SKIN

SHORT COMMUNICATION

The JAK-Cytokine Interface – A Review and Update on Prospective Clinical Considerations

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ABSTRACT

Janus kinases (JAKs) are non-receptor tyrosine kinases that work together with signal transducers and activators of transcription (STAT) proteins to form the JAK/STAT pathway. Together, this pathway is responsible for mediating a wide range of downstream cytokines and growth factors, and inhibition of various components of this pathway has been a major area of research focus in recent years. Each of the major enzymes of the family – which include JAK1, JAK2, JAK3, and Tyrosine Kinase 2 (TYK2) – or combinations of JAKs is responsible for its own set of most strongly-associated inflammatory mediators, and inhibition of specific JAKs or combination of JAKs can therefore also potentially allow for modulation of specific inflammatory factors and their associated conditions. To date, JAK inhibitors have particularly been studied in the treatment of atopic dermatitis (felt to be primarily driven by IL-4, IL-13, and IL-5), psoriasis (IL-12/IL-23), alopecia areata (IL-2, IL-15, and IFN-γ), and vitiligo (IL-15 and IFN-γ), given that these factors can all be found downstream of specific JAK/STAT pathways as shown in Figure 1. By providing a concise review of the inflammatory factors affected by each JAK, this article aims to support clinicians as they engage in the ever-growing body of research around the use of JAK inhibitors for potential treatment of dermatologic conditions.

Janus kinases (JAKs) are non-receptor tyrosine kinases that work together with signal transducers and activators of transcription (STAT) proteins to form the JAK/STAT pathway. Together, this pathway is responsible for mediating a wide range of downstream cytokines and growth factors, and inhibition of various components of this pathway has been a major area of research focus in recent years. Each of the major enzymes of the family – which include JAK1, JAK2, JAK3, and Tyrosine Kinase 2 (TYK2) – or combinations of JAKs is responsible for its own set of most strongly-associated inflammatory mediators (**Figure 1**), and inhibition of specific JAKs or combination of JAKs can therefore also potentially allow for modulation of specific inflammatory factors and their associated conditions. This article will attempt to provide a concise review of the inflammatory factors affected by each JAK, and to support clinicians as they engage in the ever-growing body of research around the use of JAK inhibitors for potential treatment of these conditions.

Atopic dermatitis represents one of the most studied, and consequently most targeted, conditions for JAK inhibition to date, with three FDA approvals of JAK inhibitors, two

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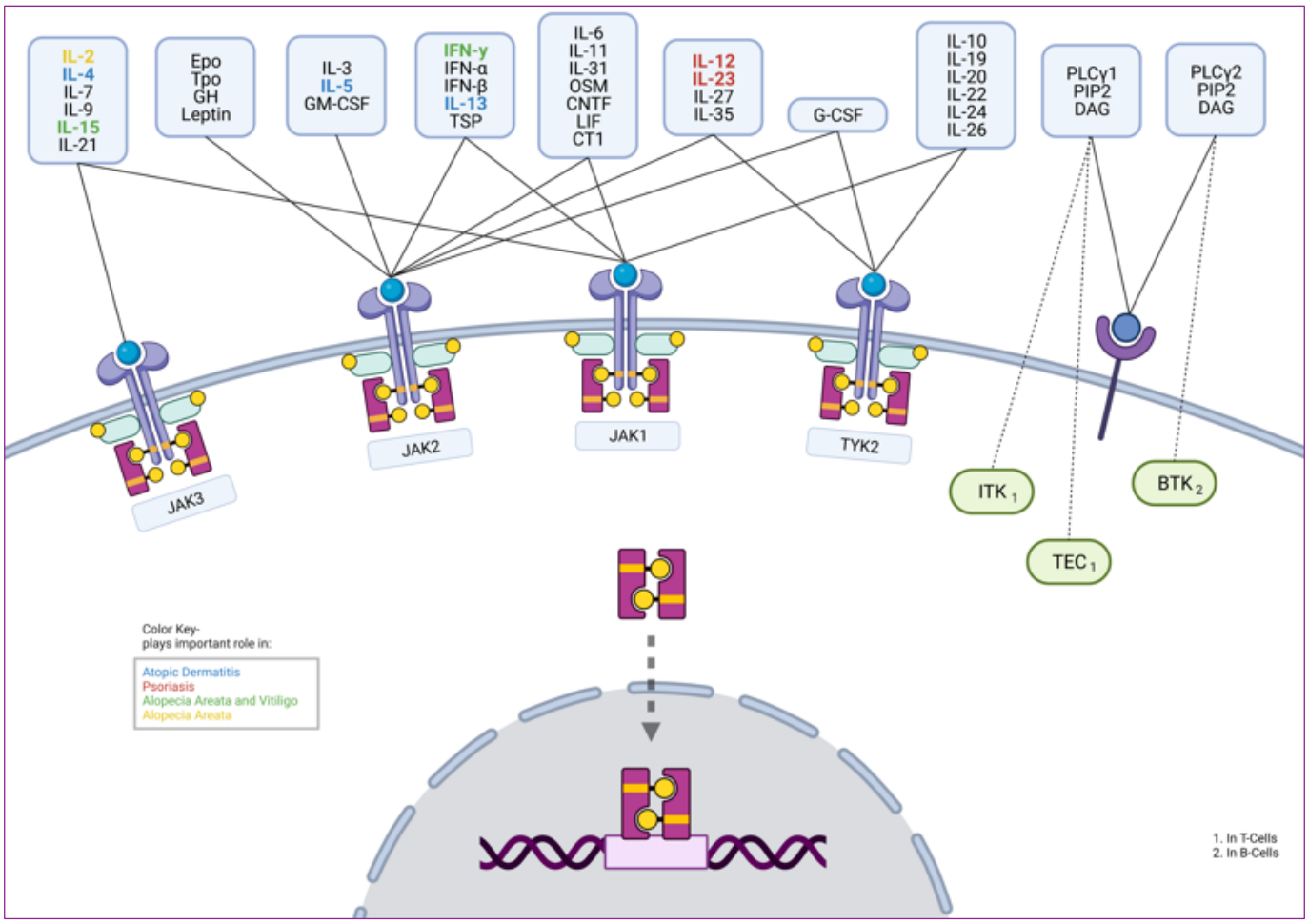

Figure 1. Interactions between various cytokines and JAK1-3, TYK2, ITK, TEC, and BTK.

systemic and one topical, for treatment of atopic dermatitis between 2021-2022. As shown in Figure 1, atopic dermatitis is classically mediated by IL-4 and IL-13 (downstream of JAK1/3 and JAK1/2 respectively) and IL-5 (downstream of JAK2)[1]. Early FDA approvals of JAK inhibitors for atopic dermatitis have emphasized the role of JAK1 inhibition, with topical ruxolitinib inhibiting JAK1/2 and oral upadacitinib and abrocitinib more selectively focusing on JAK1[1-2]. With a number of selective JAK3 inhibitors in the pipeline, specifically focused on vitiligo and alopecia areata, future research may also evaluate whether selective JAK3 inhibition is also able to successfully treat atopic dermatitis via its inhibition of IL-4 while avoiding the broader set of cytokines and growth factors downstream of JAK1.

Psoriasis is primarily mediated by the IL-12/IL-23 pathway[3], which as shown in Figure 1 is downstream of JAK2/TYK2. Through this lens, one can understand why deucravacitinib – a selective TYK2 inhibitor – demonstrates efficacy and has gained FDA approval for treatment of psoriasis[4], and why less selective JAK inhibitors such as tofacitinib (which inhibits JAK1/2/3 and was FDA-approved for psoriatic arthritis[5]) demonstrated efficacy as well. However, as shown in Figure 1, both TYK2 and JAK1/2/3 also act on a very wide range of off-target

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downstream factors, raising the question of whether IL-12, IL-23, and/or IL-17 can be more selectively targeted in future generations of JAK inhibitors.

Alopecia areata is driven by inflammation believed to be mediated by IL-2 and IL-15 (which is downstream of JAK1/3, as shown in Figure 1), as well as IFN-γ (downstream of JAK1/2)[6]. The first FDA-approved JAK inhibitor for alopecia areata was oral baricitinib[7], which inhibits JAK1/2 and therefore likely impacts all of these factors. Vitiligo is also driven by IL-15 (downstream of JAK1/3) and IFN-γ (downstream of JAK1/2)[8-9], and like alopecia areata saw its first FDA approved JAK inhibitor in the form of a JAK1/2 inhibitor (topical ruxolitinib).

More recently, there has been increasing research evaluating the potential for more targeted inhibition of JAK3 for alopecia areata and vitiligo, given it is still upstream of both IL-2 and IL-15 with fewer off-target factors than those downstream of JAK1/2. Interim results for ritlecitinib (a selective JAK3 inhibitor) in phase 3 alopecia areata studies[10] and phase 2b vitiligo studies[11] may potentially support this hypothesis, highlighting the potential promise of targeted inhibition aimed at specific cytokines of interest.

In addition to these 4 initial dermatologic conditions for which JAK inhibitors have been approved to date, there have been a broad range of additional conditions reported for which JAK inhibition may hold promise[12]. By more specifically understanding which inflammatory mediators are downstream of each specific JAK, scientists and clinicians can aim to further optimize targeting of a given condition's driving mediators, thereby maximizing impact while minimizing off-target effects and thus improving patient outcomes.

Conflict of Interest Disclosures: Dr. Hashemi has completed an externship as Entrepreneur in Residence at Gore Range Capital. Dr. Bhatia has served as an advisor, consultant, and investigator for Abbvie, Almirall, Arcutis, Arena, Beiersdorf, Biofrontera, BMS, BI, Dermavant, Galderma, InCyte, ISDIN, J&J, LaRoche-Posay, Leo, Lilly, Novartis, Ortho, Pfizer, Regeneron, Sanofi, SunPharma, and Verrica.

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