Resource Sheet 6
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Understanding JAK Inhibitors and Cicatricial Alopecia

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Janus kinase (JAK) inhibitors, like tofacitinib, ruxolitinib and baricitinib, are proposed treatments for alopecia areata. The JAK family is a group of non-receptor signaling molecules that are important in gene expression and include the molecules JAK1, JAK2, JAK3, and TYK2. The JAK-Signal Transducers and Activator of Transcription (STAT) pathway was discovered about 30 years ago and since then, studies have shown that they are involved in many growth pathways within the human body. The JAKs are located within the cell membrane. When a signaling molecule binds the extracellular portion of the tyrosine kinase domain, the JAKs are phosphorylated and become active. The activated JAKs activate STAT proteins, which enter the nucleus of the cell and bind DNA, regulating gene expression. A simple diagram of the JAK-STAT pathway is depicted in Figure 1.

As mentioned before, JAK inhibitors have demonstrated hair regrowth in patients with alopecia areata. Alopecia areata is an autoimmune disease that leads to patches of hair loss mainly on the scalp, and in some patients, it can affect the entire scalp (alopecia totalis) or the entire body (alopecia universalis). The proposed mechanism is that T-cells, a type of white blood cell, produce interferon-gamma, which binds to its receptor on the surface of hair follicles and activates the JAK-STAT pathway. This leads to production of interleukin 15, which binds to its receptor on T-cells and activates JAK-STAT. Ultimately, this leads to a cycle of inflammation in the hair follicle and hair loss. JAK inhibitors are small molecules that inhibit phosphorylation of JAK and effectively reduce intracellular signaling of the JAK-STAT pathway.

Tofacitinib, ruxolitinib, and baricitinib are the three JAK inhibitors that have demonstrated effectiveness in patients with alopecia areata and are currently being studied in clinical trials. These medications were originally approved to treat blood disorders and rheumatoid arthritis. Tofacitinib, an inhibitor of JAK1 and JAK3, was the first JAK inhibitor studied in clinical trials and is most commonly prescribed for alopecia areata compared to the other two JAK inhibitors. Ruxolitinib and baricitinib are inhibitors of JAK1 and JAK2. Oral formulations of tofacitinib and ruxolitinib induced remarkable hair regrowth at the end of 6 months compared to topical formulations. Topical formulations may be a more desirable option because it will localize the effects to the site of application. Unfortunately, the efficacy of topical JAK inhibitors remains undetermined. Most patients who stop taking oral JAK inhibitors will experience a relapse in hair loss, so patients will likely need to take this medication indefinitely. Side effects of JAK inhibitors include headache, weight gain, and upper respiratory infections. Less commonly, increased risk

of some cancers, infection, low platelets or white blood cells, and high cholesterol can also occur. These potential side effects can be mitigated by using topical formulations when available. The pros of oral medications are the ease of patient administration and compliance. Overall, JAK inhibitors are a promising treatment for patients with alopecia areata who do not respond to other first-line treatments.

Figure 1: JAK-STAT pathway

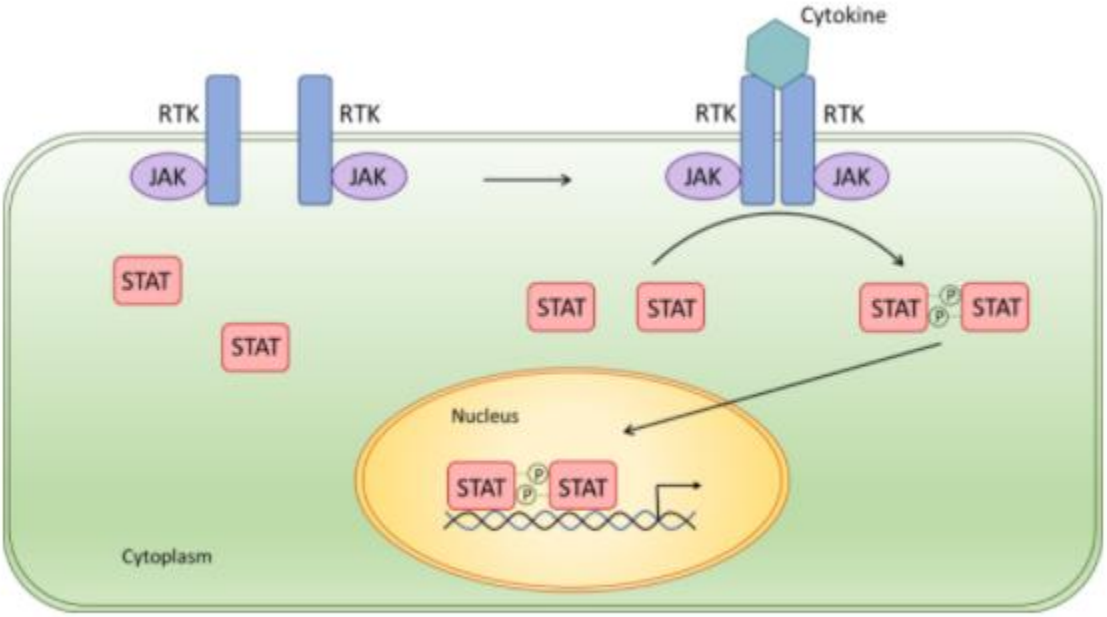

Figure 4. Schematic JAK-STAT signal pathway.

https://www.creativebiomart.net/resource/signal-pathway-jak-stat-signal-pathway-389.htm

Sources

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