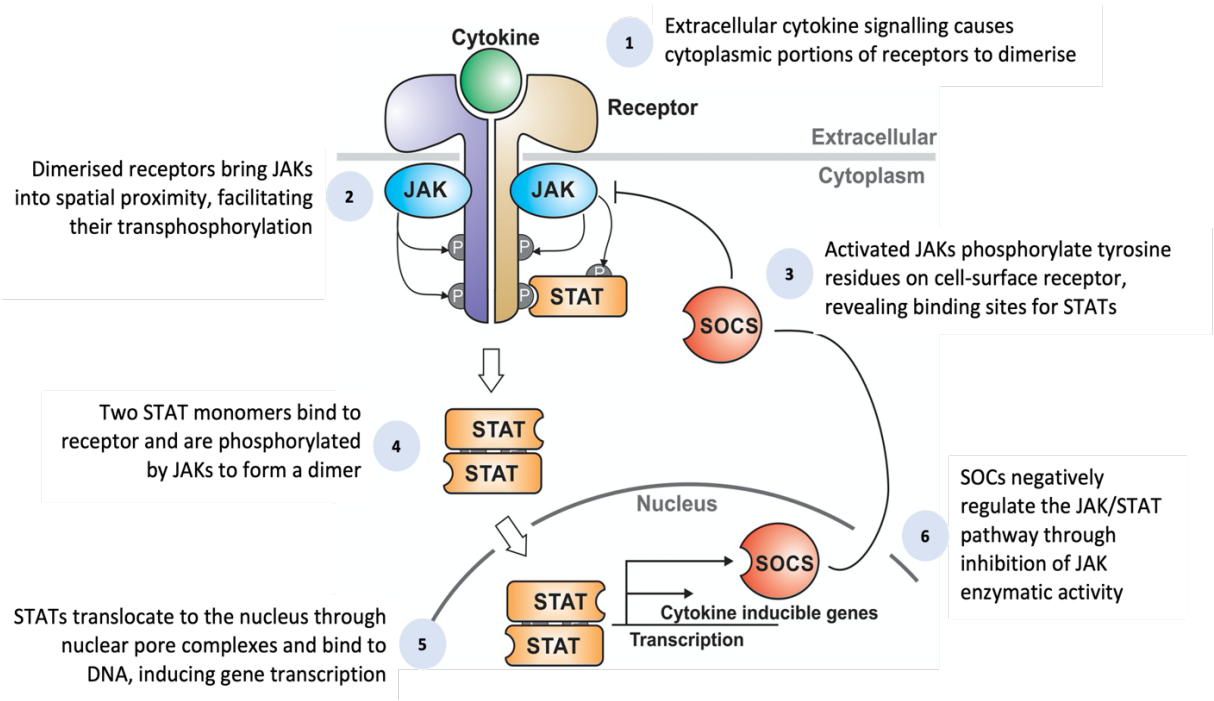

Figure one: essential mechanism of the JAK/STAT signalling pathway

The JAK/STAT signalling pathway initiates when a cytokine binds to its cell surface receptor, causing the cytoplasmic portions of the receptors to dimerize. This brings the JAKs into spatial proximity and enables them to activate each other through transphosphorylation[v]. The activated JAKs then phosphorylate tyrosine residues on the cell-surface receptor, revealing the binding sites for STAT proteins. Two STAT monomers bind to the receptor and are phosphorylated by JAKs to form a dimer, causing their dissociation from the receptor. Finally, the dimerized STATs translocate to the nucleus through nuclear pore complexes and bind to DNA, inducing the transcription of target genes.

Many common skin diseases are grounded in 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 different biological functions of individual members of the JAK/STAT family. For example, STAT6 is a mediator of T_h2 cytokines, which predominate the pathogenesis of atopic dermatitis[vi]. In contrast, STAT3 promotes the development of T_h17 cells, and overexpression of STAT3 has been strongly associated with psoriasis[vii]. IFN-γ and TFN-α signal through the STAT1 pathway to suppress melanocyte pigmentation, a critical pathway in vitiligo pathogenesis[viii].

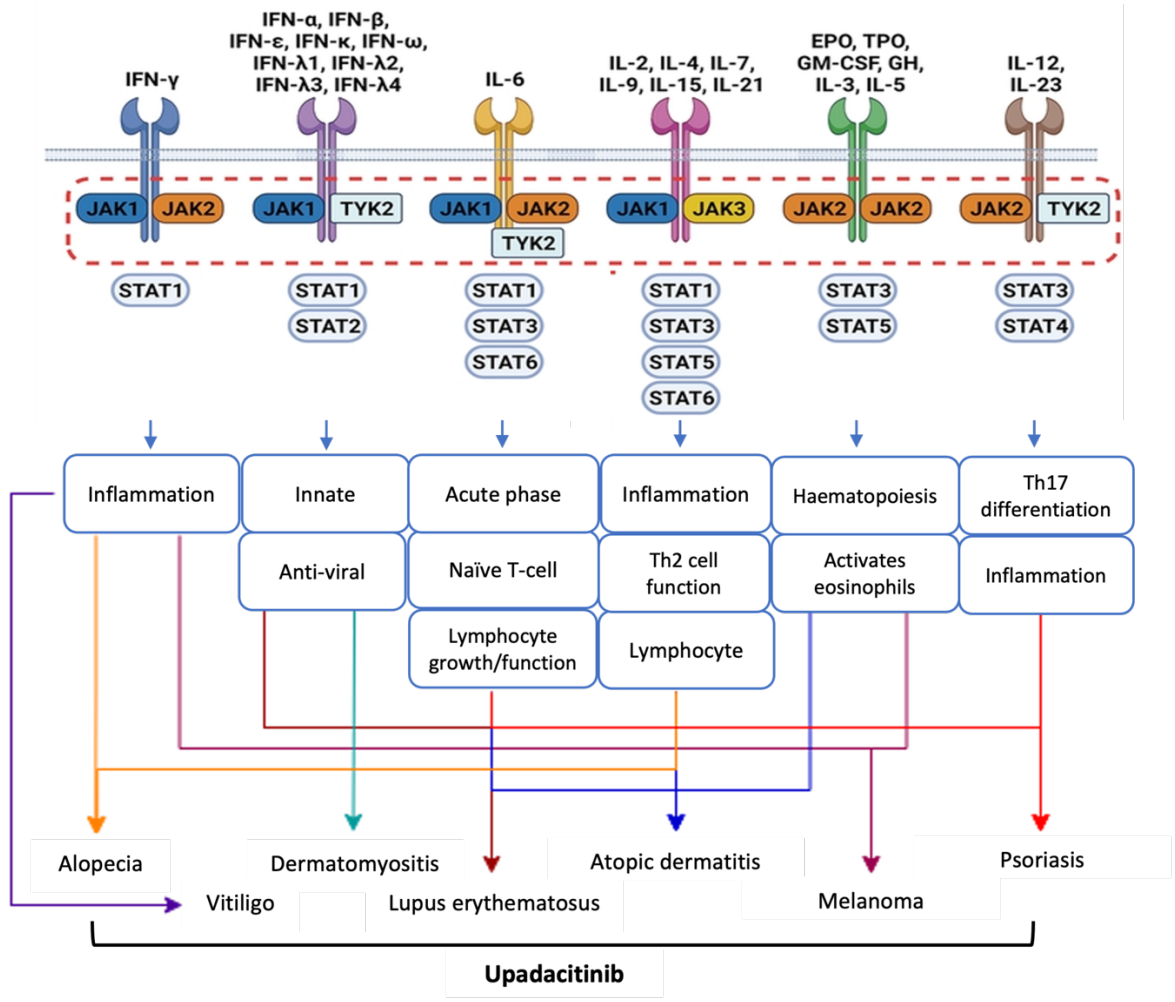

Figure two: ligands and biological functions of the JAK/STAT family and their role in the pathogenesis of common skin diseases

As figure two shows, cytokines have pleiotropic and redundant effects through the JAK/STAT system. Therefore, multiple cytokines and their downstream JAK/STAT signalling proteins are involved in a diverse range of skin diseases. In atopic dermatitis, foreign antigens that ingress into the epidermis stimulate the release of danger signals, activating T_h2 immune cells to produce a range of cytokines.

For example, IL-4 activates the JAK1/JAK3/STAT6 pathway, driving further T_h2 cell differentiation and overregulation of T_h2 immune responses. This pathway also stimulates plasma cell class-switching to IgE, which binds to mast cells and stimulates histamine release. IL-5 signals through the JAK2/STAT5 pathway to activate eosinophils, a key mediator overexpressed in atopy. Moreover, the characteristic symptom of pruritis is effected through IL-31 and the JAK1/2 and STAT1/3/5 pathway, while IL-22 signals through JAK1 and STAT1/3/5 to cause epidermal hyperplasia and lichenification[ix].

JAK/STAT Biomarkers

But 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. Studies have shown decreased STAT1 expression in melanoma patients [x] and non-inducible STAT1 phosphorylation in 63% of tumours. This is consistent with the understanding that STAT1 is a "tumour-suppressor" transcription factor that transmits the anti-tumour effects of interferons and mediates tumour cell sensitivity to pro-apoptotic signals. Dysregulation of basal STAT1 expression has thus been a proposed mechanism by which melanoma cells escape immunosurveillance[xi]. Conversely, melanoma cells exhibit constitutional rather than rapid, transient activation of STAT3, an "oncogenic" factor that promotes cell proliferation, angiogenesis, and metastasis. Not surprisingly then, meta-analyses have associated elevated STAT3 expression with poorer prognosis in melanoma[xii] and, indeed, most solid tumours[xiii]. Recent studies further reveal that the ratio of STAT1 to STAT3 may be a strong predictor of melanoma progression[xiv]. Overall, JAK/STAT molecules have 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 (figure three). For example, STAT3 has been included as a new at-risk genetic locus for atopic dermatitis[xv] and psoriasis[xvi]. In acne, the commonest skin disease worldwide, JAK1 and 3 are overexpressed in biopsy studies of skin lesions[xvii]. The potential applications of JAK/STAT biomarkers include identifying individuals susceptible to disease, monitoring treatment, and predicting therapeutic responses. However, 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, crucial to discovering new drug targets that might transform therapeutics.

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

Figure three: genetic associations and functional biomarkers in common skin diseases

Transforming the Future of Therapeutics

Treating skin diseases is a significant challenge. Too often, chronic skin diseases are refractory to therapies, yet, the adverse effects of long-term corticosteroid and immunosuppressant use are

dilemmatic. In this context, there is substantial space for novel therapies with a better equilibrium of efficacy versus 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 signal transduction of overactive immune pathways leading to skin diseases. Indeed, JAKis are more than a theoretical ideal. In New Zealand, Medsafe approved upadacitinib, a second-generation JAK1 inhibitor, for the treatment of moderate to severe AD in 2021[xxvii]. Globally, a variety of JAKis are approved for or currently under trial for a wide range of common skin conditions, summarized in figure four[xxviii].

Drug	Selectivity	Approved Uses	Proven Benefits in Clinical Trials
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
Baricitinib	JAK1, JAK2	Severe alopecia areata	Psoriasis, alopecia areata, atopic dermatitis, lupus erythematosus
Upadacitinib	JAK1	Moderate-to-severe atopic dermatitis	Atopic dermatitis, psoriasis
Delgocitinib	Non-selective	Atopic dermatitis	Atopic dermatitis, alopecia areata
Abrocitinib	JAK1	Refractory moderate-to-severe atopic dermatitis	Atopic dermatitis, psoriasis
Deucravacitinib	TYK2	Moderate-to-severe plaque psoriasis	Psoriasis

Figure four: approved JAK/STAT inhibitors in the treatment of skin diseases

Will JAKis be the solution to treatment failure in skin diseases? Indeed, the strongest advantage of JAKis is their superior efficacy compared to existing therapies. For example, upadacitinib achieves the therapeutic endpoint for atopic dermatitis in 74% of patients compared to only 23% of patients taking a placebo and 61% taking dupilumab, the current best treatment[xxix]. Similar benefits have also been seen with tofacitinib in psoriasis[xxx], with studies supporting a relatively rapid effect onset by four weeks and sustained efficacy through two years[xxxi]. JAKis are also orally or topically administered, unlike injected biologic agents, allowing less hospital dependence and better suiting some patients' preferences. What is also unparalleled about JAKis is their broad applicability in dermatology. Common skin diseases are often influenced by multiple cytokines, making JAKis an attractive therapy compared to agents that only one cytokine, like biologics[xxxii]. Moreover, 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, making them more effective than therapies that target one immune cell type. JAKis also synergistically or indirectly interfere with cytokines that are not ligands of the JAK/STAT pathway, culminating in even greater clinical efficacy against various pathogenic pathways. Thus, a single agent can effectively treat patients with coexisting autoimmune or inflammatory diseases, such as both rheumatological and dermatological conditions.

A caveat of their broad-spectrum activity is the risk of collateral damage. Common adverse effects of JAKis are mild and include an increased risk of infection, headache, nausea, diarrhoea, and acne and pruritis with topical agents[xxxiii]. However, growing safety concerns have led to "black label" warnings on some approved JAKis in many countries. Serious infections with tuberculosis and Herpes zoster reactivation have been seen, as well as potential increased risks of venous thromboembolism and reversible haematological abnormalities, including lymphopenia, thrombocytopenia, and anaemia[xxxiv].

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 and low absolute risk of potentially serious adverse events compared to their benefits[xxxv]. 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 requires us to consider several practical limitations. In Aotearoa, accessibility is a considerable barrier. New Zealand 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 any Western European country[xxxvi]. PHARMAC currently funds only two JAKis, and the lack of choice or potential of switching to another drug may lead to suboptimal treatment in non-responsive or intolerant patients. Why does Aotearoa face more barriers to accessing the potentially transformative future of JAKis? An essential determinant to access is cost-effectiveness. New Zealand faces relatively higher prices for therapeutics, yet healthcare spending per capita is lower than in other Western European countries, leading to more difficulty affording innovative treatments. JAKis must also compete for funding against other novel developments, but their relative cost-effectiveness is relatively low. The incremental cost-effectiveness ratio of upadacitinib is £219,734 per quality-adjusted life year (QALY) compared to dupilumab for the treatment of AD[xxxvii]. Beyond economic factors, access is also defined by clinical practice and guidelines. Newer treatments tend to be listed under the PHARMAC special authority system, meaning more restrictive eligibility guidelines, longer approval processes, and administrative hurdles, reducing the timeliness and ease of access.

If JAKis gain a prominent role in future therapeutics for skin diseases, then equity must be considered. Disproportionate care is a significant issue for Māori and Pacifica, who suffer a higher prevalence of common skin conditions, are more likely to present with more advanced skin cancer, and have the highest hospitalization rates for serious skin infections among children. Yet, Māori and Pacifica are less likely to be provided with biological therapy[xxxviii] and referred to secondary specialist services like dermatologists than Europeans[xxxix]. It is a hopeful vision that the prospect of JAKis may help reduce unmet needs and future health inequities in skin disease. Ultimately, the goal of improving health outcomes with novel therapies requires us to promote an inclusive healthcare system that provides whānau with equitable opportunities to access innovative treatments.

Conclusion

Since the first generation of JAK/STAT inhibitors in the 1990s, these small molecules have transformed therapeutics in many fields of medicine. Decades of research on the JAK/STAT signalling pathway have now led to transformative impacts in the commonest skin diseases today. We now know of more molecular biomarkers that may predict disease and offer prognoses for skin conditions both common and malignant. More significantly, JAK/STAT inhibitors have emerged as an innovative new drug class with a broad potential to overcome the current treatment challenges in dermatology. Conversely, their transformative potential may be limited by their emerging safety concerns, access barriers, and cost-effectiveness. As a novel development, further studies are also needed to clarify their long-term efficacy and safety and whether research findings are generalizable to real-world settings and 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 transform the future of therapeutics.

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