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

"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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Introduction

Skin diseases are the 4th leading cause of non-fatal disease burden worldwide (1). Emerging knowledge targeting inflammatory pathways through the inhibition of Janus kinase-signal transducer and activator of transcription (JAK/STAT) shows strong potential to treat skin diseases that were once limited to few generalised medications with numerous side effects (1). Potential 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, alopecia areata and very recent developments show some potential promise in the treatment of melanoma. We have already seen subsequent generations of JAK inhibitors become selective for particular domains, enhancing their effectiveness and reducing their side effects (2). JAK inhibitors will enable us to move towards simpler, more effective and better tolerated treatments for common skin diseases (2). These new treatments will transform diseases once considered to be lasting burdens with substantial effects on life, to diseases that barely scratch the surface.

How does the JAK/STAT pathway work?

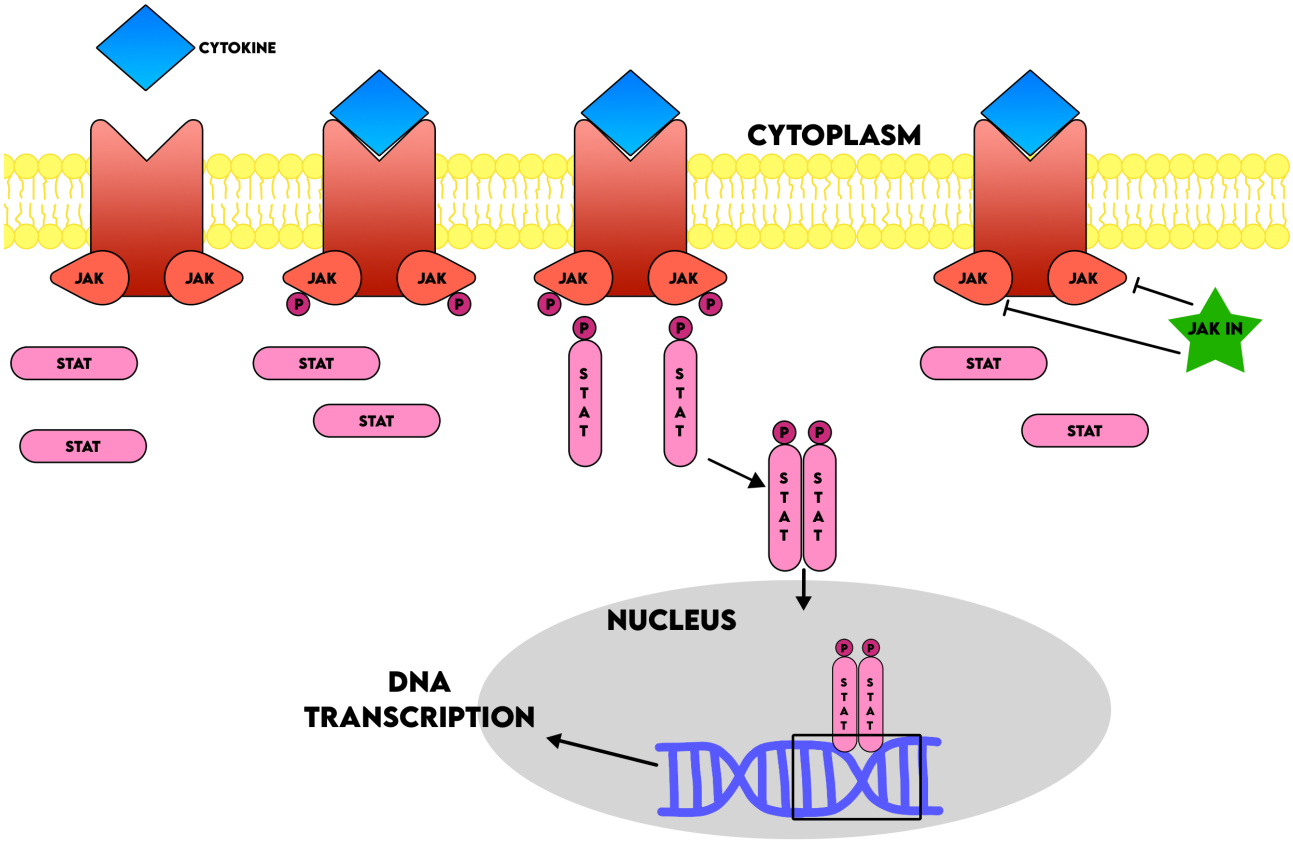

Figure 1 - JAK/STAT consists of three components: The receptor, janus kinase (JAK) and the signal transducer and activator of transcription (STAT). Specific ligands such as Interferon or Interleukin bind the receptor on the cell surface. This causes autophosphorylation of the tyrosine component on JAK to activate its kinase function, which subsequently activates the STAT component. The phosphorylated STAT dimerises and translocates into the nucleus and promotes 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.

Atopic dermatitis (*Mate harehare*)

Atopic dermatitis (AD), Eczema or *mate harehare* is the most common chronic inflammatory skin disease worldwide (3). Patients with AD can suffer from a range of mild localised itch and pain to severe systemic symptoms (4). These often lead to sleep disturbance and reduced quality of life (4). Comorbidities with AD are quite prevalent within patients, with atopic associated disease like asthma and hay fever and additional comorbidities like depression, anxiety and attention deficit hyperactivity disorder (4). 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 (4). According to WHO Global Burden of Diseases, at least 230 million people worldwide have AD (5). Whilst prevalence is highest in infancy, AD can arise at any point in life (4). New Zealand has a prevalence of 15% for AD for the age group of 6-7 years, with with Māori and Pasifika having the highest prevalence of symptoms (6).

Current knowledge on the acute immunopathogenesis of AD suggest it is initiated by T-helper cell release of interleukin, most of which relies of the subsequent activation of JAK/STAT (7). JAK inhibitors thus provide the ability to target core inflammatory components of the disease whilst avoiding harmful immunosupression from steroids (7). Phase III trials for topical and systemic JAK inhibitors for the treatment of AD have been successful and numerous in their reporting of efficacious and safe data (7). However, these trials have highlighted the variability of the clinical response (7). This likely means that a standardised approach will be useful for certain subgroups of patients, but in future, phenotype or endotype based stratification may be necessary for a more optimal risk-benefit ratio with precision medicines (8). Baricitinib, Upadacitinib and Abrocitinib have been approved for the treatment of moderate or severe AD in patients by both the Food and Drug Administration and the European Medicines Agency (7). A better understanding of JAK/STAT and the role it plays in this once complex disorder, has opened the pipeline for many new compounds that are well tolerated and provide rapid relief of pruritis, inflammation and eczematous itch (8). Non-specific and adequately effective existing treatments will soon be withdrawn in the place of optimised long term disease modifying management.

Psoriasis (*Mate tongatonga uri*)

Psoriasis or *mate tongatonga uri* is a chronic inflammatory skin condition that causes increased rates of inflammatory arthritis, cardiometabolic disease and mental health disorders (9). The most common variant is plaque psoriasis, characterised by erythematous scaly patches or plaques that commonly affect extensor surfaces (9). Psoriasis affects men and women equally, with the global prevalence rate around 2-3% of the population, however, rates are estimated to be between 8-11% in higher income countries (10). Notably, a large proportion of psoriasis remains undiagnosed, so true rates are likely higher than these estimates (10).

Age standardised prevalence for psoriasis in New Zealand in 2019 was an estimated 1888.3 per 100,000 people, just under 3 times higher then the global rate and higher then most other high income countries (10). Whilst ethnicity data is fairly sparse, 26.42% of psoriasis patients treated at Auckland District Health Board between 2009 and 2014 were Māori or Pasifika, a figure greater than the 19.1% Māori and Pasifika seen in the general population of that area (11). Particularly of note, 5.68% were Samoan (11).

Current oral therapies like methotrexate, cyclosporine and acitretin are associated with several side effects, drug interactions and long term toxicity (12). In psoriasis, the IL-23/IL-17 axis is currently considered to be crucial to the pathogenic pathway, which has opened the possibility for JAK inhibitors to create a clinically effective treatment that has an easier synthesis, reduced costs and lower immunogenicity (12). The results of clinical trials performed so far indicate that inhibition of JAK/STAT is effective in treatment of psoriasis and psoriatic inflammatory arthritis (12). Despite completion of a large phase III psoriasis clinical trial, tofacitinib was declined approval by the FDA until additional safety analyses were completed (12). Pfizer has since ceased development specifically for psoriasis due to the non-specificity of JAK inhibitors and low therapeutic index (12). The FDA later approved tofacitinib for psoriatic arthritis which indicates that JAK inhibitors could be developed into a formulation that is approved for psoriasis when evidence of long term clinical efficacy and safety becomes available (12). This future treatment will likely enable patients to use a long term medicine with a smaller side effect profile, reducing comorbidities and improving 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 (13). Globally, AA is estimated to have a lifetime prevalence of 2.11% (13). 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 (14). These therapies come with side effects and are thus typically only used for short-term use (14). JAK/STAT provides the pathogenesis for AA through the cellular response to proinflammatory cytokines IFN-γ and IL-15 and their crucial role in maintaining the penetration into intrafollicular locations by CD8+ NKG2D+ T cells and subsequent initiation of autoimmune attack (14). JAK inhibition is thus an appealing option to block activation of the T cell mediated immune response

through blocking the downstream signalling of proinflammatory cytokines (14). This would inhibit production of T helper cells and restore the anagen phase of the hair follicle by promoting activation or simulation of hair follicle stem cells (14). The overall response rates of tofacitinib (pan-JAK), ruxolitinib (JAK1/2), and baricitinib (JAK1/2) have been reported to be remarkable for severe AA. However, these results were variable, ranging from 30% to 92% (14). In children, tofacitinib has also been shown to be a viable treatment with an acceptable efficacy (15). Side effects of these treatments exist, but they are typically considered safe and tolerable (14). Current experimental treatment has shown discontinuation of JAK inhibitors appears to lead to the recurrence of AA in 17.9% to 31.3% of patients (16). Recent developments researching a topical JAK3 inhibitor have shown to permanently reverse the AA phenotype in mice, which provides a hopeful glimpse into what might be possible for patients with AA in the future (17). Upon completion of phase III large-scale double blind randomised clinical trials, it is likely that JAK inhibitors will become first line interventions for severe AA (16).

Melanoma (*Mate pukupuku kiri manauri*)

Melanoma or *mate pukupuku kiri manauri* arises from the malignant transformation of melanocytes into metastatic melanoma as a result of a process of exogenous and endogenous factors (10). It is the most prevalent fatal skin cancer and incidence rates have risen across the world over the past fifty years (18). New Zealand has one of the highest incidence (35.8/100,000 people) and mortality (3.5/100,000 people) rates of melanoma in the world (19). 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 (20). As melanoma thickness is one of the most significant prognostic indicators, this proves to be a significant burden of mortality for these minorities (20). Recent preventive measures across Australasia have shown initial successes in the stabilisation and decreasing incidence rate of melanoma in recent years (12). Current management consists of a wide local excision with various thicknesses used as a safety margin, depending on staging (18). Patients with later stage melanomas must often undergo adjuvant treatment (18).

Recent evidence has come forward about inhibition of JAK/STAT to promote endogenous immunity against melanoma (21). Immune checkpoint blockers (ICBs) cause strong clinical benefits in patients with advanced

cancer and are rapidly being approved and integrated as first-line cancer care (21). However, 75% of advanced melanoma patients do not respond to anti-CTLA-4, a type of ICB, due to deactivation of IFN-γ signalling genes (21). This prevents most melanomas from IFN-γ induced cell death and decreased infiltration of CD8+ T cells, allowing evasion of endogenous immunosurveillance and ICB induced anti-tumour immunity (21). Human melanomas with attenuated IFN-γ signalling or ICB resistance exhibit upregulated target genes in the JAK1/2 pathway (21). Thus Ruxolitinib, a selective JAK1/2 inhibitor has the potential ability as a targeted therapy for ICB resistant melanoma by enabling patients with melanoma to fight against the cancer endogenously (21). 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 pathophysiology has enabled advancements in the treatment of a number of diseases that had previously minimal options. JAK inhibitors will enable us to move beyond broad systemic steroid therapies in our treatment of common skin conditions, taking these previously life-long diseases and turning them into something manageable and sustainable. With inflammatory diseases like atopic dermatitis, psoriasis and alopecia areata, emerging research around JAK inhibitors paves the way for long term disease management strategies and a shift away from steroid treatments. 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.

Bibliography

1. Seth D, Cheldize K, Brown D, Freeman EE. Global burden of skin disease: inequities and innovations. Current dermatology reports. 2017;6(3):204-10.
2. Gündüz Ö. JAK/STAT pathway modulation: Does it work in dermatology? Dermatologic Therapy. 2019;32(3):e12903.
3. Rodrigues MA, Torres T. JAK/STAT inhibitors for the treatment of atopic dermatitis. Journal of Dermatological Treatment. 2020;31(1):33-40.
4. Siegels D, Heratizadeh A, Abraham S, Binnmyr J, Brockow K, Irvine AD, et al. Systemic treatments in the management of atopic dermatitis: a systematic review and meta−analysis. Allergy. 2021;76(4):1053-76.
5. Deckers IA, McLean S, Linssen S, Mommers M, Van Schayck C, Sheikh A. Investigating international time trends in the incidence and prevalence of atopic eczema 1990–2010: a systematic review of epidemiological studies. PloS one. 2012;7(7):e39803.
6. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. Journal of Allergy and Clinical Immunology. 2009;124(6):1251-8.e23.
7. Tsiogka A, Kyriazopoulou M, Kontochristopoulos G, Nicolaidou E, Stratigos A, Rigopoulos D, et al. The JAK/STAT Pathway and Its Selective Inhibition in the Treatment of Atopic Dermatitis: A Systematic Review. Journal of Clinical Medicine [Internet]. 2022; 11(15).
8. Bieber T. Atopic dermatitis: an expanding therapeutic pipeline for a complex disease. Nature Reviews Drug Discovery. 2022;21(1):21-40.
9. Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. Jama. 2020;323(19):1945-60.
10. Damiani G, Bragazzi NL, Karimkhani Aksut C, Wu D, Alicandro G, McGonagle D, et al. The Global, Regional, and National Burden of Psoriasis: Results and Insights From the Global Burden of Disease 2019 Study. Front Med (Lausanne). 2021;8:743180.
11. Lee M, Lamb S. Ethnicity of psoriasis patients: an Auckland perspective. The New Zealand medical journal. 2014;127(1404):73-4.
12. Nogueira M, Puig L, Torres T. JAK inhibitors for treatment of psoriasis: focus on selective TYK2 inhibitors. Drugs. 2020;80(4):341-52.
13. Lee HH, Gwillim E, Patel KR, Hua T, Rastogi S, Ibler E, et al. Epidemiology of alopecia areata, ophiasis, totalis, and universalis: A systematic review and meta-analysis. Journal of the American Academy of Dermatology. 2020;82(3):675-82.
14. Dillon KL. A Comprehensive Literature Review of JAK Inhibitors in Treatment of Alopecia Areata. Clin Cosmet Investig Dermatol. 2021;14:691-714.
15. Behrangi E, Barough MS, Khoramdad M, Hejazi P, Koltapeh MP, Goodarzi A. Efficacy and safety of tofacitinib for treatment of alopecia areata in children: a systematic review and meta−analysis. Journal of Cosmetic Dermatology. 2022.
16. Fukuyama M, Ito T, Ohyama M. Alopecia areata: Current understanding of the pathophysiology and update on therapeutic approaches, featuring the Japanese Dermatological Association guidelines. The Journal of dermatology. 2022;49(1):19-36.
17. Dai Z, Chen J, Chang Y, Christiano AM. Selective inhibition of JAK3 signaling is sufficient to reverse alopecia areata. JCI insight. 2021;6(7).

18. Schadendorf D, van Akkooi ACJ, Berking C, Griewank KG, Gutzmer R, Hauschild A, et al. Melanoma. The Lancet. 2018;392(10151):971-84.
19. Bolick NL, Geller AC. Epidemiology of melanoma. Hematology/Oncology Clinics. 2021;35(1):57-72.
20. Sneyd MJ, Cox B. Melanoma in Maori, Asian, and Pacific peoples in New Zealand. Cancer Epidemiol Biomarkers Prev. 2009;18(6):1706-13.
21. Shen H, Huang F, Zhang X, Ojo OA, Li Y, Trummell HQ, et al. Selective suppression of melanoma lacking IFN-γ pathway by JAK inhibition depends on T cells and host TNF signaling. Nature communications. 2022;13(1):1-17.