Impaired Autophagy in Psoriasis and Atopic Dermatitis: A New Therapeutic Target?

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Dysfunctional autophagy is linked to various diseases, including psoriasis and atopic dermatitis. Recent evidence suggests that exposure of keratinocytes to TNF-α results in impaired autophagy and lysosomal function. The skin of patients with psoriasis and atopic dermatitis reveals a decreased expression of lysosomal cathepsins. Impaired autophagy is presumably involved in inflammation and disturbed keratinocyte differentiation, whereas stimulating autophagy might be a treatment option in inflammatory skin disease.

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Autophagy is an essential biological process that involves intracellular quality control, metabolism, and cell survival and that enables cells to recycle cytoplasmic materials under stress conditions. Macroautophagy, which is the best understood form of autophagy, has been also implicated in several aspects of the immune response, including lymphocyte development, innate immunity, antigen presentation, and antigen receptor signaling (Deretic, 2021). During autophagy, cytoplasmic material is identified by autophagy receptors, such as p62/SQSTM1, and collected in double-membrane autophagosomes. These structures subsequently fuse with lysosomes, where the cargo is degraded by acidic hydrolases, such as proteases of the cathepsin family. Owing to its fundamental role in cellular homeostasis, deregulated autophagy has been associated with various diseases, including cancer, metabolic disorders, neurodegeneration, cardiovascular and liver diseases, as well as infections and autoimmune diseases. Moreover, in recent years, an increasing number of studies identified a role for autophagy in the pathogenesis of skin diseases.

In their new article in the *Journal of Investigative Dermatology*, Klapan et al. (2021) demonstrate alterations of the autophagic process in atopic dermatitis (AD) and psoriasis. Initial analyses suggested an increase in autophagic flux because high expression of the ATG5, ATG7, and ATG8, which are essential for autophagosomal elongation, was found in AD and psoriasis skin biopsies. Short-term treatment of human primary keratinocytes (KCs) with TNF-α, a central regulator of these inflammatory skin diseases, also confirmed an increase in the autophagic capacity. Surprisingly, AD and psoriasis biopsies as well as long-term TNF-α–treated KCs exhibited an accumulation of p62/SQSTM1, which is normally degraded during the autophagic process, indicating that despite the increased initiation of autophagosome formation, the processing of the cargo is impaired. Further analysis revealed that the amount and activity of cathepsins D and L, both components of the lysosome, were significantly decreased in long-term TNF-α–treated KCs and in lesional skin, indicating a functional impairment of autophagy in AD and psoriasis (Figure 1).

The consequences of diminished autophagy for the manifestations of inflammatory skin diseases are highly complex and are not well-understood. Because the differentiation of KCs depends on functional autophagy, decreased cathepsins D and L expression might contribute to the parakeratosis observed in psoriasis (Akinduro et al., 2016). Moreover, defects in autophagy and KC differentiation might be involved in the disturbed epithelial barrier that is present in psoriatic plaques. In fact, autophagy is regarded as a cell-autonomous antimicrobial defense mechanism in several epithelial tissues.

Another prominent function of autophagy in immunity is the inhibition of proinflammatory cytokine synthesis, including that of IL-1β and type-I interferons. Autophagy has been correlated with the degradation of central innate immune sensors such as cGAS, RIG-I, and TLR3 in various cell types (Deretic, 2021). Autophagy also negatively regulates KC inflammatory responses through the scaffold protein p62/SQSTM1. The p62 protein is not only a cargo receptor for autophagy but also a multifunctional signaling hub for the activation of proinflammatory transcription factors, including NF-κB and NRF2 (Sánchez-Martín et al., 2019). Thus, the stabilization of p62 owing to defective autophagy, as observed by Klapan et al. (2021), might increase the activity of these transcription factors and result in the production of proinflammatory cytokines, another hallmark of psoriasis and AD (Lee et al., 2011). A similar link between skin inflammation and autophagy is reflected by genetic variants of *AP1S3*, an autophagy regulator that has been found to be mutated in pustular psoriasis. KCs lacking *AP1S3* not only reveal defective autophagy and p62 accumulation but also promote skin inflammation as a consequence of increased NF-κB activation and secretion of IL-1β and IL-36 (Mahil et al., 2016). It is interesting to note that polymorphisms in the autophagy regulator *ATG16L1* are associated with psoriasis (Douroudis

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Clinical Implications

- Long-term exposure to TNF-α suppresses autophagy and lysosomal function in keratinocytes.
- Expression of lysosomal proteases, including cathepsins, is decreased in the skin of patients with psoriasis and atopic dermatitis.
- Stimulation of autophagy might be exploited as a treatment strategy for patients with inflammatory skin disease.

et al., 2012). Several earlier GWASs had identified *ATG16L1* as a susceptibility gene in Crohn's disease and ankylosing spondylitis, suggesting that impaired autophagy might be a general feature contributing to the pathogenesis of autoinflammatory diseases.

It is uncertain whether the reactivation of normal autophagy could present a valid strategy for the treatment of psoriasis and other inflammatory skin diseases. The fact that some current antipsoriasis drugs, such as retinoids, are described to increase autophagy would support this hypothesis. However, other autophagy-mediated functions might be detrimental for the treatment of skin-related autoimmune diseases. For instance, the recognition of autoantigens presented by KCs is crucial for the development of psoriasis. Increased protein degradation through autophagy might increase the presentation of autoantigens and thus the activation of autoreactive T cells.

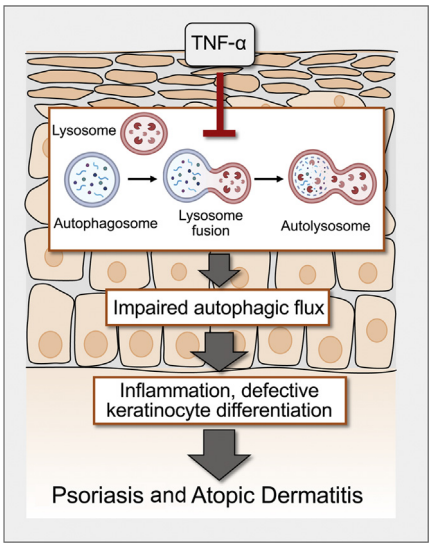

Figure 1. TNF-α–mediated impairment of autophagy in keratinocytes during inflammatory skin disease. Long-term exposure of keratinocytes to TNF-α results in the impairment of autophagic flux and reduced fusion of autophagosomes with lysosomes. Although the mediators as well as the exact site of TNF-α action during autophagy are unknown, inhibition of autophagy could result in reduced keratinocyte differentiation, epithelial barrier dysfunction, and enhanced inflammation. Inhibition of autophagy might thereby contribute to psoriasis and atopic dermatitis, and stimulation of autophagy might be a novel treatment option for inflammatory skin diseases.

Hyperplasia of KCs is another hallmark of psoriasis. How increased autophagy, which constitutes an additional source of amino acids, nucleotides, and carbohydrates, will affect the survival and proliferation of KCs is unclear. Because inflammatory skin diseases are characterized by a tight interplay between KCs and various immune cells, such as T cells and dendritic cells, the effect of an autophagy activator on these cell types also has to be considered. Various studies show that TCR stimulation increases autophagy, whereas mice lacking essential regulators of autophagy exhibit reduced frequencies of thymocytes as well as $CD4^+$ and $CD8^+$ peripheral T cells (Merkley et al., 2018). Moreover, cathepsins, in particular cathepsin S, have been reported to cleave and thereby activate the proform of IL-36γ, an important proinflammatory mediator in psoriasis (Ainscough et al., 2017). Thus, boosting autophagy in autoimmune diseases might promote T-cell survival and the inflammatory responses leading to exacerbation of the disease. In contrast, autophagy stimulation could reduce the secretion of IL-1β and IL-23 from antigen-presenting cells and hence prevent the differentiation of naive $CD4^+$ T cells into the T helper type 17 lineage, which could have a beneficial impact on psoriasis treatment (Merkley et al., 2018). Which effects of autophagy modulation on KCs and immune cells are dominant in the pathological situation should be carefully evaluated in in vivo models and will dictate the potential of autophagy modulators for the treatment of inflammatory skin diseases.

As with many intriguing articles, the study by Klapan et al. (2021) raises more questions than it answers. For instance, it will be interesting to investigate how other key cytokines involved in psoriasis and AD, including IL-17A or IL-4, influence autophagy, either alone or in combination with TNF-α. In addition, the downstream mediators in the TNF-α signaling pathway that inhibit autophagic flux as well as the exact target in the autophagic process remain unknown. It has also been found that p38 kinase, which is stimulated by TNF-α and upregulated in inflammatory skin disease, phosphorylates ATG5 and thereby inhibits the autophagic flux (Keil et al., 2013). It will be intriguing to investigate whether available gene-targeted mice deficient in autophagy regulators or selected cathepsins are hypersensitive to experimental psoriasis or AD. Finally, it will be most important to explore whether pharmacological activation of autophagy has beneficial effects on the treatment of inflammatory skin diseases.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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Targeting the FcRn: A Novel Approach to the Treatment of Pemphigus

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Pemphigus is a debilitating autoimmune blistering disorder mediated by IgG autoantibodies to desmosomal cadherins that requires novel steroid-sparing therapies. In this phase 1b/2 trial reported by Werth et al. (2021), the FcRn inhibitor ALXN1840 induced rapid and sustained clinical improvement in patients with chronic, active, refractory pemphigus. FcRn inhibition is a promising new approach to the treatment of pemphigus and other autoantibody-mediated autoimmune disorders.

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Pemphigus is a group of autoimmune blistering disorders mediated by directly pathogenic IgG antibodies that bind desmosomal components critical to keratinocyte cell–cell adhesion in the skin and mucous membranes, leading to acantholysis. Resulting blisters of the skin and mucous membranes are painful and cause significant morbidity and mortality (Figure 1). The primary autoantigens are the cadherins desmoglein (DSG) 1 and 3, and circulating levels of autoantibodies correlate with disease activity (Kasperkiewicz et al., 2017). Mainstays of pemphigus therapy include systemic corticosteroids, B-cell depletion with rituximab, the immunosuppressants mycophenolate mofetil and azathioprine, and intravenous Ig (IVIg). Mortality is approximately two- to three-fold higher in patients with pemphigus than in the general population, principally because of the risk of infection (Huang et al., 2012; Langan et al., 2008), highlighting the need for novel therapeutic strategies that act rapidly and are minimally immunosuppressive.

The FcRn is a major histocompatibility complex (MHC) class I–related receptor consisting of a heavy α-chain and β2-microglobulin. Initially named for its critical role transporting IgG from maternal to fetal circulation across the placenta, FcRn is expressed by multiple cell types, including vascular endothelial cells and antigen-presenting cells (APCs). On vascular endothelial cells, FcRn binds IgG but not other antibody isotypes, protecting it from intracellular degradation. Endocytosed FcRn–IgG complexes are sorted into recycling endosomes and transported back to the cell membrane, where IgG is released. In contrast, unbound Ig is sorted into lysosomes and degraded. Thus, FcRn is the reason why the serum half-life of IgG is significantly longer than that of other isotypes (approximately 21 days) and why Fc engineering is part of the innovation of second-generation therapeutic mAbs, increasing in vivo half-lives. On APCs, FcRn plays a role in antigen uptake and presentation on MHC molecules, required for T-cell activation, thus bridging humoral and cellular adaptive immune responses. Finally, FcRn regulates serum albumin homeostasis by binding albumin at a distinct noncooperative site (Patel and Bussel, 2020; Qiao et al., 2008). FcRn inhibitors, which function as competitive inhibitors of IgG for FcRn binding, are a promising new therapeutic approach for decreasing pathogenic IgG in autoantibody-mediated autoimmune disorders. In pemphigus, the anticipated effect is reduction of circulating IgG, IgG immune complexes (ICs), and anti-DSG1 and anti-DSG3 IgGs, leading to reduced disease activity (Figure 2).

ALXN1840 (SYNT001) is a humanized IgG4 antibody that blocks binding of IgG and IgG ICs to the FcRn. Its efficacy in reducing circulating IgG and IgG ICs in humans was previously demonstrated (Blumberg et al., 2019). In a new article of the *Journal of Investigative Dermatology*, Werth et al. (2021) describe a multicenter, open-label safety and tolerability phase 1b/2 trial demonstrating the efficacy and safety of ALXN1840 in patients with chronic, active pemphigus who did not respond satisfactorily to conventional treatments with high-dose corticosteroids, immunosuppressants, or anti-CD20–mediated B-cell depletion. Eight patients with pemphigus (one foliaceous and seven vulgaris) completed five weekly intravenous doses of ALXN1830 (10 mg/kg). Four of eight completed the 112-day follow-up period and four were withdrawn owing

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