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REVIEW ARTICLE

OX40 in the Pathogenesis of Atopic Dermatitis—A New Therapeutic Target

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Abstract

Atopic dermatitis (AD) is a chronic, heterogeneous, inflammatory disease characterized by skin lesions, pruritus, and pain. Patients with moderate-to-severe AD experience chronic symptoms, intensified by unpredictable flares, and often have comorbidities and secondary complications, which can result in significant clinical burden that impacts the patient's overall quality of life. The complex interplay of immune dysregulation and skin barrier disruption drives AD pathogenesis, of which T-cell-dependent inflammation plays a critical role in patients with AD. Despite new targeted therapies, many patients with moderate-to-severe AD fail to achieve or sustain their individual treatment goals and/or may not be suitable for or tolerate these therapies. There remains a need for a novel, efficacious, well-tolerated therapeutic option that can deliver durable benefits across a heterogeneous AD patient population. Expression of OX40 [tumor necrosis factor receptor superfamily, member 4 (TNFRSF4)], a prominent T-cell co-stimulatory molecule, and its ligand [OX40L; tumor necrosis factor superfamily, member 4 (TNFSF4)] is increased in AD. As the OX40 pathway is critical for expansion, differentiation, and survival of effector and memory T cells, its targeting might be a promising therapeutic approach to provide sustained inhibition of pathogenic T cells and associated inflammation and broad disease control. Antibodies against OX40 [rocatinlimab (AMG 451/KHK4083) and telazorlimab (GBR 830)] or OX40L [amlitelimab (KY1005)] have shown promising results in early-phase clinical studies of moderate-to-severe AD, highlighting the importance of OX40 signaling as a new therapeutic target in AD.

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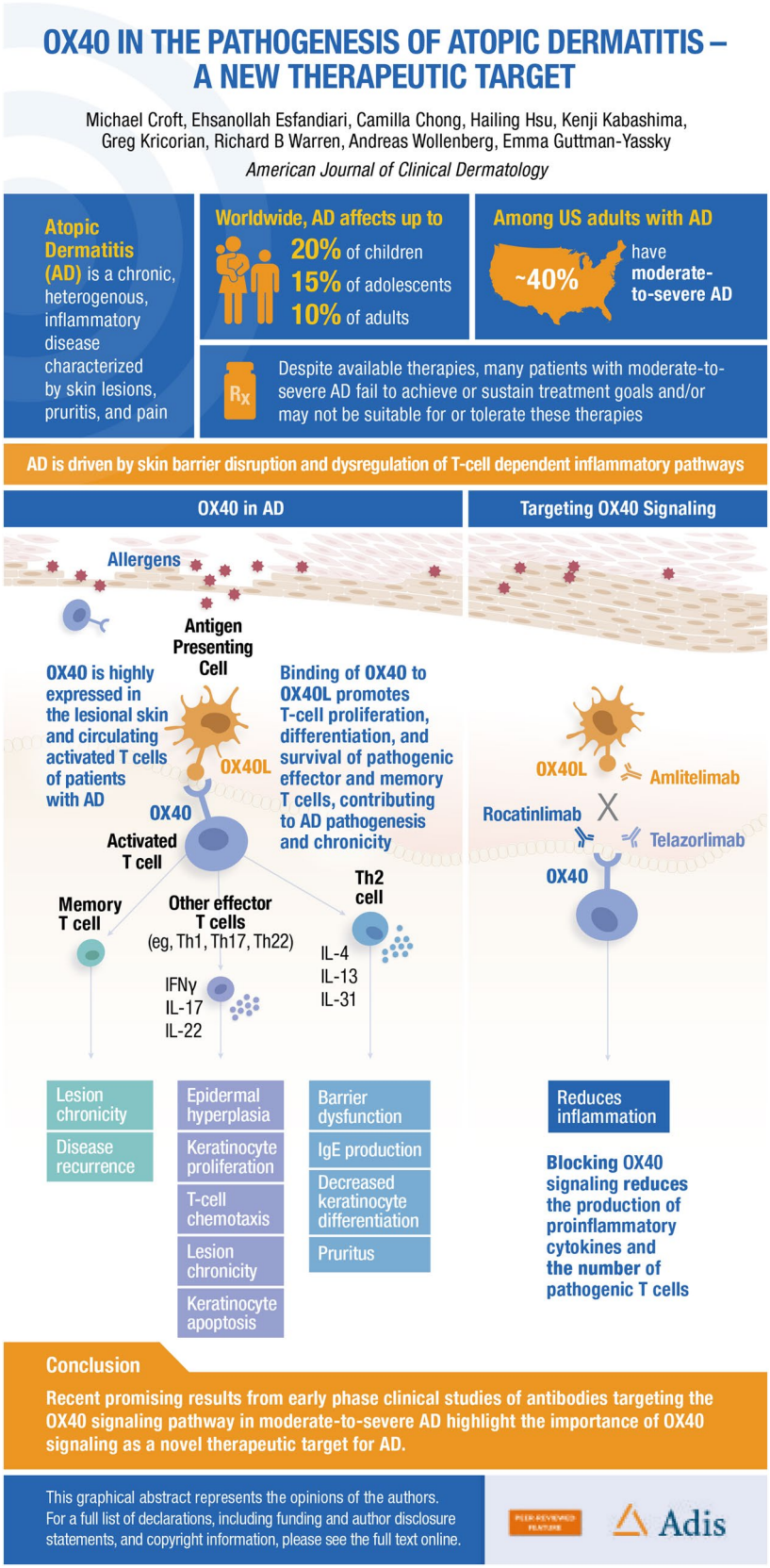
Graphical Abstract



Key Points

Atopic dermatitis (AD) is a chronic, inflammatory skin disease involving a complex interaction between skin barrier dysfunction and T-cell-mediated inflammation.

OX40, an important T-cell co-stimulatory molecule, is highly expressed in activated T cells of patients with AD; binding of OX40 to its ligand (OX40L) promotes expansion, differentiation, and survival of pathogenic effector and memory T cells.

Recent promising results from early phase clinical studies of antibodies against OX40 (rocatinlimab; telazorlimab) or OX40L (amlitelimab) in moderate-to-severe AD highlights the potential for targeting the OX40 pathway as a novel therapeutic approach for the treatment of AD.

1 Introduction

Atopic dermatitis (AD) is a chronic, heterogeneous, inflammatory disease characterized by skin lesions, pruritus, and pain [1, 2]. It is the most common inflammatory skin disease that affects nearly 20% of children, 15% of adolescents, and 10% of adults worldwide [3–6]. In the USA, an estimated 15% of children, 9% of adolescents, and 7% of adults have AD [3, 5, 6]. Among US adults with AD, approximately 40% are affected by moderate-to-severe disease [7]. While AD typically occurs in childhood, it may continue into adulthood and ~ 25% of patients develop AD in adulthood [8, 9].

AD is driven by skin barrier disruption and dysregulation of T-cell-dependent inflammatory pathways [1, 10]. Variations in lesion phenotype and/or location seen in individuals with AD [8, 11] are attributed to multiple underlying inflammatory pathways that may evolve over time [1, 3, 8, 12–15]. T cells play a central role in many of the inflammatory pathways involved in AD pathogenesis [15, 16], and the influx and expansion of T cells within the skin and the release of various proinflammatory cytokines contribute to multiple aspects of AD pathogenesis [1, 14–16].

Patients with moderate-to-severe AD experience chronic symptoms, intensified by unpredictable flares. Skin pain, pruritus, irritability, sleep disturbance, interference with daily activities of school or work, and psychological stress [17, 18] lead to decreased quality of life (QoL) and significant societal and humanistic burden on patients, their families, and/or caregivers [1, 3, 12, 13]. In addition, patients often have comorbidities and secondary complications that increase the burden of disease [1, 19]. AD and its associated comorbidities and complications contribute to substantial economic burden through direct healthcare costs and indirect costs, such as loss of work productivity and absenteeism [3].

Treatment of AD remains a challenge due to its heterogeneity and highly fluctuating and unpredictable course of disease. Recent advances in understanding the pathophysiology of disease have contributed to the discovery of many new targeted therapies that have expanded treatment options for patients with AD [1, 20]. This review provides an overview of the pathogenesis of AD and the need for improved therapeutic options, and highlights new targets in OX40 [tumor necrosis factor receptor superfamily, member 4 (TNFRSF4)] and OX40 ligand [OX40L; tumor necrosis factor superfamily, member 4 (TNFSF4)] that may be advantageous given the multifaceted nature of AD. Treatment approaches aimed at these novel molecules, which can affect multiple immune pathways central to disease pathogenesis, have the potential to control AD effectively regardless of the subtype or stage of the disease.

2 Atopic Dermatitis Pathogenesis

The pathogenesis of AD is complex and multifactorial, as epidermal barrier disruption, immune dysregulation, environmental allergens, and genetic predisposition all play pathogenic roles to initiate and sustain chronic inflammation in AD [21].

Local skin inflammation and epidermal barrier dysfunction are apparent contributors of AD pathogenesis [1, 3]. Local skin inflammation, evident as acute or chronic skin lesions, shows immune infiltration of predominantly CD4+ T cells, skin-resident dendritic cells, innate lymphoid cells, and Langerhans cells [22]. Even in the absence of visible skin lesions, the presence of immune infiltrates in non-lesional skin of patients with AD, together with a pre-activation of skin dendritic cells [23, 24], suggests the underlying inflammatory processes [25, 26]. Ongoing subclinical inflammation may manifest itself by structural changes, such as hyperkeratosis, skin hyperplasia, intercellular endothelial edema with venule alteration, and basement membrane thickening [27]. Systemic inflammation plays an equally critical role in patients with AD [1, 3]. Studies have shown increased inflammatory markers from various T-cell subsets in blood from patients with moderate-to-severe AD compared with controls, and these increases correlated with greater baseline AD severity [26]. The common coexistence of AD, allergic rhinitis, and asthma further supports the involvement of systemic inflammation as high levels of circulating inflammatory cytokines in patients with AD may impact lungs, airways, and other mucosal surfaces [28–31].

Underlying the heterogeneous clinical features, AD harbors a highly diverse endotype repertoire [32, 33]. While

Th2 is the predominant inflammatory pathway in AD [16], other T-cell subsets (e.g., Th1, Th17, and Th22) and their associated cytokines also contribute to disease pathology. The degree of involvement of various subsets of T-cell-dependent inflammatory pathways is different by disease stage or by age [15] and across populations by ethnicity [1, 11, 14].

AD can evolve from an initial, acute, Th2-dominated phase characterized by diffuse lesions to a chronic phase marked by the concomitant presence of Th1, Th17, and Th22 cells that contribute to epidermal thickening and the development of poorly demarcated, scaly patches and plaques with excoriation and lichenification [15, 32, 34–37]. Activated memory T cells are significantly increased in AD lesions and may amplify and sustain the overall immune response, influencing disease severity, recurrence, and chronicity [38–40]. In particular, the chronic nature of AD is linked to the long-lived potential of antigen-responding T cells [40–42]. Effector T cells also survive as memory T cells, which enable rapid recall effector responses when antigen is re-encountered and lead to the self-renewal of the long-lived memory T cell populations thought to be responsible for disease recurrence [40, 42]. Compared with adult AD, pediatric AD is associated with reduced levels of Th1-driven inflammation [43] and increased levels of Th17- and Th22-driven inflammation [14, 32], reflecting the higher incidence of impetiginized, weeping lesions [2].

AD is disproportionately more prevalent in patients of color [11]. Although Th2 immune activation is consistently observed among different ethnicities, Asian and African American patients with AD exhibit varying levels of Th1, Th17, and Th22 activation compared with white patients with AD; these differences may contribute toward phenotypic features commonly observed in Asian and African American populations [11, 14, 32, 44].

The diversity of immune responses in AD and their respective epidermal barrier correlates suggest that targeting the Th2 pathway on its own may not be adequate to achieve an optimal clinical response in patients with AD. New therapeutic approaches that target multiple T-cell subsets and a broader spectrum of immune pathways may provide clinical benefits across heterogeneous patients with AD [45, 46].

3 Need for Improved Therapeutic Options for Atopic Dermatitis

The treatment goals for AD are to optimize long-term outcomes by minimizing flares, comorbidities, secondary complications, and potential adverse effects, as well as to decrease treatment burden for patients [13, 47–49]. Current treatment options for AD include topical regimens, phototherapy, systemic immune modulators, biologics, and small molecule Janus kinase (JAK) inhibitors [46–51].

Despite standard use of topical agents, a significant proportion of patients with moderate-to-severe AD require systemic add-on therapy due to limited efficacy of topical agents and their potential association with skin thinning or application site pain, burning, and stinging [50, 52, 53]. The use of systemic corticosteroids is generally discouraged by clinical practice guidelines except in special circumstances [31, 47–49, 54]. Conventional systemic immunosuppressive agents (e.g., methotrexate, cyclosporine, azathioprine) are recommended by current guidelines for the treatment of refractory AD, but mainly used off-label [31, 47, 48, 55].

Approved biologics, including the interleukin (IL)-4/IL-13 receptor alpha subunit (Rα) inhibitor dupilumab and the IL-13 inhibitor tralokinumab [46, 48], are additional add-on treatment options for patients with moderate-to-severe AD whose disease was not adequately controlled with topical therapies. However, in pivotal phase 3 trials, more than 60% of patients receiving dupilumab (with topical agents as needed) or tralokinumab (combined with topical corticosteroid) could not achieve clear or almost clear skin after 16 weeks of treatment [56, 57] and in a retrospective cohort study, 35% of patients lost or partially lost the response to dupilumab after 12 months of treatment [58, 59]. The use of dupilumab has also been shown to lead to adverse skin reactions such as rosacea, alopecia, and psoriasis [60–64] and arthralgia [65–68], which indicate possible skewing toward Th1- or Th17-mediated inflammation when only the Th2 pathway is inhibited by dupilumab. The waning efficacy and dermatologic eruptions/joint pain observed with dupilumab or tralokinumab further support that although AD is a largely Th2-driven disease, biologics specifically targeting cytokines in the Th2 immune pathway are not sufficient and may even lead to safety issues related to only targeting the Th2 arm of the T-cell response [46, 48, 60–64].

Management strategies for patients who do not respond sufficiently or lose response to biologics are limited, including escalating biologic dose or frequency, adding a traditional systemic immunosuppressive agent, or initiating alternative systemic treatments such as JAK inhibitors [46, 48, 58]. JAK inhibitors are broad-acting therapeutics, but may be associated with significant safety concerns including the boxed warning related to cardiovascular and cancer risks [46, 48, 69] based on studies in rheumatoid arthritis [46, 70, 71]. In patients with AD, however, both risk factors and cardiovascular adverse events are less prevalent compared with rheumatoid arthritis [72]. The European Medicines Agency has published risk factors for patients using JAK inhibitors, but not changed the dermatological indications for the substance class [73].

Many patients may also fail to reach or maintain treatment goals because of issues with safety or tolerability [1,

20]. Side effects are associated with not only JAK inhibitors, but also biologics, such as ocular and skin AEs for dupilumab or tralokinumab [60–64, 74–76]. Fear of side effects from medications has been shown to impact adherence, and poor adherence can be a major limiting factor to achieving optimal disease outcomes in patients with AD [77]. Dosing frequency/regimen complexity with available systemic therapies may also negatively affect adherence to treatment [77].

In summary, despite available therapies, many patients with moderate-to-severe AD fail to achieve or sustain treatment goals and/or may not be suitable for, or tolerate, these therapies. Thus, there remains a need for a novel, highly efficacious, well-tolerated therapeutic option that can deliver durable benefits across AD patient populations.

4 Role of OX40 Signaling in T-cell Responses and Atopic Dermatitis Pathogenesis

T-cell-dependent inflammation, a key contributor of AD pathophysiology, is mediated by antigen stimulation through T-cell receptors, along with ligation of co-stimulatory molecules, particularly those in the TNF receptor superfamily [78]. One of these, the OX40 co-stimulatory signaling pathway, plays a critical role in effector function and long-lasting T-cell responses through promoting the development of memory T cells [79–82], and has been implicated in AD pathogenesis [83].

OX40 belongs to a class of inducible co-stimulatory receptors and is predominantly expressed on T cells following their activation, including primary effector Th2 cells and other T-cell subsets such as Th1, Th17, and Th22 [84], and is not constitutively expressed on naïve CD4+ or CD8+ T cells. OX40 expression is further enhanced by various cytokines including IL-1, IL-2, IL-4, and TNFα [83, 84]. Following antigen stimulation, OX40 is rapidly and transiently expressed on both effector and memory T cells upon activation [84, 85], making OX40 a potential therapeutic target for T-cell-mediated diseases. The binding partner of OX40, OX40 ligand (OX40L), is a co-stimulatory molecule mainly expressed on antigen-presenting cells (APCs), such as B cells, Langerhans cells, and dendritic cells, and other cells such as type 2 innate lymphoid cells (ILC2), endothelial cells, fibroblasts, and mast cells [85, 86]. Binding of OX40L to OX40 promotes trimerization of OX40 monomers, recruitment of TNF receptor associated factor (TRAF) proteins, and activation of downstream nuclear factor kappa B (NF-κB) and phosphoinositide 3-kinase (PI3K)/Akt signaling, which enhances effector T-cell proliferation and survival, induces memory T-cell generation and persistence, and upregulates proinflammatory cytokine production [85].

OX40 pathway activation is involved in both systemic and local inflammation in patients with AD [83, 87] (Fig. 1). Systemically, while OX40L expression, primarily by monocytes, shows no differences between patients with AD and healthy controls, OX40 expression is elevated in circulating CD4+ T cells from patients with AD [87]. In the peripheral blood of patients with AD, the expression of OX40 is increased on activated skin-homing CD4+ T cells, compared with activated CD4+ T cells without skin-homing antigen expression [87]. Locally, the numbers of OX40+ cells (presumably T cells) and OX40L+ dendritic cells are greater in the lesional skin of patients with AD compared with psoriatic and non-lesional skin [88–90]. One study showed that in patients with AD, OX40+ T cells were increased as much as tenfold in lesional skin compared with non-lesional skin [88]. In skin biopsies of AD lesions, OX40+ dermal cells

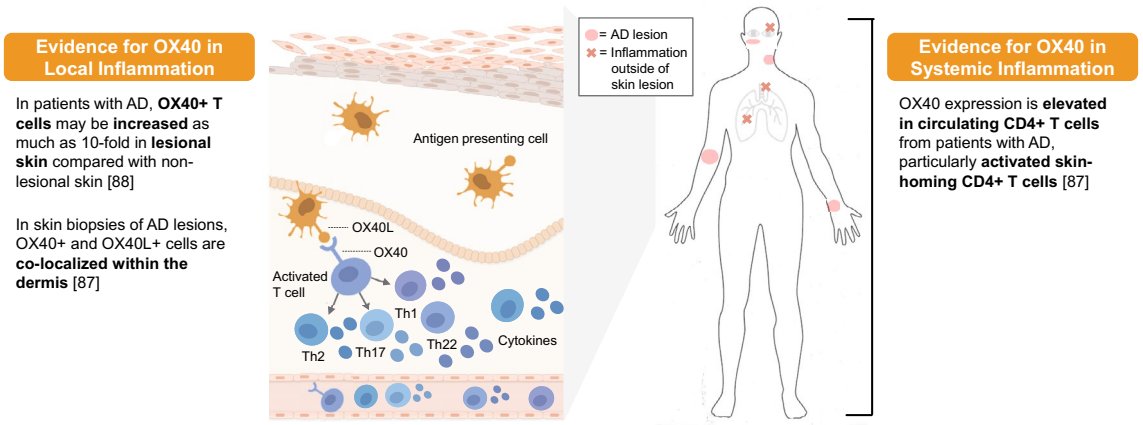


Fig. 1 Involvement of OX40 in local and systemic inflammation in atopic dermatitis. Evidence supports that OX40 expression may drive both local and systemic inflammation in patients with atopic dermatitis. *AD*, atopic dermatitis; *CD*, cluster of differentiation; *IL*, interleukin; *OX40*, OX40 receptor; *OX40L*, OX40 ligand; *Th*, T helper cell.

and OX40L+ cells (suggested to be mast cells) were found colocalized within the dermis [87] and OX40L expression was visualized on keratinocytes [88, 90], suggesting local activity of OX40 signaling.

Although few specifics are known at present in patients with AD, OX40 might be important at several phases of AD development. During the acute stage of AD, it is likely that OX40 signaling is involved in Th2-driven inflammation, amplifying skin barrier disruption and development of symptoms such as pruritus. In early pathogenesis, Langerhans cells and inflammatory dendritic epidermal cells recognize foreign antigens that penetrate the skin through a disrupted epidermal barrier, subsequently priming Th2 cells [21, 91]. Barrier-disrupted keratinocytes can also produce cytokines, such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. As these molecules have been shown to stimulate APCs to express OX40L, this could further potentiate T-cell expansion and differentiation by enhancing OX40 signals delivered to T cells [92–94] (Fig. 2). Similarly, OX40L has been found to be induced on ILC2 that are also regulated by these innate cytokines, and interactions between ILC2 and T cells involving OX40L and OX40 could also contribute to initial priming of Th2 cells [86]. Activated Th2 cells upregulate production of IL-14, IL-13, and IL-31, which further disrupts epidermal barrier function by suppressing the expression of barrier-related genes such as terminal keratinocyte differentiation gene filaggrin as well as promoting epidermal hyperplasia [16, 83, 95, 96]. IL-4 and IL-13 bind to IL-4Rα expressed on T cells, B cells, macrophages, and other immune cells to promote inflammation and immunoglobulin E class switching [21, 97]. Sensory neurons express receptors for various cytokines released by skin cells and immune cells, including IL-4, IL-13, IL-31, and TSLP, to transmit pruritus and pain signals to the central nervous system, causing atopic itch, pain, and scratching [16, 91] (Fig. 2).

Transition from the acute to chronic stage of AD could also be controlled by OX40. Prolonged expression of proinflammatory cytokines, together with continued antigen presentation, may sustain expression of OX40 on activated T cells (Fig. 2). As OX40 expression is not confined to the Th2 subset, OX40 signaling may also enhance Th1 and Th17/22 pathways by driving the expansion of these T-cell subsets and by enhancing interferon gamma (IFN-γ), IL-17, or IL-22 production, resulting in sustained accumulation and activity of effector and memory Th1, Th17, and Th22, as well as Th2 cells [15, 16, 85]. A mechanistic biomarker study in humans has shown that blocking OX40 signaling not only modulates Th2 signatures [IL-31, CCL11, thymus- and activation-regulated chemokine (TARC; CCL17), and TSLP receptor], but also reduces signatures of other immune pathways upregulated in AD lesional skin, including Th1 signatures (IFN-γ

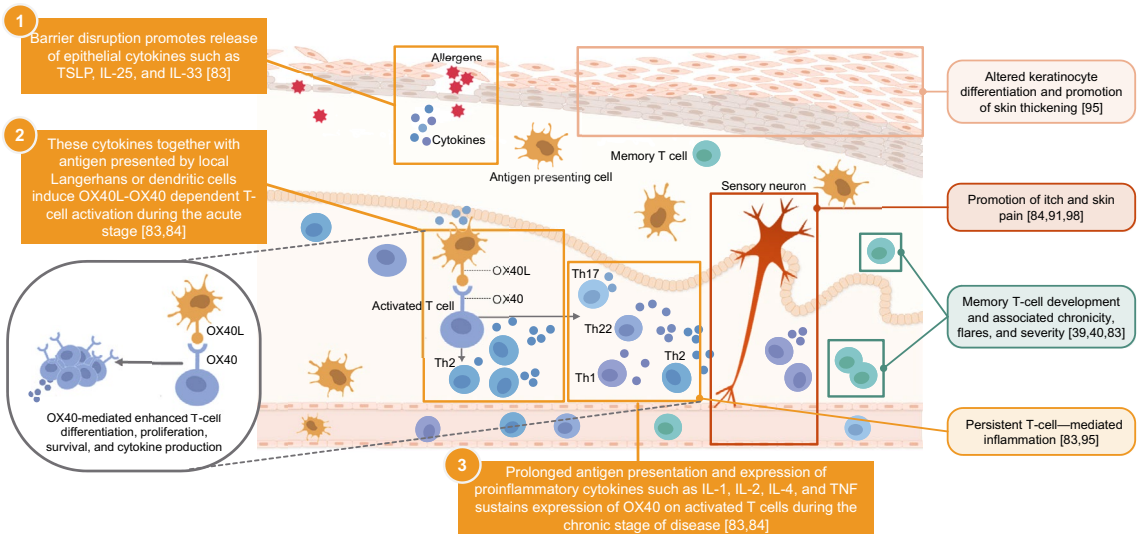


Fig. 2 Role of OX40 signaling in atopic dermatitis pathogenesis. Square textboxes present an overview of the inflammatory response in atopic dermatitis skin lesions. In atopic dermatitis, expression of OX40 on effector T cells is hypothesized to be induced early by skin barrier disruption and sustained by prolonged expression of proinflammatory cytokines [83, 84]. OX40L is expressed on the surface of activated antigen presenting cells such as Langerhans cells and dendritic cells and other cells (not shown in the figure) such as type 2 innate lymphoid cells, mast cells, and keratinocytes [85, 86, 88]. Round textboxes present the key aspects of atopic dermatitis pathogenesis hypothesized to be driven and sustained by OX40 signaling. The OX40 pathway is believed to play a central role in T-cell expansion, effector function development, and subsequent memory T-cell formation, which drives local and systemic inflammation of AD [12, 83, 84, 87, 95]. *AD*, atopic dermatitis; *IL*, interleukin; *OX40*, OX40 receptor; *OX40L*, OX40 ligand; *Th*, T helper cell; *TNF*, tumor necrosis factor; *TSLP*, thymic stromal lymphopoietin.

and IFN-γ-induced chemokine CXCL10) and Th17/Th22 signatures (IL-23p19/IL-8/S100As) [98].

During the chronic stage of AD, OX40-mediated signals are also likely to promote the survival of various types of pathogenic T cells, which are involved in further attracting circulating immune cells to the epidermis, altering keratinocyte differentiation, and inducing epidermal thickening [95] (Fig. 2). IFN-γ produced by Th1 cells promotes cutaneous inflammation and keratinocyte apoptosis [97]. IL-17 produced by Th17 cells induces other inflammatory mediators that promote influx of T cells to lesional AD skin [97]. IL-22 produced by Th22 cells contributes to epidermal hyperplasia [97]. As signaling via OX40 has also been shown to enhance the survival of activated effector T cells when they transition into memory T cells [80, 82, 85], this induction of memory generation and persistence may additionally contribute to the chronicity of AD [40] (Fig. 2). Which cells might provide OX40L during the chronic phases of AD is unclear, but mast cells, ILC2, dendritic cells, Langerhans cells, and keratinocytes are all possibilities [85, 86, 88, 90].

In summary, increased OX40 signaling in several phases of AD disease pathogenesis would implicate a key role for the OX40 pathway in local and systemic inflammation by promoting expansion, differentiation, and survival of pathogenic T cells and subsequent T-cell memory formation, contributing to the chronic course of the disease.

5 Targeting OX40

Considering the diverse disease endotypes, targeting OX40 signaling is a promising therapeutic approach to provide sustained inhibition of pathogenic Th2 cells and other T-cell subsets associated with inflammation in AD. Three antibodies against OX40 [rocatinlimab (AMG 451/KHK4083) and telazorlimab (GBR 830)] or OX40L [amlitelimab (KY1005)] are currently in clinical development for the treatment of moderate-to-severe AD (Table 1). Early phase clinical studies of these three antibodies have shown very promising results on the basis of the assessment of established instruments such as Investigator Global Assessment (IGA) 5-point scale or the Eczema Area Severity Index (EASI).

5.1 Rocatinlimab

Since OX40 expression is elevated on pathogenic T cells at sites of inflammation, targeting OX40 provides the potential for focused modulation of T cells that contribute to AD. Rocatinlimab (AMG 451/KHK4083; Table 1) is a non-fucosylated IgG1 anti-OX40 monoclonal antibody that inhibits and reduces the number of OX40+ pathogenic T cells [99–101]. In a single-arm phase 1 trial of patients with moderate-to-severe AD ($N = 22$), rocatinlimab (10 mg/kg infusions on days 1, 15, and 29) led to a 74% reduction in the EASI score from baseline to week 22, and IGA 0/1 [clear (0) or almost clear (1) and a minimum two-grade improvement] was achieved in 35% of the patients at week 22 [100]. In a double-blind, placebo-controlled phase 2b study of patients with moderate-to-severe AD ($N = 274$), rocatinlimab demonstrated significant improvement in efficacy parameters compared with placebo, significant modulation of AD-related biomarkers, a well-tolerated safety profile, and potential for a durable response [101]. Across all rocatinlimab dose groups [subcutaneous injections of 150 mg every 4 weeks (Q4W), 600 mg Q4W, 300 mg every 2 weeks (Q2W), 600 mg Q2W], 48–61% least squares mean percent reductions in EASI score were observed from baseline to week 16, significantly greater than the 15% reduction in the placebo group. Rocatinlimab 300 mg Q2W dose group had the largest improvements at week 16: IGA 0/1 was achieved in 31% of the patients, and 75% improvement in EASI from baseline (EASI75) was achieved in 54% of the patients, compared with IGA 0/1 of 2% and EASI75 of 11% in the placebo group. At week 36, rocatinlimab 300 mg Q2W led to 88% least squares mean percent reduction in EASI score from baseline, and the IGA 0/1 and EASI75 responses were increased to 52% and 64%, respectively. Of the patients who achieved EASI75 at week 36 across rocatinlimab dose groups, the probabilities of not relapsing at week 56 ranged from 73 to 96% after treatment discontinuation at week 36 [101]. Targeting OX40 directly provides an opportunity to achieve durable efficacy by modulating pathogenic effector and memory T cells that drive disease severity and chronicity. Biomarker analysis revealed that rocatinlimab reduced mean serum concentrations of TARC/CCL17 (Th2 signature) and IL-22 (Th17/Th22 signature) throughout the active treatment period and during the off-treatment follow-up period until week 56. Steady reduction of these biomarkers over time supports the inhibitory action of rocatinlimab on Th2, Th17, and Th22 cell activities, which in turn is expected to interrupt the cycle of inflammation and improve/restore skin barrier function [101]. Rocatinlimab was well tolerated, with pyrexia (17% versus 4% in the placebo group), chills (11% versus 0%), headache (9% versus 2%), aphthous ulcer (7% versus 0%), and nausea (6% versus 2%) as the most commonly reported AEs during the 18-week double-blind period. Pyrexia and chills were mild or moderate in intensity and occurred in most patients only after the first injection, and no patients discontinued the treatment because of these events. All monoclonal antibodies have the potential for injection reaction (e.g., pyrexia) including those targeting OX40 or OX40L [102]. No signs of immunosuppression (e.g., increased rates of infection or malignancy) or immune dysregulation (e.g., autoimmunity) were observed.

Table 1 Emerging OX40 or OX40L antibodies for moderate-to-severe atopic dermatitis

Biologic agent	Target	Study type	Study duration	Dose	# of patients	Primary endpoint(s) results	References
Rocatinlimab (AMG 451 /KHK4083)	OX40	Phase 1	22 weeks	10 mg/kg infusions on days 1, 15, and 29	22	Safety profile: No deaths, serious AEs, or discontinuations due to AEs Common treatment-emergent AEs: mild or moderate pyrexia and chills No clinically meaningful changes in the laboratory, vital signs, and electrocardiogram values	[100]
		Phase 2b	56 weeks	Subcutaneous injections of 150 mg Q4W, 600 mg Q4W, 300 mg Q2W, 600 mg Q2W for 36 weeks	274	Least-squares mean change in EASI (95% CI) from baseline to week 16: 150 mg Q4W: − 48.3% (− 62.2, − 34.0; $P = 0.0003$ versus placebo) 600 mg Q4W: − 49.7% (− 64.3, − 35.2; $P = 0.0002$ versus placebo) 300 mg Q2W: − 61.1% (− 75.2, − 47.0; $P < 0.0001$ versus placebo) 600 mg Q2W: − 57.4% (− 71.3, − 43.4; $P < 0.0001$ versus placebo) Placebo: − 15.0% (− 28.6, − 1.4)	[101]
Telazorlimab (GBR 830/ISB 830)	OX40	Phase 2a	85 days	10 mg/kg infusions on days 1 and 29	62	Treatment-emergent AEs: Headache most common, but with no clinically meaningful differences between telazorlimab and placebo Postprocedural infection and myalgia occurred more frequently with telazorlimab than placebo Change in biomarkers: Telazorlimab showed inhibition of Th1, Th2, and Th17/Th22 signatures mRNA expression in lesional skin Telazorlimab led to greater reductions of epidermal hyperplasia measures versus placebo	[98]
		Phase 2b	66 weeks	Subcutaneous injections of 300 mg Q2W and 600 mg Q2W	462	Mean change in EASI (SD) from baseline to week 16: 300 mg Q2W: − 57.6% (36.2) versus placebo, − 42.1% (38.2) ($P = 0.008$) 600 mg Q2W: − 59.7% (27.1) versus placebo: − 43.3% (41.2) ($P = 0.008$)	[103, 104]

Table 1 (continued)

Biologic agent	Target	Study type	Study duration	Dose	# of patients	Primary endpoint(s) results	References
Amlitelimab (KY1005)	OX40L	Phase 2a	36 weeks	200 mg loading/100 mg maintenance infusions Q4W (low dose); 500 mg loading/250 mg maintenance Q4W (high dose)	89	Treatment-emergent AEs: Headache, upper respiratory tract infection, hyperhidrosis, pyrexia, increased aspartate aminotransferase and iron deficiency anemia more frequent in the amlitelimab groups versus the placebo group up to week 16 (difference of ≥ 5%) Least-squares mean change in EASI (95% CI) from baseline to week 16: Lose dose: − 80.1% (− 95.6, − 64.7; $P = 0.009$ versus placebo) High dose: − 70.0% (− 85.0, − 54.6; $P = 0.072$ versus placebo) Placebo: − 49.4% (− 66.0, − 32.7)	[102]
		Phase 2b	52 weeks	Subcutaneous injections of 250 mg Q4W with 500 mg loading; 250 mg, 125 mg, or 62.5 mg Q4W without loading	390	Difference from placebo in least-squares mean change in EASI (95% CI) from baseline to week 16: 250 mg with loading: − 32.1% (− 43.9, − 20.3; $P < 0.0001$) 250 mg: − 27.3% (− 39.1, − 15.6; $P < 0.0001$) 125 mg: − 22.2% (− 34.0, − 10.4; $P = 0.0002$) 62.5 mg: − 30.2% (− 41.9, − 18.5; $P < 0.0001$)	[110]

AE, adverse event; *CI*, confidence interval; *EASI*, Eczema Area Severity Index; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *SD*, standard deviation

Consistent safety findings were reported during the whole study period to week 56. Rocatinlimab is currently being further explored in adults and adolescents with moderate-to-severe AD in the comprehensive phase 3 ROCKET program (clinicaltrials.gov, NCT05899816; NCT05651711; NCT05704738; NCT05398445; NCT05633355; NCT05724199) and its long-term extension study (clinicaltrials.gov, NCT05882877).

5.2 Telazorlimab

Telazorlimab (GBR 830/ISB 830; Table 1) is a humanized IgG1 neutralizing monoclonal antibody against OX40 that blocks the interaction with OX40L, and was evaluated in a phase 2a trial and a phase 2b trial of patients with AD. The phase 2a trial ($N = 62$) efficacy results showed that on day 71, telazorlimab (10 mg/kg infusions on days 1 and 29) led to a 50% improvement in EASI from baseline (EASI50) in 77% of patients versus 38% of placebo-treated patients; and IGA 0/1 was achieved by 23% of telazorlimab-treated patients compared with 13% of placebo-treated patients [98]. Telazorlimab was well tolerated. The most common treatment-emergent AE was headache, with no clinically meaningful differences between telazorlimab (13%) and placebo (25%). Treatment-emergent AEs that occurred more frequently in the telazorlimab group than in the placebo group were postprocedural infection (9% versus 0%) and myalgia (7% versus 0%). Telazorlimab showed inhibition of Th1, Th2, and Th17/Th22 signature mRNA expression in lesional skin, as well as greater reductions of hyperplasia measures (epidermal thickness and epidermal proliferation markers) compared with placebo [98]. The phase 2b trial ($N = 462$) efficacy results were mixed. Telazorlimab was associated with significant improvement in EASI: percent reduction from baseline in EASI score at week 16 with telazorlimab high-dose regimens was 58% with subcutaneous injections of 300 mg Q2W versus 42% with placebo and 60% with 600 mg Q2W versus 43% with placebo treatment. Numerical improvements were also seen with the two high doses of telazorlimab as compared with placebo for EASI-75 (24% versus 11% and 25% versus 19%, respectively) and IGA 0/1 (13% versus 5% and 12% versus 5%, respectively), but the differences were not statistically significant [103, 104]. The most commonly reported treatment-emergent AEs with telazorlimab were AD (300 mg versus placebo: 22% versus 21%; 600 mg versus placebo: 35% versus 16%), nasopharyngitis (21% versus 9%; 16% versus 9%), upper respiratory tract infection (16% versus 5%; 8% versus 7%), and headache (11% versus 10%; 8% versus 7%) in the phase 2b trial [103, 104]. Currently there are no ongoing or planned trials of telazorlimab for the treatment of AD. However, further development of telazorlimab for rheumatoid arthritis or other autoimmune diseases is likely [105].

5.3 Amlitelimab

Amlitelimab (KY1005; Table 1) is a human IgG4 antibody that binds to OX40L and blocks OX40L from inducing signals through OX40 [106–109]. In a phase 2a study of patients with moderate-to-severe AD ($N = 88$), amlitelimab low-dose regimen (200 mg loading/100 mg maintenance infusions Q4W) resulted in a mean percentage change of EASI from baseline to week 16 of 80%, versus 49% with placebo [102]. Patients receiving high-dose regimen (500 mg loading/250 mg maintenance infusions Q4W) had 70% change of EASI from baseline compared with 49% in the placebo group. IGA 0/1 was achieved in 44% and 37% of patients receiving low- or high-dose amlitelimab compared with 8% of placebo-treated patients [102]. Treatment-emergent AEs more common with either low-dose or high-dose amlitelimab versus placebo included headache (10% versus 3%), upper respiratory tract infection (10% versus 3%), hyperhidrosis (7% versus 0%), pyrexia (7% versus 0%), aspartate aminotransferase increased (7% versus 0%), and iron-deficiency anemia (7% versus 0%) from baseline to week 16 [102]. A decrease in serum IL-22 and IL-13 levels was observed at week 16 among patients treated with amlitelimab [102]. In a phase 2b dose-ranging study, patients with moderate-to-severe AD ($N = 390$) received treatment with subcutaneous amlitelimab at 250 mg Q4W with 500 mg loading dose, or 250 mg, 125 mg, or 62.5 mg Q4W without loading dose. Amlitelimab resulted in significant improvements in percentage change in EASI from baseline to week 16 compared with placebo (difference from placebo in least squares mean change from baseline: 250 mg with loading, − 32.1%; 250 mg, − 27.3%; 125 mg, − 22.2%; 62.5 mg, − 30.2%), with improvements continuing through week 24 [110]. Amlitelimab was well tolerated across all dose groups (details of treatment-emergent AEs were not reported) [110]. Subcutaneous amlitelimab is being further evaluated in this 52-week phase 2b trial of adults with moderate-to-severe AD (clinicaltrials.gov, NCT05131477), and in phase 2 long-term extension studies (clinicaltrials.gov, NCT05492578, NCT05769777). A phase 3 study of amlitelimab (clinicaltrials.gov, NCT06130566) is scheduled to start at the end of 2023, with the efficacy and safety of two doses of subcutaneous amlitelimab compared with placebo in adults with moderate-to-severe AD. Collectively, these results from various clinical trials support the value of targeting the OX40-OX40L signaling pathway as a novel approach for AD treatment.

6 Summary

AD is a challenging disease to treat due to its multifaceted and heterogeneous nature and highly fluctuating

and unpredictable disease course. A need remains for a novel therapeutic approach targeting a broad spectrum of immune pathways and delivering durable benefits in a heterogeneous population. OX40, an inducible co-stimulatory molecule expressed on pathogenic Th2 cells and other effector T-cell subsets following their activation, is crucial for potentiating long-lasting T-cell responses, and as such represents an attractive target for limiting AD symptoms and providing long-term remission.

OX40 has a unique pattern of expression, increasing transiently only with antigen-driven T-cell receptor activation. Since OX40 is predominantly expressed on activated effector T cells, targeting the OX40 pathway does not affect homeostasis of naïve and resting memory T cells. As a result, neutralizing its activity will potentially preferentially inhibit those antigen-specific T cells involved in perpetuating and maintaining AD without generalized immunosuppression. Targeting the OX40 signaling pathway furthermore has the potential to reduce the number of a variety of activated pathogenic T cells and their memory counterparts, including Th1, Th2, Th17, and Th22 cells, which may allow far more profound disease control beyond inhibiting individual cytokines made by these cells. In addition, the OX40 pathway plays a unique role in the transition of activated effector T cells into memory T cells. Therefore, blocking OX40 potentially produces sustainable inhibitory effects on immune function, impacting the chronicity of AD. Neutralizing OX40 signaling also can limit the production of multiple proinflammatory cytokines made by T cells that promote skin thickening, providing another way to reduce inflammation. Several currently approved systemic therapies target the cytokine products of T cells (e.g., dupilumab that blocks IL-4 and IL-13 signaling by binding to IL-4Rα; tralokinumab that blocks IL-13) but are less likely to diminish the persistence of the pathogenic T cells themselves, as recently suggested from a study of T cells still present in the skin of patients treated with dupilumab [111]. Via effects on diverse pathogenic T-cell subsets and proinflammatory cytokines, blocking OX40 may have important therapeutic potential along the dynamics of the immune response in AD and provide broad disease control and persistent efficacy across heterogenous patient populations.

Recent promising results from early phase clinical studies of antibodies against OX40 or OX40L in moderate-to-severe AD highlight the potential of OX40 signaling as an important novel target for the treatment of AD that may open a new therapeutic paradigm to achieve a highly effective, durable response with the potential for disease modification.

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Declarations

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Competing interests Michael Croft has received consulting fees or speaking honoraria from Amgen, Sanofi, UCB, MedImmune, Millenium, Perseid, Celgene, Novo Nordisk, Merck, Abbvie, Tanabe, Zai Lab, Merrimack, Pfizer, Anaptysbio, Celsius Therapeutics, HifiBio, Kiniksa, Shattuck Labs, Prometheus biosciences, Invectys, Virtici, Capella bioscience, and RAPT therapeutics, and research funds from Kyowa Kirin, Bristol Myers Squib, Janssen, and Eli Lilly. He has licensed patents on OX40 and OX40L. Ehsanollah Esfandiari is an employee of Kyowa Kirin International. Camilla Chong was an employee of Kyowa Kirin International at the time of manuscript development. Hailing Hsu and Greg Kricorian are employees and stockholders of Amgen Inc. Kenji Kabashima has received consulting fees, honoraria, grant support, and/or lecturing fees from Japan Tobacco, LEO Pharma, Maruho, Mitsubishi Tanabe, Ono Pharmaceutical, Procter & Gamble, Sanofi, Taiho, and Torii Pharmaceutical. Richard B. Warren has been a consultant and/or speaker for AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly and Company, GlaxoSmithKline, Janssen, LEO Pharma, Novartis, Sanofi Genzyme, and UCB Pharma. Andreas Wollenberg has been an investigator for Beiersdorf, Eli Lilly, Galderma, LEO Pharma, MedImmune, Novartis, Pfizer, Regeneron Pharmaceuticals, and Sanofi; a consultant for AbbVie, Almirall, Anacor Pharmaceuticals, Eli Lilly, Galapagos, Galderma, LEO Pharma, MedImmune, Novartis, Pfizer, Regeneron Pharmaceuticals, Sandoz, and Sanofi, and received research grants from Beiersdorf, LEO Pharma, and Pierre Fabre. Emma Guttman-Yassky has received research funds/grants paid to her institution from Amgen, AnaptysBio, Asana Biosciences, AstraZeneca, Boehringer Ingelheim, Cara Therapeutics, Celgene, Eli Lilly, Innovaderm, Kyowa Kirin, LEO Pharma, Novartis, Pfizer, and Regeneron Pharmaceuticals, and has received consultancy fees from AbbVie, Almirall, Amgen, Arena, Asana Biosciences, Aslan Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Celgene, Connect Pharma, Eli Lilly, EMD Serono, Evidera, Galderma, Ichnos Sciences, Incyte, Janssen Biotech, Kyowa Kirin, LEO Pharma, Pandion Therapeutics, Pfizer, RAPT Therapeutics, Regeneron Pharmaceuticals, Sanofi, SATO Pharmaceutical, Siolta Therapeutics, Target PharmaSolutions, UCB, and Ventyx Biosciences.

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