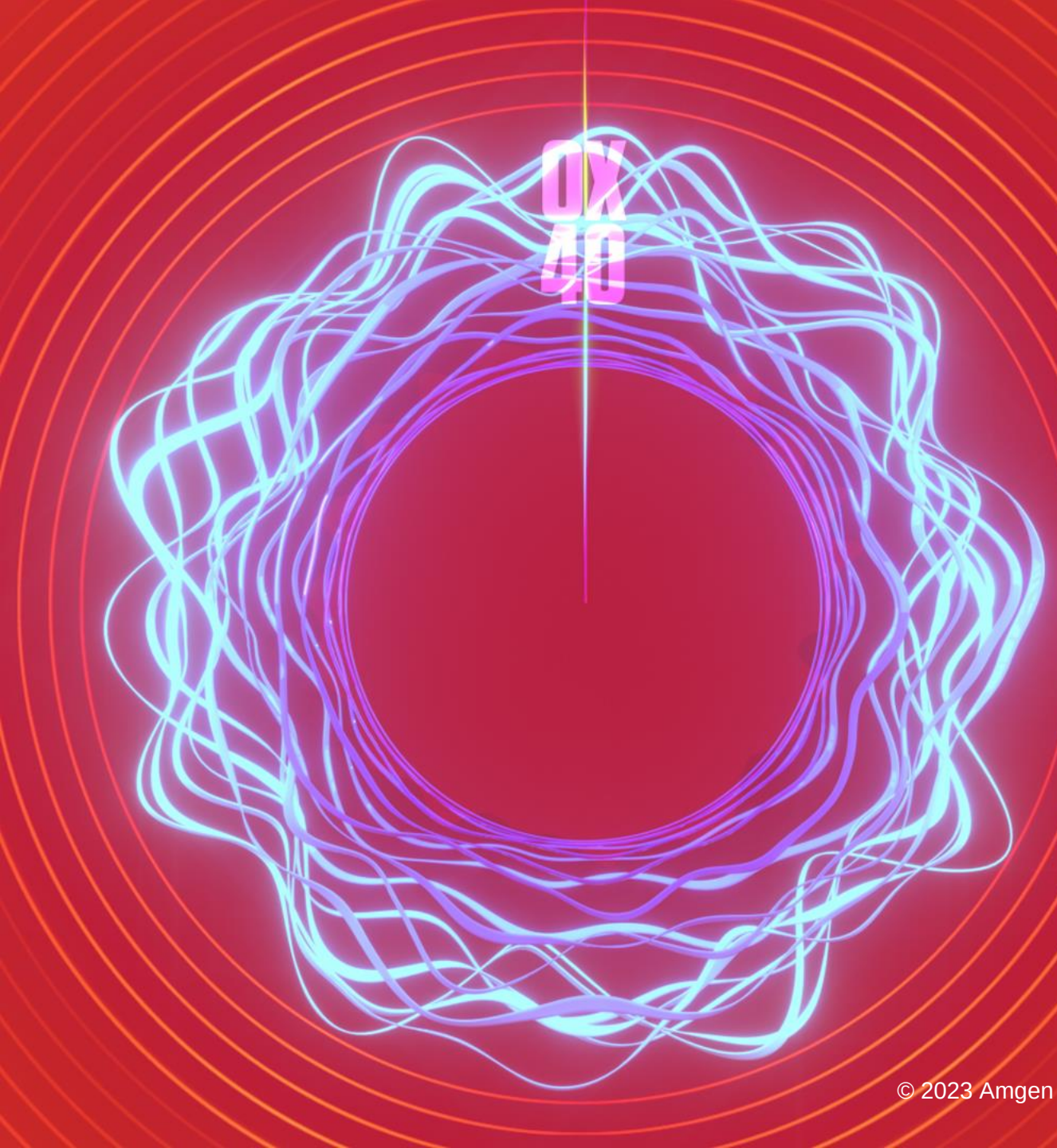

Uncovering the Critical Role of OX40 Signaling in Orchestrating Inflammation in Atopic Dermatitis

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AD, a Common, Chronic, Inflammatory Skin Disease, Can Result in Significant Disease Burden

Epidemiology

- Globally, AD prevalence is **up to 10% among adults and up to 20% among children**[1]
- AD is the 15th most common nonfatal disease and the skin disorder with the highest disease burden based on disability-adjusted life-years[1]

Burden of Disease

- AD and its most burdensome symptoms, including **itch and skin pain**, negatively impact daily living, contributing to the **burden** experienced by patients[2-6]

Chronicity

- Patients with moderate-to-severe AD experience **chronic symptoms**, which are driven in part by **long-lived pathogenic memory T cells** in the skin[7-10]

AD = atopic dermatitis.

1. Ständer S. *N Engl J Med*. 2021;384:1136-1143. **2.** Silverberg JI, et al. *Ann Allergy Asthma Immunol*. 2018;121:340-347. **3.** Reed B, et al. *Allergy Asthma Proc*. 2018;39:406-410. **4.** Grant L, et al. *Dermatitis*. 2019;30:247-254. **5.** Chang Y-S, et al. *J Allergy Clin Immunol*. 2018;142:1033-1040. **6.** Manjunath J, et al. *Dermatitis*. 2022. doi:10.1097/DER.0000000000000859. **7.** De Bruyn Carlier T, et al. *J Autoimmun*. 2021;120:102634. **8.** Guttman-Yassky E, et al. *Lancet*. 2022. doi:10.1016/S0140-6736(22)02037-2. **9.** Egeberg A, et al. *Eur J Dermatol*. 2021;31:752-758. **10.** Chen L, et al. *Cell Mol Immunol*. 2020;17:64-75.

T-Cell–Mediated Inflammation Drives Heterogeneity and Creates Challenges in Moderate-to-Severe AD Management

T-Cell–Driven Inflammation

- Inflammation in AD is primarily driven by **pathogenic T cells** present in both the **skin and blood**[1,2]
- Pathogenic T cells **release various cytokines** associated with AD disease activity[1,2]

Heterogeneity & Management

- Patients with **moderate-to-severe AD may require systemic therapy** due to inadequate control with topical therapy alone[3,4]
- Some patients on current systemic therapies **may not meet treatment goals** due to disease heterogeneity preventing a durable treatment response[5,6]

AD = atopic dermatitis.

1. De Bruyn Carlier T, et al. *J Autoimmun*. 2021;120:102634. **2.** Weidinger S, et al. *Nat Rev Dis Primers*. 2018;4:1. **3.** Simpson EL, et al. *J Am Acad Dermatol*. 2017;77:623-633. **4.** Ratchataswan T, et al. *J Allergy Clin Immunol Pract*. 2021;9:1053-1065. **5.** Newsom M, et al. *Drugs*. 2020;80:1041-1052. **6.** Wang C, et al. *Int J Dermatol*. 2020;59:253-256.

Challenges and Future Approaches to the Management of Moderate-to-Severe AD

Topical Therapies

Despite standard use of topicals, **patients with moderate-to-severe AD often require systemic therapy** due to inadequate control of their disease[1,2]

Current Systemic Therapies

Many patients with moderate-to-severe AD treated with current systemic therapies **fail to reach and/or maintain adequate control of their disease due to lack of durable response or safety/tolerability issues**[2-5]

Future Approaches

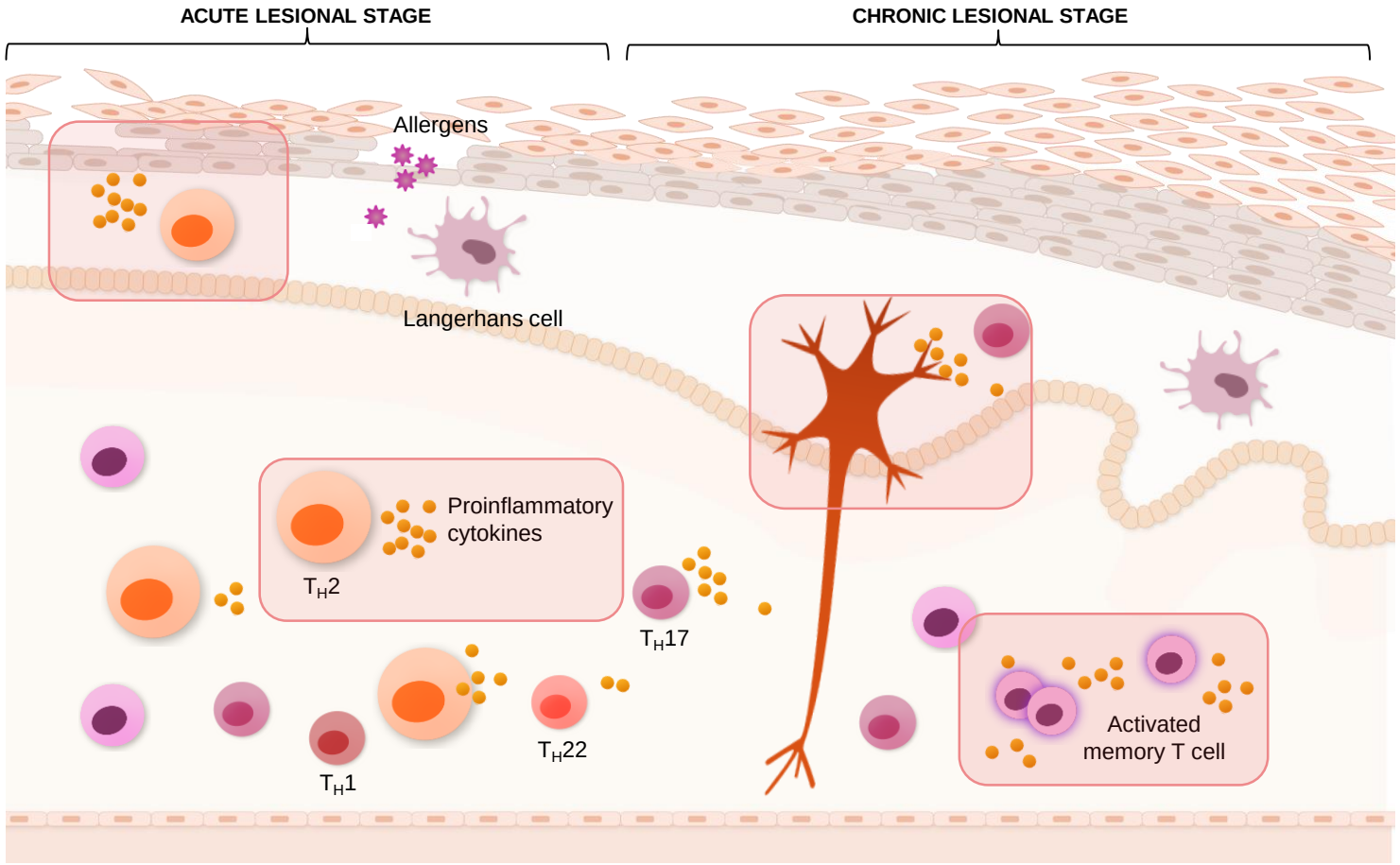
Considering these challenges, additional research is underway seeking to identify distinct inflammatory pathways and cell types that contribute to the heterogeneity of AD pathogenesis[3,6]

AD = atopic dermatitis.

1. Simpson EL, et al. *J Am Acad Dermatol*. 2017;77:623-633. **2.** Gorritz M, et al. *J Dermatolog Treat*. 2022;33:2510-2517. **3.** Ratchataswan T, et al. *J Allergy Clin Immunol Pract*. 2021;9:1053-1065. **4.** Boguniewicz M, et al. *J Allergy Clin Immunol Pract*. 2017;5:1519-1531. **5.** Zhang Y, et al. *Front Immunol*. 2022;13:923362. **6.** Cabanillas B, et al. *Curr Opin Allergy Clin Immunol*. 2017;17:309-315.

Pathogenic Effector and Memory T Cells Contribute to Multiple Inflammatory Mechanisms That Drive AD Pathogenesis

- T cells are the most abundant infiltrate in lesional skin[1,2]
- Multiple cytokines (eg, IL-4, IL-13, IL-31) released by pathogenic T cells affect various aspects of AD pathophysiology:[2,3]
  - Inflammation
  - Epidermal dysfunction
  - Pruritus and skin pain
  - Flares and chronicity
- T-cell–mediated inflammation is driven by pathogenic effector and memory T cells[2]



AD = atopic dermatitis; IL = interleukin; T_H = T helper cell.

1. Weidinger S, et al. *Nat Rev Dis Primers*. 2018;4:1. **2**. De Bruyn Carlier T, et al. *J Autoimmun*. 2021;120:102634. **3.** Kwatra SG, et al. *Clin Transl Immunology*. 2022;11:e1390.

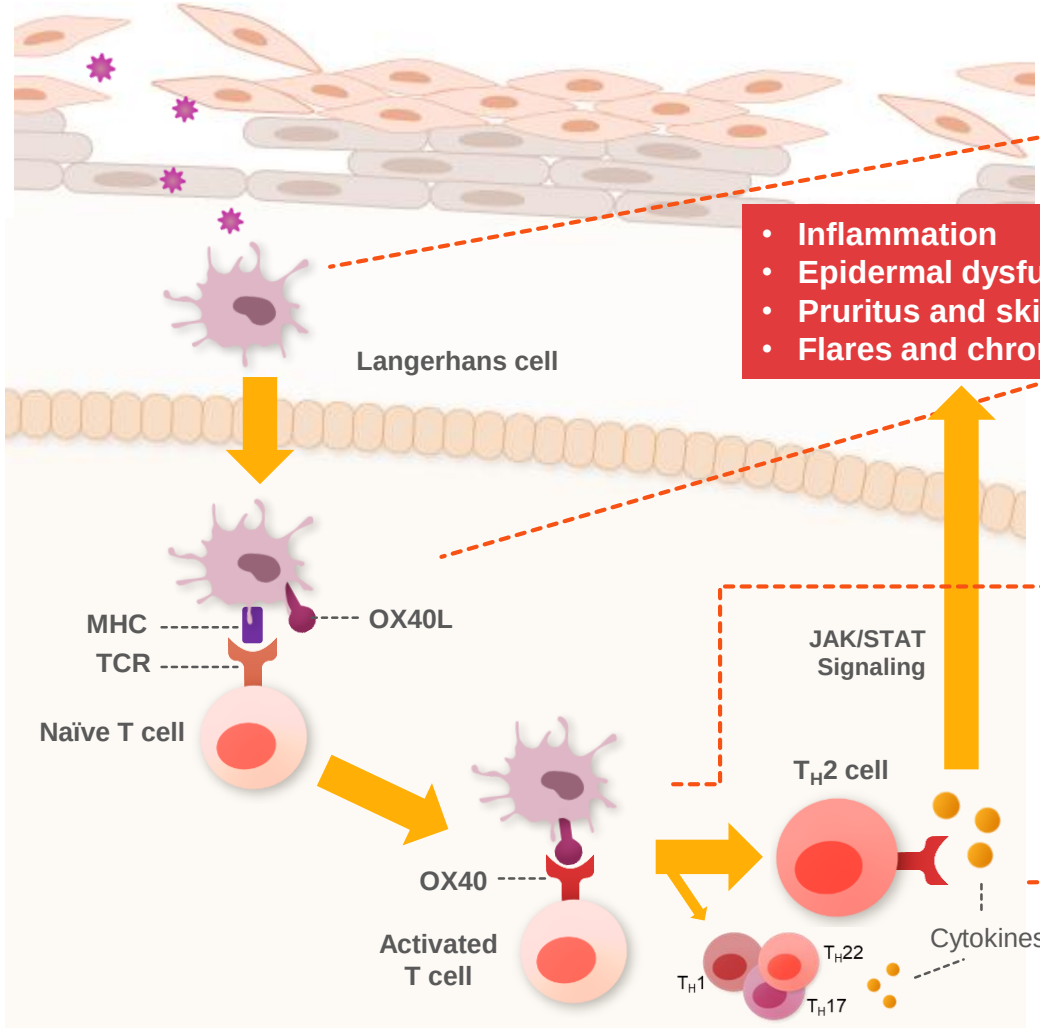
Binding of OX40 to OX40L Drives Pathogenic T-Cell Expansion, Differentiation, and Proinflammatory Cytokine Production

	OX40 (Receptor Expressed on T Cells)	OX40L (Ligand Expressed on APCs)
Description	• **OX40 is a co-stimulatory molecule (receptor)** expressed on the surface of activated T cells[1]	• **OX40L is a cell-surface molecule that binds to OX40,** triggering downstream activity in T cells[1]
Expression	• OX40 is expressed on **activated effector and memory T cells** but not on resting or naïve T cells[1] • OX40 expression is **enhanced by various cytokines** (eg, IL-1, IL-2, IL-4, TNF-α)[1]	• OX40L is **preferentially found on activated APCs** but is **broadly expressed** on other cell types, including endothelial cells, mast cells, and smooth muscle cells[1,3,5]
Expression in AD	• **OX40 expression is significantly increased on skin-homing T cells** from patients with AD versus healthy controls[2]	• **No difference in OX40L expression** on monocytes was observed in patients with AD versus healthy controls[2]
Signaling	• Binding of OX40 to OX40L **activates the OX40 pathway in pathogenic T cells**[1,3,4] • OX40 pathway activation drives the **expansion, differentiation, and survival of activated pathogenic T cells**, as well as enhances the production of proinflammatory cytokines[1,5] • OX40 signaling does not require **JAK/STAT pathway** activation[4,5]	

AD = atopic dermatitis; APC = antigen-presenting cell; IL = interleukin; OX40 = OX40 receptor; OX40L = OX40 ligand; TNF = tumor necrosis factor.

1. Furue M, et al. *J Clin Med*. 2021;10:2578. **2.** Elsner JSH, et al. *Acta Derm Venereol.* 2020;100:adv00099. **3.** Mascarelli DE, et al. *Front Cell Dev Biol*. 2021;9:692982. **4.** Fu Y, et al. *Acta Pharm Sin B*. 2020;10:414-433. **5.** Croft M, et al. *Immunol Rev*. 2009;229:173-191.

Critical Role of OX40 Signaling in Orchestrating T-Cell Driven Inflammation and AD Pathogenesis



- **Inflammation**
- **Epidermal dysfunction**
- **Pruritus and skin pain**
- **Flares and chronicity**

Langerhans cells are activated upon encounter with antigens that penetrate skin and express OX40L[1-3]

Following TCR/MHC interaction, naïve T cells become activated and **express OX40**[1,4,5]

OX40 signaling leads to the activation of downstream pathways that **drive T-cell proliferation, survival, differentiation, and effector function**[3-6]

Downstream of OX40 signaling, T_H2 cells in AD skin secrete cytokines that drive inflammation and AD pathogenesis[1,7,8]

Other T-cell subsets (eg, T_H1 T_H17, T_H22) involved in AD pathogenesis undergo this same process[2,8-10]

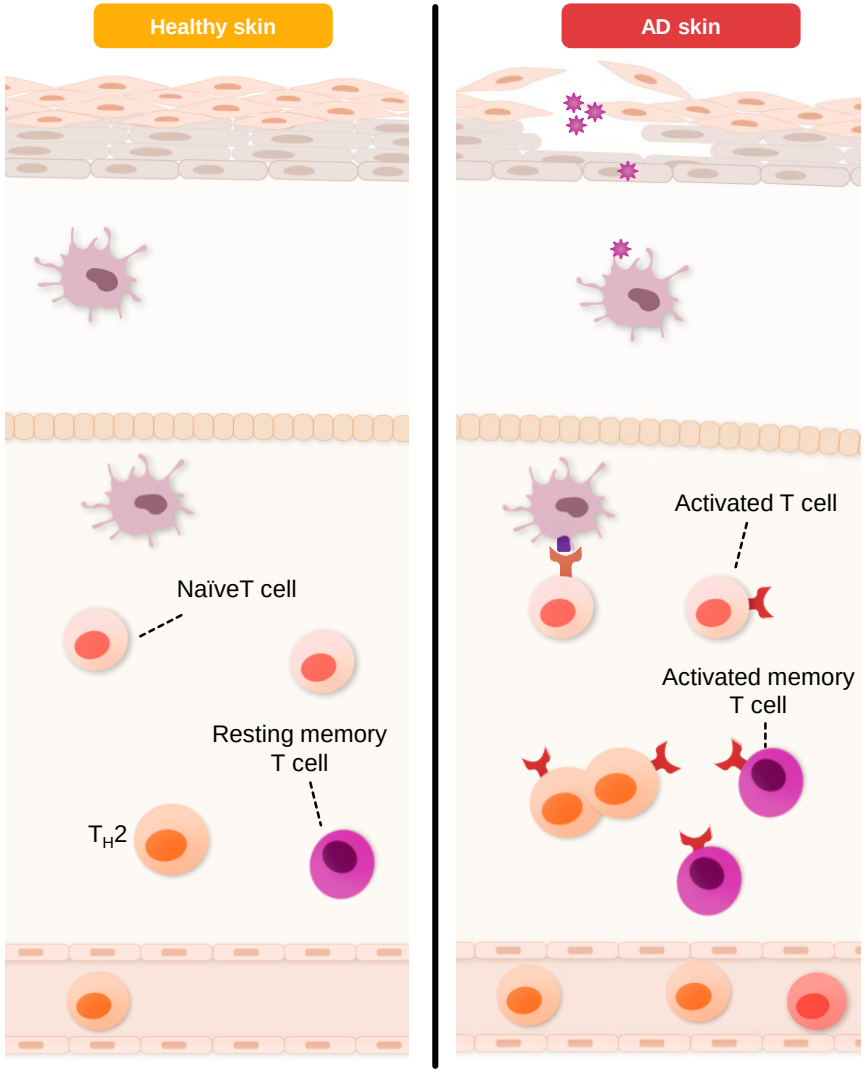
OX40 signaling in effector T cells also promotes development of memory T cells, which contribute to the chronic nature of AD[1,3,11]

AD = atopic dermatitis; MHC = major histocompatibility complex; OX40 = OX40 receptor; OX40L = OX40 ligand; TCR = T-cell receptor; T_H = T helper cell.

1. Furue M, et al. *J Clin Med*. 2021;10:2578. **2.** Guttman-Yassky E, et al. *Semin Cutan Med Surg*. 2017;36:100-103. **3.** Croft M, et al. *Immunol Rev*. 2009;229:173-191. **4.** Magee CN, et al. *Am J Transplant*. 2012;12:2588-2600. **5.** Goronzy JJ, et al. *Arthritis Res Ther*. 2008;10(suppl 1):S3. **6.** Mascarelli DE, et al. *Front Cell Dev Biol*. 2021;9:692982. **7.** Krohn IK, et al. *Allergy*. 2022;77:827-842. **8.** De Bruyn Carlier T, et al. *J Autoimmun*. 2021;120:1026345. **9.** Kumar S, et al. *Int J Mol Sci*. 2019;20:2159. **10.** Fu Y, et al. *Acta Pharm Sin B*. 2020;10:414-433. **11.** Chen L, et al. *Cell Mol Immunol*. 2020;17:64-75.

Evidence for OX40 in T-Cell–Driven Systemic Inflammation

- In skin biopsies of AD lesions, OX40- and OX40L-positive cells are **co-localized within the dermis**[1]
- OX40 expression is **significantly increased on circulating, skin-homing, CD4+ T cells** from patients with AD compared to healthy controls[1]
- **No difference in OX40L expression** on monocytes was observed in patients with AD versus healthy controls[1]
- OX40+ pathogenic T cells **were better able to migrate to the skin** due to expression on skin-homing cells[1]
- Cytokines enhanced by OX40 signaling may drive tissue **inflammation outside of skin lesions** (eg, lungs, airways, and other mucosal surfaces)[2-5]



AD = atopic dermatitis; CD = cluster of differentiation; OX40 = OX40 receptor; OX40L = OX40 ligand; T_H = T helper cell.

1. Elsner JSH, et al. *Acta Derm Venereol.* 2020;100:adv00099. **2.** Furue M, et al. *J Clin Med*. 2021;10:2578. **3.** Lebwohl MG, et al. *J Clin Aesthet Dermatol*. 2013;6(suppl 7):S2-S18. **4.** Ungar B, et al. *J Invest Dermatol*. 2017;137:603-613. **5.** Boguniewicz M, et al. *J Allergy Clin Immunol Pract.* 2017;5:1519-1531.

Summary

Disease Burden and Remaining Challenges in Moderate-to-Severe AD

- Patients with moderate-to-severe AD may not achieve their treatment goals or may have tolerability issues with current topicals or systemic treatments[1-4]

T Cells and AD Pathogenesis

- AD, a chronic, heterogeneous, inflammatory disease characterized by skin redness, pruritus, and pain, is driven by T-cell–mediated inflammation[5-8]
- Pathogenic effector and memory T cells play a critical role in driving AD pathogenesis[9]

OX40 in AD

- OX40 expression is increased on pathogenic T cells in patients with AD[10-16]
- OX40 pathways drive local and systemic inflammation by promoting expansion, differentiation, and survival of pathogenic T cells and subsequent T-cell memory formation[10-16]

AD = atopic dermatitis; OX40 = OX40 receptor.

1. Bieber T. *Nat Rev Drug Discov*. 2022;21:21-40. **2.** Zhang Y, et al. *Front Immunol*. 2022;13:923362. **3.** Ratchataswan T, et al. *J Allergy Clin Immunol Pract*. 2021;9:1053-1065. **4.** Alexander H, et al. *F1000Res*. 2019;8:132. **5.** Silverberg JI. *Clinical Management of Atopic Dermatitis*. 1st ed. West Islip, NY: Professional Communications, Inc; 2018. **6.** Weidinger S, et al. *Nat Rev Dis Primers*. 2018;4:1. **7.** Czarnowicki T, et al. *J Allergy Clin Immunol*. 2019;143:1-11. **8.** Guttman-Yassky E, et al. *Semin Cutan Med Surg*. 2017;36:100-103. **9.** De Bruyn Carlier T, et al. *J Autoimmun*. 2021;120:102634. **10.** Furue M, et al. *J Clin Med*. 2021;10:2578. **11.** Guttman-Yassky E, et al. *J Allergy Clin Immunol*. 2019;144:482-493.e7. **12.** Elsner JSH, et al. *Acta Derm Venereol.* 2020;100:adv00099. **13.** Croft M, et al. *Immunol Rev*. 2009;229:173-191. **14.** Czarnowicki T, et al. *Allergy*. 2017;72:366-372. **15.** Chen L, et al. *Cell Mol Immunol*. 2020;17:64-75. **16.** Chu K-L, et al. *J Immunol*. 2020;204:477-485.