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IL-17 May Be a Key Cytokine Linking Psoriasis and Hyperglycemia

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Psoriasis is associated with the metabolic syndrome, an interconnected group of conditions characterized by significant morbidity and mortality, although the causal mechanisms are still under investigation. Ikumi et al. provide evidence of a link—involving IL-17—between psoriasis and hyperglycemia in humans and mice.

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Psoriasis and the metabolic syndrome

In addition to the morbidity directly attributable to psoriasis, patients are at an increased risk of developing a large number of comorbidities. These comorbidities cluster into what has been termed the metabolic syndrome, representing dyslipidemia, insulin resistance, and central obesity, with secondary cardiovascular and hypertensive disease (Takeshita et al., 2017). Although major adverse cardiovascular events are more prevalent among patients with severe psoriasis, a large prospective cohort study found that psoriasis alone does not appear to a risk factor—rather it is the association with key comorbidities (Parisi et al., 2015). Obesity is often one of the initial signs observed in a patient who develops the metabolic syndrome, but it is also known to be an independent risk factor for psoriasis (Kassi et al., 2011; Takeshita et al., 2017). Finally, genetic variations in *IL-23* are independently associated with psoriasis severity and type 2 diabetes (Eirís et al., 2014).

Although the mechanisms behind these complex relationships have yet to be fully elucidated, it is currently known that psoriasis results from the interplay between genetic and environmental factors, leading to chronic dysregulated cutaneous and systemic inflammation centered around the IL-23/IL-17 T-cell axis (Hawkes et al., 2017). Ikumi et al. (2019) bring us one step closer to piecing this puzzle together by providing compelling evidence for a link between psoriatic inflammation and hyperglycemia, via IL-17.

Severity of psoriasis correlates with hyperglycemia in humans and improves with anti–IL-17A monoclonal antibody treatment

Ikumi et al. (2019) studied 39 patients with psoriasis and found a significant positive correlation between patients' Psoriasis Area Severity Index (PASI) score and their serum glycated hemoglobin (HbA1c) level, which reflects the average serum glucose level over the previous few months (Spearman $\rho = 0.582$ [95% CI = 0.3177–0.7623], $P = 0.0001$). In addition to finding a correlation between the HbA1c level and total PASI score, there was also a correlation with the erythema component of the PASI score. Patients were divided into two groups based on psoriasis severity; those with very severe psoriasis (PASI $\geq$ 20) had a significantly higher HbA1c compared with those with moderate to severe psoriasis (PASI $<$ 20). While intriguing, these findings require replication in larger cohorts. These data are consistent with findings from previous epidemiological studies that suggested an association between the severity of psoriasis and the likelihood of a patient developing hyperglycemia (Langan et al., 2012),

Because of a finding of improved insulin sensitivity and reduced serum IL-17 levels in two patients following successful treatment with bath psoralen and UVA, the authors investigated whether biologic treatment with anti–IL-17A mAbs improved glucose homeostasis. Anti–IL-17A mAbs are currently available commercially as either secukinumab or ixekizumab, and a 90% to 100% improvement in PASI scores (termed PASI 90 or PASI 100) has been observed with their use in a significant number of patients (Hawkes et al., 2017). In a cohort of 14 patients, anti–IL-17A mAb treatment significantly reduced HbA1c levels, measured immediately before and while undergoing treatment. In 13 patients, the second HbA1c level was measured after at least 4 months of anti–IL-17A mAb treatment, whereas in one patient, the second HbA1c level was measured after 2 weeks of therapy. Improvement was noted in patients with a borderline or normal HbA1c as well as in the five patients in the cohort who were already established on antidiabetic medications. No correlation was found between delta PASI and delta HbA1c, suggesting that although treatment of cutaneous psoriasis improved serum glucose levels, the underlying mechanism relies on more than just IL-17. These findings of improved glucose homeostasis after successful treatment of psoriasis may also relate to the improvement of psoriasis itself. However, these results are not directly comparable, as glucose homeostasis was assessed in different ways, and the small sample size requires replication in a larger cohort.

Imiquimod-treated mice have hyperglycemia that responds to anti–IL-17A mAb treatment

The second section of the paper by Ikumi et al. (2019) details the use of an imiquimod (IMQ)-induced mouse

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Clinical Implications

- In humans, serum glucose levels correlated with psoriasis severity, as measured by the Psoriasis Areas Severity Index (PASI) score.
- The imiquimod-induced mouse model of psoriasis resulted in hyperglycemia and impaired glucose tolerance but not insulin resistance.
- Treatment with anti–IL-17A monoclonal antibodies reduced serum glucose levels in humans and mice, although the reduced serum glucose levels did not correlate with the degree of skin improvement observed, and the skin lesions were largely unchanged in mice.

model of cutaneous inflammation to explore the potential link between psoriasiform inflammation and glucose metabolism. The authors then attempted to tease out the underlying mechanisms for this inflammation by targeting the pathways involving IL-17.

IMQ-induced cutaneous inflammation is a commonly used mouse model of psoriasis. Psoriasiform dermatitis is generated by the topical administration of IMQ, a toll-like receptor 7/8 ligand that causes psoriatic-like inflammation through the IL-23/IL-17 axis (van der Fits et al., 2009). Advantages of this model include how topical IMQ not only induces systemic inflammation but also eliminates the requirement of obese mice, a potential confounder (Okin and Medzhitov, 2016). However, the model has been criticized for inducing common cytokine pathways present in a variety of skin diseases with strain-dependent effects (Swindell et al., 2017).

Using the IMQ-induced mouse model, the authors created a psoriasis-like phenotype of the skin overlying the ear and back of the mice. Within 7 days the IMQ-treated mice had erythema, scaling, and increased thickness as assessed by a local PASI score, as previously described (van der Fits et al., 2009). The authors confirmed the histological appearance of psoriasiform features in the mouse skin through evidence of epidermal hyperproliferation and parakeratosis.

Compared with the control mice, the IMQ-treated mice exhibited significantly increased fasting glucose levels. Upon the administration of intravenous glucose, the IMQ-treated mice had significantly higher initial serum glucose levels—although this difference was not sustained at 120 minutes, which would be typical of impaired glucose tolerance—with a significantly muted initial insulin response. The IMQ-treated mice exhibited no difference in their response to insulin injection compared with the control mice, suggesting that the mice were not insulin resistant. HbA1c levels were not measured because of the short duration of the protocol. Taken together, these findings suggest that IMQ-treated mice display dysregulated glucose metabolism consistent with prediabetes.

To investigate the mechanisms underlying the dysregulated glucose metabolism in the IMQ-treated mice, the authors used an ex vivo histopathological approach with hematoxylin and eosin (H&E) staining and anti-insulin staining, demonstrating that the islet cells of the IMQ-treated mice were intact and similar in appearance to the islets from control-vehicle–treated mice. Furthermore, pancreatic islets isolated from the IMQ-treated mice functioned comparably to those of the control mice in response to differing glucose environments (a 3 mM basal state and a 20 mM response state). The livers of the IMQ-treated mice, assessed ex vivo with H&E staining, were macroscopically similar to those of the control mice, and no derangement was observed in the two liver function tests: aspartate aminotransferase and alanine aminotransferase.

In summary, the IMQ-treated mouse model causes dysregulated glucose metabolism with hyperglycemia caused by the lack of stimulation of insulin secretion, rather than insensitivity or inability to secrete insulin.

The final stage of the work performed in the mouse model by Ikumi et al. (2019) aimed to assess the effects of anti–IL-17A mAb on hyperglycemia. This is because the IMQ mouse model mediates inflammation through IL-23/IL-17 as mentioned previously (van der Fits et al., 2009); IL-17A blockade in humans improved hyperglycemia, and murine pancreatic islets express IL-17 receptors (Han et al., 2011). Compared with IMQ-treated mice injected with an IgG isotope, the mice treated with the anti–IL-17A mAb demonstrated an improvement in their hyperglycemia toward the baseline (vehicle), although a significant difference between the vehicle and the anti–IL-17A mAb cohort remained. It is important to note that in contrast to the marked improvement in PASI scores observed in patients with psoriasis treated with anti–IL-17A mAb, very little improvement was observed in the skin of the IMQ-treated mice that were given anti–IL-17A mAb compared with the IMQ-treated mice that were given an IgG isotope. This offers further evidence that although the IMQ-treated mouse model causes inflammation phenotypically similar to that observed in humans, the underlying mechanisms driving this differ.

Closing remarks

Psoriasis is a multimorbid disease with significant patient impact, and effectively treating the condition—and its associated comorbidities—requires a good understanding of the immunopathological pathways underpinning this disease. Ikumi et al. (2019) have provided intriguing data, suggesting how a cutaneous and systemic connection between psoriasis and diabetic states exists in both mice and humans and that IL-17 may play a contributory role.

In IMQ-treated mice, anti–IL-17A mAbs improve hyperglycemia, which compares favorably to humans. However, consistent with previous studies, the role of IL-17 in murine skin lesions is less clear and is likely overshadowed by other cytokines (Swindell et al., 2017). In humans, the role of IL-17 in type 1 (autoimmune) diabetes is already under investigation (Baharlou et al., 2016), and it has been suggested that anti–IL-17A mAb may have a role in the prevention of diabetic end-organ damage (Mohamed et al., 2016; Qiu et al., 2017).

The authors found that successful treatment of psoriasis in humans with the anti–IL-17A mAbs secukinumab and ixekizumab improved hyperglycemia even in patients who were below the HbA1c threshold for diabetes. However, these findings are limited by the small sample size, and therefore, further studies are needed to examine this correlation in detail. In rheumatoid arthritis, another systemic inflammatory disease associated with diabetes and increased cardiovascular mortality, successful cytokine blockade with biologics can improve the HbA1c levels of patients (Otsuka et al., 2018). Although the mechanisms underlying this finding undoubtedly differ, it highlights how the effective treatment of a systemic inflammatory disease can have beneficial effects downstream. In dermatology, the treatment of conditions such as psoriasis is moving toward holistic management and risk prevention. If we can demonstrate systemic benefits to biologic treatment, we will be one step closer to achieving this.

With this in mind, it will be interesting to see the results of the METABOLYX trial that is due to be completed in 2021 (Clinicaltrials.gov, 2018). This study is a randomized controlled trial of secukinumab alone versus secukinumab plus lifestyle intervention; it has a target enrollment of 760 patients, with a primary outcome of PASI 90 at 28 weeks but importantly with secondary outcomes, including a change in waist circumference and a change in HbA1c and fasting plasma glucose levels at 8, 16, and 28 weeks.

CONFLICT OF INTEREST

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