ACADEMIC: ESSAY

Turning JAK STATic, a peek into the future of dermatology therapeutics

Lathan Thomas

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

Introduction

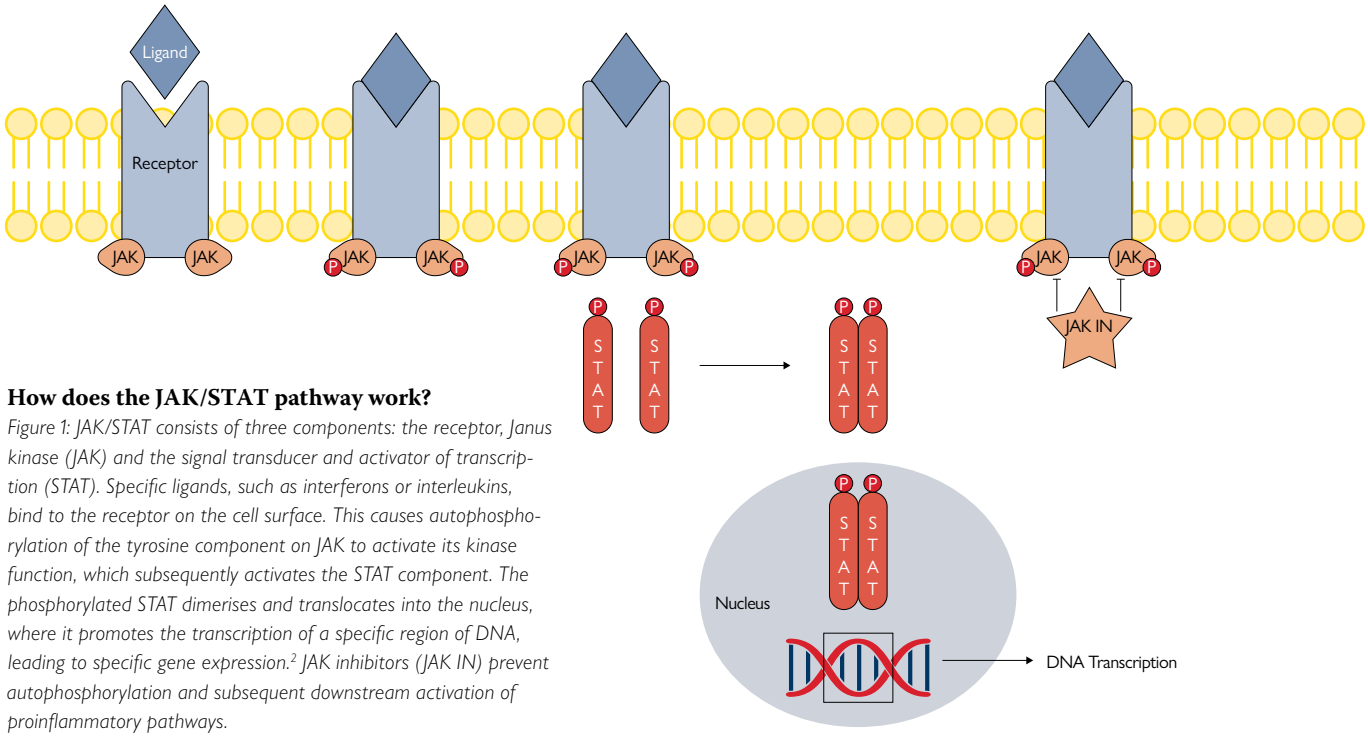
Skin diseases are the fourth leading cause of non-fatal disease burden worldwide.[1] Emerging knowledge targeting inflammatory pathways through the inhibition of Janus kinase signal transducers and activators of transcription (JAK/STAT) shows strong potential to treat skin diseases that are currently limited to only a few generalised medications with numerous side effects.[1] These precise therapies continue to be developed through the effects of JAK inhibitors and their ability to restrict downstream proinflammatory pathways. These treatments have shown efficacious results with good safety profiles in atopic dermatitis, psoriasis, and alopecia areata. Additionally, very recent developments show potential promise in the treatment of melanoma.[2] We have already seen subsequent generations of JAK inhibitors have become selective for particular domains, enhancing their effectiveness and reducing their side effects.[3] JAK inhibitors will enable us to move towards simpler, more effective and better-tolerated treatments for common skin diseases.[3]

Atopic dermatitis *(mate harehare)*

Atopic dermatitis (AD), eczema, or *mate harehare* is the most common chronic inflammatory skin disease worldwide.[4] Symptoms of AD vary from mild localised itch and pain to severe systemic symptoms.[5] These often lead to sleep disturbance and reduced quality of life.[5] Diseases associated with atopy, such as asthma and hay fever, are common comorbidities with AD.[5] Additionally, AD has also been associated with depression, anxiety and attention deficit hyperactivity disorder.[5] Mild cases of AD can be adequately controlled with topical treatments or in combination with phototherapy, but moderate to severe cases require steroid treatment with cyclosporine, methotrexate, prednisone, or other similar drugs.[5]

The Global Burden of Disease Study reports that AD affects up to 2.4% of the population worldwide but can vary substantially among different countries.[6] Whilst prevalence is highest in infancy, AD can arise at any point in life.[5] The prevalence of AD in New Zealand is 15% for the age group of six to seven years, with Māori and Pasifika populations having the highest prevalence of symptoms.[7]

Current knowledge of the acute immunopathogenesis of AD suggests that AD arises from the JAK/STAT-mediated activation of T-helper cells and subsequent release of interleukin.[8] JAK inhibitors



How does the JAK/STAT pathway work?

Figure 1: JAK/STAT consists of three components: the receptor, Janus kinase (JAK) and the signal transducer and activator of transcription (STAT). Specific ligands, such as interferons or interleukins, bind to the receptor on the cell surface. This causes autophosphorylation of the tyrosine component on JAK to activate its kinase function, which subsequently activates the STAT component. The phosphorylated STAT dimerises and translocates into the nucleus, where it promotes the transcription of a specific region of DNA, leading to specific gene expression.[2] JAK inhibitors (JAK IN) prevent autophosphorylation and subsequent downstream activation of proinflammatory pathways.

thus provide the ability to target core inflammatory components of the disease whilst avoiding harmful immunosuppression from steroids.[8] Phase III trials for topical and systemic JAK inhibitors in the treatment of AD have been successful and numerous in their reporting of efficacious and safe data.[8] However, these trials have highlighted variability in the clinical response.[8] This suggests that a standardised approach will be useful for certain subgroups of patients, but in the future, phenotype or endotype based stratification may be necessary for a more optimal risk-benefit ratio with precision medicines. [9] Baricitinib, upadacitinib, and abrocitinib have been approved for the treatment of moderate or severe AD by both the Food and Drug Administration and the European Medicines Agency. [8] New Zealand is following this trend with the approval of upadacitinib for moderate to severe AD. [10]

A better understanding of JAK/STAT and its role in this complex disorder has opened the pipeline for many new compounds that are well tolerated and provide rapid relief of pruritis, inflammation, and eczematous itch.[9] It is possible that non-specific but adequately effective existing treatments will soon be withdrawn in the place of specific, optimised long-term disease modifying management.

Psoriasis *(mate tongatonga uri)*

Psoriasis or *mate tongatonga uri* is a chronic inflammatory skin condition with various subtypes, commonly characterised by erythematous scaly patches or plaques on extensor surfaces.[11] Psoriasis is associated with increased rates of inflammatory arthritis, cardiometabolic disease, and mental health disorders.[11] Psoriasis affects men and women equally, with the global prevalence of 2–3%.[11] However, the prevalence is estimated to be between 8–11% in higher income countries.[12] Notably, a large proportion of psoriasis remains undiagnosed, thus the true prevalence is likely higher than these estimates.[12] Age standardised prevalence of psoriasis in New Zealand in 2019 was an estimated at 1888.3 per 100,000 people, just under three times higher than the global rate and higher than most other high income countries.[12] Whilst ethnicity data is fairly sparse, 26% of psoriasis patients treated at Auckland District Health Board between 2009 and 2014 were Māori or Pasifika, a figure greater than the 19% Māori and Pasifika seen in the general population of that area.[12] Particularly of note, 5.7% of psoriasis patients were Samoan.[13]

Current oral therapies, such as methotrexate, cyclosporine, and acitretin are associated with several side effects, drug interactions, and long-term toxicity.[14] In psoriasis, the JAK/STAT-mediated IL-23/IL-17 cytokine axis is currently considered to be crucial to the pathogenic pathway, which has opened the possibility for JAK inhibitors to be used in the creation of a clinically effective treatment with an easier synthesis, reduced costs, and lower immunogenicity.[14] The results of clinical trials performed thus far indicate that inhibition of JAK/STAT is effective in the treatment of psoriasis and psoriatic inflammatory arthritis.[14] Despite the completion of a large phase III psoriasis clinical trial, tofacitinib was declined approval by the FDA until additional safety analyses were completed. However, it was later approved for psoriatic arthritis.[14] Recent literature has focused on selective inhibition of the tyrosine kinase 2 protein, a type of JAK protein. [15] Phase III clinical trials using deucravacitinib showed statistically significant improvements in multiple efficacy end points compared to placebo.[15] Future developments in the treatment of psoriasis will likely enable patients to use a long-term medicine with a smaller side effect profile, reduced comorbidities, and improved health outcomes.

Alopecia Areata

Alopecia areata (AA) is a common autoimmune disease characterised by non-scarring hair loss ranging from patches on the scalp to complete hair loss of the entire body and is associated with significant psychological comorbidities.[16] Globally, AA is estimated to have a lifetime prevalence of 2%.[16] To date, there is no known reliable approved treatment for AA and it is limited to non-specific broad immunosuppressants administered either locally or systemically.[17] These therapies are associated with side effects that limit their use to the short-term.[17] JAK/STAT directs the pathogenesis of AA through the cellular response to proinflammatory cytokines IFN-γ and IL-15 that play a crucial role in maintaining penetration of CD8+ NKG2D+ T cells into intrafollicular locations, which subsequently initiates the autoimmune attack.[17] JAK inhibition is thus an appealing option to block the downstream signalling of these proinflammatory cytokines.[17] This would inhibit the production of T helper cells and restore the anagen phase of the hair follicle by promoting activation or stimulation of hair follicle stem cells.[17] The overall response rates of tofacitinib (pan-JAK), ruxolitinib (JAK1/2), and baricitinib (JAK1/2) have been remarkable but variable, ranging from 30% to 92% in severe cases of AA. [17] In children, tofacitinib has also been shown to be a viable treatment with acceptable efficacy.[18] Side effects of these treatments exist, but they are typically considered safe and tolerable.[17] Current experimental treatment has shown discontinuation of JAK inhibitors appears to result in the recurrence of AA in 17% to 31% of patients.[19] Recent developments in researching a topical JAK3 inhibitor have shown it can permanently reverse the AA phenotype in mice, which provides a hopeful glimpse into what might be possible for patients with AA in the future.[20] Upon completion of phase III large-scale double-blind randomised clinical trials, JAK inhibitors will likely become a first-line intervention for severe AA.[19]

Melanoma *(mate pukupuku kiri manauri)*

Melanoma or *mate pukupuku kiri manauri* arises from the malignant transformation of melanocytes into melanoma due to a combination of exogenous and endogenous factors.[21] It is the most prevalent fatal skin cancer and incidence rates have risen across the world over the past 50 years.[21] New Zealand has one of the highest incidence (35.8 per 100,000 people) and mortality (3.5 per 100,000 people) rates of melanoma in the world.[22] In New Zealand, NZ European/Pākehā males have the highest age-standardised incidence rate but strikingly, Māori and Pasifika melanomas tend to be deeper and at a more advanced stage when diagnosed.[23] As melanoma thickness is one of the most significant prognostic indicators, it proves to be a significant burden of mortality for these minority groups.[23] Recent preventive measures across Australasia have shown initial successes in stabilising and reducing the incidence rate of melanoma in recent years.[13] The current management consists of a wide local excision with a safety margin of variable thickness, depending on staging.[21] Patients with later stage melanomas often need to undergo adjuvant treatment.[21]

Recent evidence has come forward about the inhibition of JAK/STAT to promote endogenous immunity against melanoma.[2] Immune checkpoint blockers (ICBs) have strong clinical benefits in patients with advanced cancer and are rapidly being approved and integrated as first line cancer care.[2] However, 75% of advanced melanoma patients do not respond to anti-CTLA-4, a type of ICB, due to the deactivation of IFN-γ signalling genes. [2] This prevents most melanomas from IFN-γ induced cell death and decreases infiltration of CD8+ T cells, allowing evasion of endogenous immunosurveillance and ICB induced anti-tumour immunity. [2] Human melanomas with attenuated IFN-γ signalling or ICB resistance exhibit upregulated target genes in the JAK1/2 pathway. [2] Thus ruxolitinib, a selective JAK1/2 inhibitor, has the potential to serve as a targeted therapy for ICB resistant melanoma by enabling patients with melanoma to fight against the cancer endogenously. [2] Understanding the role of JAK/STAT in melanoma and utilisation of emerging medicines has the potential to contribute to future declines in the mortality rate of melanoma in New Zealand.

Conclusion

Unravelling the role of JAK/STAT in the pathophysiology of several dermatological diseases has enabled the development of targeted pharmacological treatments with improved outcomes. JAK inhibitors will enable us to move beyond broad systemic steroid therapies in the treatment of common skin conditions, taking these previously lifelong

diseases and turning them into something manageable and sustainable. The role of JAK inhibitors in melanoma has the potential to enhance immunotherapy and improve the immune system's ability to attack cells, providing an exciting glimpse into the future of dermatology.

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About the author

› Lathan Thomas is currently a trainee intern at the University of Otago, Christchurch. This essay was submitted to the New Zealand Dermatological Society in 2022 for the Wilson-Alison Memorial Assay Competition, an annual competition available to 4th year medical students at the University of Auckland and the University of Otago. The Wilson-Alison Memorial Prize was originally endowed by N M Peryer Ltd to commemorate the work of the late Dr H W Wilson of Auckland and the late Dr P E Allison of Christchurch, who were pioneers of dermatology in New Zealand. From 2013, the New Zealand Dermatological Society Incorporated (NZDSI) has provided support for this prize. Lathan's essay was selected as the winning essay from the University of Otago in 2022.

Declarations

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Ethical approval/patient consent

Ethical approval and patient consent were not required for this research.

Correspondence

Lathan Thomas: thola888@student.otago.ac.nz