Atopic Dermatitis and its Pathophysiology- A Critical Review

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Abstract: Atopic Dermatitis (AD) is a chronic, relapsing, inflammatory skin disease. Loss of function or mutation in filaggrin lead to skin barrier disruption that initiate AD. Later Type 2 cytokines promote skin inflammation and cause immune dysregulation which is also important in the pathogenesis of the disease. Alteration in skin host-biome interaction help to propagate the immune response. IgE mediated allergic sensitization and environmental factors such as climate, urban vs rural life, diet, breast feeding, smoking exert effect that are also involved in the pathophysiology of AD. Recent findings on AD and the possible mechanism of its pathophysiology are discussed in this review which will help us to find potential therapeutic approach for this disease.

Keywords: Atopic Dermatitis, Pathophysiology, Skin barrier, Filaggrin, Tight junction, Innate immunity, Adaptive immunity, Microbiome


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Introduction

Atopic Dermatitis (AD) is a chronic inflammatory skin disease which commonly affects children but adult onset is also found and follows a relapsing course (Kulthanan et al., 2007). AD effects up to 15-20% of children and 1-3% of adult worldwide and its incidence has enhanced by 2-3 folds during past decades in industrialized countries (Nutten, 2015). Atopic comorbidities such as food allergies, asthma, hay fever, eosinophilic esophagitis and non-atopic comorbidities such as allergic contact dermatitis, anxiety, depression, sleep disturbances are associated with AD and the relation of these comorbidities with AD is multifactorial (Silverberg, 2019). AD is of three types on the basis of patient’s age and lesional distribution – (i) Infantile (0-2years), (ii) Childhood (2-12years), and (iii) Adolescent. In infantile AD, skin lesions are present on face or trunk or extensor areas and clinical signs are characterized by edema, xerosis, oozing. In Childhood AD, skin lesions are present...
in the hands, feet, wrists, ankles, antecubital and popliteal regions and clinical signs involved eczema with lichenified papules and plaques. In Adult AD, skin lesions are present in flexural folds, face, neck, hands, feet, fingers, upper arms. Large lichenified plaques are found as clinical signs (Spergel and Paller, 2003).

Skin barrier dysfunction and immune dysregulation are mainly associated with AD and play a crucial role in the pathogenesis (Novak and Leung, 2011). Skin Barrier dysfunctioning caused due to loss of function mutation in filaggrin, decrease in ceramide level and tight junction barrier function (Zaniboni et al., 2016). Immune dysregulation of innate and adaptive immunity is also involved in the pathophysiology of AD. Toll like receptors, NOD like receptors and antimicrobial peptides play a major role in the innate immune responses. Dysregulation of helper T cells, B cells, TH2 cytokines are mainly involved in adaptive immune response. Alterations of skin’s host-microbiome interaction are also involved in the AD pathophysiology (Gavrilova, 2018).

Role of specific allergens is also found in increasing skin inflammation in AD patients. Food, aeroallergens as well as self-allergens can trigger symptoms of AD. So, they must have a crucial role in AD pathogenesis (Heratizadeh, 2016). The worldwide prevalence of AD is suggesting except for immunological and skin barrier alterations, various environmental factors may also be able to trigger AD and is critical in clinical expression of AD. Environmental factors like climate, urbanization, western diet, breast feeding and tobacco smoke are important for the onset of the disease (Bonamonte et al., 2019).

In this review, the pathophysiology of AD is discussed focusing on causes of skin barrier dysfunction and immune dysregulation, microbial colonization, allergic reaction and environment factors which are also involved in disease pathogenesis are discussed.

(i) Skin barrier dysfunction in AD:

Normal function of skin barrier:
The skin acts as barrier between the organism and its external environment and provide protection to the organism. Skin barrier prevents microbial infection by producing antimicrobial peptides and proteins such as defensins. The antimicrobial peptides inhibit the invasion of microbes and thus play a crucial role in host’s innate defense. Lamellar body is also necessary in epidermal permeability barrier formation (Lee et al., 2006). The outer most layer of skin is stratum corneum (SC) that is continuously regenerated by keratinocytes and help an individual in maintaining a balanced bacterial flora and release immune signaling compounds. SC release interleukin-1 alpha (IL-1α) that initiate the inflammatory cascade. IL-1α stimulate the keratinocytes and fibroblast to release other proinflammatory cytokines such as IL-1β, IL-6, IL-8, TNFα and this cascade leads to vasodilation and subsequent inflammatory reactions (Pouillot et al., 2008).

Filaggrin, a structural protein of stratum corneum help to aggregate keratin filaments together and in this way maintain the hydration of SC and help skin to maintain its acidic pH (Kim et al., 2019).

Epithelial cells in the airways act as frontline of mucosal immunity. Apical junctional complexes such as tight junctions and adherens junction together promote cell-cell interaction and regular movement of ions and macromolecules. Regulation of airway epithelial barrier function is important for preventing allergic airway inflammation. The tight junction protein, Claudine-1 have been found to function in skin barrier (Georas and Rezaee, 2014). According to ‘brick and Mortar model’ proposed by Elias, keratinocyte derived a nucleated cells named corneocytes (Brick) are surrounded by intercellular lipid matrix (Morter) which together provide structural support to SC.
corneocytes act as water barrier because of their ability to retain water and prevent loss of water from the epidermis (Pouillot et al., 2008). Lipids present in SC (e.g., ceramides, free fatty acids and cholesterol) play an important role in skin barrier functioning because transport of substances takes place through the lipid bilayer. The level of these lipids are altered in skin barrier dysfunction (Jungersted et al., 2008). Thus, filaggrin protein, lipids and tight junctions help the skin barrier to function normally.

**Lipids:**

Ceramide level decreases in AD patients with both lesional and non-lesional skin types and the ceramide/cholesterol ratio also decrease in AD patients (Jungersted et al., 2010). Increase in pH and elevation in the degradation of ceramide generating enzymes including acidic sphingomyelinase and β glucocerebrosidase and upregulation in the production of IFN-γ, all together prevent the synthesis of ceramides in AD patients. Elevation in the production of TH2 derived cytokines IL-4 and IL-13 also lead to decrease in the levels of ceramide. In AD patients with lesional skin, increased IFN-γ decreases expression of ELOV1 and ELOV4, fatty acid elongases which in turn reduce the length of N acyl fatty acids in ceramides and FFAs and cause abnormalities in epidermal lipid organization (Elias and Wakefield, 2014).

**Filaggrin:**

Filaggrin acts as the first line of host defense against allergens and pathogens and important for maintaining water balance in the skin (Drislane and Irvine, 2019). Loss of function mutation of filaggrin lead to skin barrier dysfunction and strongly associated with Atopic Dermatitis (Palmer et al., 2006). In patients with AD, those who has FLG mutations, there is a predisposition for distinct profile of disease than patients without FLG mutations. AD patients who have FLG mutation show severe skin lesions and are susceptible to multiple allergens than patients without mutations. Tight junction which are important in maintaining cell to cell integrity, are decreased in filaggrin deficient persons (Irvine et al., 2011).

In a study, it is seen that only 63% of individuals with loss of function mutation in FLG develop Atopic dermatitis while 40% of individuals who has normal FLG protein also develop AD (Palmer et al., 2006). The expression of hornerin and filaggrin family member2 (FLG2) that related to FLG, is also reduced in AD patients with both lesional and non lesional skin. Proinflammatory cytokines such as IL-4, IL-13, IL-25 downregulate the expression of proFLG, HRNR and FLG2 and thus disrupt the epidermal barrier (Pellerin et al., 2013). FLG mutations increase pH of skin and activate serine proteases that lead to barrier dysfunction and protease activation leads to TH2 inflammatory responses in patients with AD (Thyssen and Kezic, 2014).

**Tight junction:**

Tight junctions are considered as second physical barrier in the epidermis and is able to control permeability of soluble molecules selectively (Yang et al., 2020). The main components of tight junctions are claudin protein, junctional adhesion molecule A, occluding and tricellulin (De Benedetto et al., 2010). In an experiment where Claudin1 (CLDN1) protein was knock out in mice, epidermal defect arises and trans epidermal water loss is also seen (Furuse et al., 2002). In AD patients with lesional skin, lowering of CLDN1 levels leads to decrease in tight junction barrier function and elevate the level of TEWL. Decrease in CLDN1 elevate the expression of proinflammatory cytokine IL-1β and indicate its role in inflammatory immune response (Bergmann et al., 2020).
(ii) Immune Dysregulation in AD:

Innate immunity:

Keratinocytes of the epidermis express several pattern recognition receptors (PRRs) which are important in intracellular signal transduction of pathogens. Some important PRRs are Toll like receptors (TLRs), Nod like receptors (NLRs), Rig-1 like receptors (RLRs), C type lectin receptors (CLRs). PRRs stimulate keratinocytes to produce proinflammatory cytokines like IL-1, IL-6, IL-10 and TNF which are important in tissue injury or microbial stimulation and skin barrier function. TLR2, TLR9, NOD1 and NOD2 polymorphisms have a high influence on the AD pathology (Bitschar et al., 2017).

Toll like receptors:

Impaired Toll like receptors (TLRs) are found to be linked with immune dysregulation and important in the pathophysiology of AD (Bitschar et al., 2017). TLR2 help to combat *Staphylococcus aureas*, a commensal bacterium but in mice with impaired TLR2 function, the colonization rate of *Staphylococcus aureas* is elevated than normal one. TLR2 R753Q polymorphism is found in high frequency (12%) in adult AD patients whose skin is colonized with *S. aureas*. Monocytes from AD patients with TLR2 R753Q mutant show increased production of IL-6 and IL-12 that enhance the skin inflammation when compared to monocytes with no mutation (Niebuhr et al., 2008). In a study among Italian children, role of TLR4 gene polymorphisms in the pathogenesis of AD is also found along with TLR2 gene polymorphisms. TLR4 mainly acts as receptor for lipopolysaccharide in the gram-negative bacteria. The binding of TLR4 and CD14 with lipopolysaccharide results in intracellular Ca²⁺ dependent response and induce the secretion of proinflammatory cytokines and chemokines. The frequency of TLR4 D299G is higher in Italian AD children (14.9%) than in controls (6.6%) (Salpietro et al., 2011). TLR9 activation is associated with IgE class switching of B cells in murine and it implies there might be a connection between TLR9 functioning and pathogenesis of AD. TLR9 promoter polymorphism C-1237T is found to be associated with immune responses in AD patients (Novak et al., 2007).

NOD like receptors:

NOD1 and NOD2 are intracellular receptors that respond to peptidoglycan cell wall of *S. aureus*. NOD1 and NOD2 polymorphism are associated with AD pathology. NOD2 are able to induce inflammatory response in presence of TLR signal (Bitschar et al., 2017). NOD2 mediate the recognition of *S. aureus* by inducing IL-17C expression in keratinocytes. Impaired recognition of *S. aureus* by NOD2 may lead to *S. aureus* colonization seen in case of AD (Roth et al., 2014).

Antimicrobial peptides:

Antimicrobial peptide (AMP) play a crucial role in the innate immune system and inhibit bacterial, viral, fungal and protozoal infection. AMPs are mainly produced from the keratinocytes, mast cells, phagocytes and some major AMPs are defensing, cathelicidin, ribonucleases and dermicidin. Dysregulated production of AMP lead to the development of chronic inflammatory diseases such as Atopic Dermatitis, Psoriasis. (Marcinkiewicz and Majewski, 2016).

Defensins can initiate antimicrobial activity against Gram negative and Gram positive bacteria. Defensins stimulate the production of proinflammatory cytokines including IL-6, IL-10 and chemokines. Defensins are also important in cutaneous wound healing (Marcinkiewicz and Majewski, 2016).
Human cathelicidin LL-37 is a peptide that can disrupt bacterial membrane and also have antifungal activity against yeasts. They promote differentiation of dendritic cells derived from monocytes and stimulate angiogenesis (Marcinkiewicz and Majewski, 2016). Cathelicidin enhance the secretion of proinflammatory cytokine such as IL-6, IL-10 from keratinocytes (Hata and Gallo, 2008).

Decreased expression of defensin and cathelicidin is seen in the skin of AD patients. Expression of another AMP named dermicidin is also decreased in AD patients (Marcinkiewicz and Majewski, 2016).

(iii) TSLP mediated immune response:
Thymic stromal lymphopoietin (TSLP) is an IL-7 like cytokine and connected with the pathogenesis of atopic dermatitis (Tsilingiri et al., 2017). Epithelial cells express TSLP at the barriers or faces of the skin, lung, gut. The receptor for TSLP is composed of a chain specific for TSLP and the IL-7Ra chain. The receptor is expressed in dendritic cells, macrophages, B cells, T cells, basophils and eosinophils. The expression of TSLP is higher in the epidermis of lesional skin of AD patients when compared to the skin of normal patients (Indra, 2013). TSLPR trigger signaling and activates transcription by activating STAT5 by phosphorylating JAK1 and JAK2 (Ciaferoni and Spergel, 2014). TSLP induces expression of OX-40 ligand in human dendritic cells and thus induce inflammatory TH2 cell to generate TH2 cytokines IL-4, IL-5, IL-13 and TNFα but in turn inhibit IL-10 production in presence of IL-12 (Liu, 2007).

DC derived TSLP promote TH2 differentiation by directly acting on Naïve CD4+ T cells and TH2 responses are critical for allergic inflammation and have a role in the development of AD. Overexpression of TSLP lead to skin inflammation, a major characteristic of AD (Zhang et al., 2012). Downregulation of TSLP by the application of Dieckol, a phlorotannin is helpful to alleviate the symptoms of AD in NC/Nga mouse model (Yang et al., 2016).

(iv) ILC mediated immune responses:
Innate lymphoid cells (ILCs) are derived from common lymphoid progenitor in the bone marrow and T cell factor (TCF1), RORα, GATA binding protein 3 and notch signaling regulate its development. ILCs are of three types ILC-1, ILC-2, ILC-3 and among them ILC-2 is found to be involved in allergic diseases like Atopic Dermatitis. ILC2 are present in blood, spleen, liver, intestine, lung, lymph nodes and lymphoid clusters (McKenzie, 2014). Skin ILC2 lack common lineage markers but express CD45+, IL7Ra, CRTH2. In an experiment, peripheral blood and acute skin lesions of adult AD patient was examined for the presence of ILC2 and significantly more ILCs are found in the skin biopsies from AD patients than healthy controls. ILC2s can induce skin allergies by producing TH2 cytokines such as IL-5 and IL-13. The receptors for IL-25, IL-33 and TSLP are upregulated in ILCs of AD patients. Being stimulated by IL-33, the production of Type 2 cytokines and the migration of ILC-2 are enhanced. KLRG1(killer cell lectin like receptor G1) E-cadherin ligation alters ILC function and inhibit the type 2 cytokines secretion. In the skin lesion of AD patients, downregulation of E cadherin expression is found, thus type 2 cytokine production increases and promote inflammation. Knockout of IL-25 and IL-33 from BALB/C mice resulted in decrease in skin inflammation, while in acute lesional skin of AD patients’ expression of IL-25 and IL-33 is enhanced (Salimi et al., 2013).

(v) Adaptive immunity:
Allergic disease such as Atopic Dermatitis may
be a result of dysregulation of immune cells including TH2 cells, B cells, basophils, eosinophils, mast cells and some major cytokines like IL-4, IL-5, IL-9, IL-13, IL-25, IL-31, IL-33 and thymic stromal lymphopoietin (TSLP) from epithelial cells.

During allergic sensitization, dendritic cells (DCs) capture, process and then transport the antigen to lymph node where it is presented on MHC Class 2 molecules to CD4+ TH2 cell. TH2 cells produce cytokines IL-4 and IL-13 and promote IgE isotype class switching of B cells and this later ensures the development of allergen specific memory Th2 and B cells (Palomares, 2017). TSLP, IL-25, IL-33 links the innate immunity to adaptive immunity and promote TH2 cytokine responses by TH2 polarization via dendritic cells (Brandt and Sivaprasad, 2011).

Helper T cells are important in continuation of AD response for both acute and chronic phase of AD. In the acute phase TH2, Th22 and TH17 cells play major role while in the chronic phase TH1, TH2 and TH22 play major role (Gavrilova, 2018). In acute phase, TH2 cells being stimulated by activated dendritic cells produce IL-4, IL-5, IL-13, IL31 and lead to skin barrier dysfunction, suppression of antimicrobial peptides and produce itch symptoms (Kim et al., 2019). In AD patients the level of TH2 cytokines are increased along with increase in IgE levels. IgE levels is higher in adult AD patients when compared to children (Brandt and Sivaprasad, 2011).

**IL-4:**
IL-4 is an important TH2 cytokine that lead to the differentiation of TH2 cells and promotes IgE isotype switching of B cells. Overexpression of IL-4 generates all the hallmarks of AD including pruritis, increase in IgE level and elevated inflammatory cells. IL-4 decrease the expression of FLG, involucrin, loricrin and lead to barrier dysfunction and increase allergen permeability through skin (Brandt and Sivaprasad, 2011). IL4 and IL13 closely resemble each other in terms of sequence homology and function (Brandt and Sivaprasad, 2011).

**IL-13:**
IL13 is another TH2 cytokine that mediates the allergic inflammation and expressed in both acute and chronic phase of AD (Brandt and Sivaprasad, 2011). IL-13 promotes IgE production, dermal fibrosis, angiogenesis and increase vasculature in the inflammation site and enhance inflammation of TH2 cells in the skin. IL-13 is crucial for the pathogenesis in AD because of its ability to generate chronic inflammatory response in the skin of AD patients (Zheng et al., 2009). IL-4 and IL-13 induce expression of an extracellular matrix (ECM) protein named peristatin by the activation of JAK-STAT pathway. Peristatin induce proinflammatory cytokines production and activate NF-κB which acts on dendritic cells and increase Type 2 inflammation. The expression of peristatin is elevated in inflammatory sites in allergic diseases such as AD (Izuhara et al., 2017).

**IL-5:**
IL-5 is another important TH2 cytokine produced from TH2 cells and mast cells. It acts as a modulator of eosinophil chemotaxis and survival. The level of IL-5 is elevated in skin lesions of patient with AD (Gavrilova, 2018). IL-5 is responsible for the prolong survival of eosinophil and number of eosinophils increase in AD patients with lesional skin. IL-5 and IL-5 receptor alpha polymorphism found to be involved in development of AD in Korean population (Namkung et al., 2007).

**IL-31:**
IL-31, produced from TH-2 cells is a potent pruritogenic cytokine. The induction of IL-31 is
mediated by IL-4/STAT6 and IL-33/ NF-κB signaling. Its receptor IL-31R is expressed in immune cells including macrophages, dendritic cells, basophils, keratinocytes. IL-31 and its receptor affect TH2 mediated immune responses. Transcription factor EPAS1 induces IL-31 gene expression in CD4+T cells. When EPAS1 gene is knocked down from AD patients, IL-31 gene expression also decreases. IL-31 promotes itch response, scratching behaviour and skin lesions in rodents, dogs, monkeys. IL-31 promotes pruritic response which is prevalent AD (Furue et al., 2017). Besides TH2, the gene expression level of TH2 and TH17 are also elevated in acute AD patients. The level of IL-17 and IL-22 which are produced from TH17 and TH22, respectively, are increased in acute or chronic AD lesions. The level of TH17 and IL-17 is upregulated in patients with psoriasis when compared to AD patients (Gittler et al., 2012). In the chronic phase, TH1 produce Interferon-γ that induces activated macrophages, M1 cells. These activated macrophages promote chronic inflammation of AD (Kasraie and Werfel, 2013).

Another cytokine IL-12 is also involved in the chronic AD. IL-12 is produced from macrophages and dendritic cells and play major role in the regulation of IFN-γ production and stimulate cytokine lymphocytes for maturation. The level of IL-12 mRNA is upregulated in the lesional skin of AD patients that can be downregulated by the application of topical corticosteroid (Yawalkar et al., 2000).

(vi) Microbiome:
In the skin of AD patients, reduction in bacteria including Strep tococcus, Propionibacterium, Acinetobacter, Corynebacterium is found while Staphylococcus is increased during AD flares (Dybboe et al., 2017). The alteration of the skin microbiome results from skin barrier dysfunction and decreased expression of antimicrobial proteins in the skin and these disrupt the host and microbe homeostatis (Schommer and Gallo, 2017).
S. aureas triggers T cell independent B cell proliferation and also induce release of proinflammatory cytokines (e.g., TSLP, IL-4, IL-12, IL-22) and results in TH2 skewing and skin inflammation (Kim et al., 2019). High prevalence of S. aureas and methicillin resistant S. aureas is found in the skin lesions of AD patients (Cavalcante et al., 2015).

S. aureas in the skin of AD patient, skews the immune response toward TH2 via monocyte derived activated Langerhans cell (Iwamoto et al., 2017).

(vii) Allergens in AD:

AD is associated with elevated serum IgE levels, sensitization to food allergens and aeroallergens (i.e., house dust mites) in approximately 80% of adult AD patients. AD patients with IgE mediated alleragy show enhanced surface expression of FcεRI on epidermal DCs and high lesional cytokine expression that nonallergic AD patients. In AD patients with high IgE sensitization, the severity of the disease increase (Werfel, 2009).

Food allergens:

In adults, T cell mediated immune response to birch pollen related food such as apple, carrot, celery and hazelnut is found. Food can provoke flares of AD and it is seen in a study of Placebo-controlled food challenges with birch pollen related food. This prove food allergy are also associated with pathogenesis of AD (Heratizadeh, 2016).

Aeroallergens:

Epicutaneous application of aeroallergens (HDM) on non-lesional skin of AD patients can induce eczematous reaction in AD patients. Atopy patch test (APT) are used for studying IgE sensitization in AD patients due to HDM (Werfel, 2009). In a recent study, a human keratinocyte cell line was treated with HDM extract for 48 h and 72 h and keratinocyte proliferation is shown. HDM also increase the expression of IL-22Rα and increase the production of IL-22 from T cells. IL-22 increase the release of proinflammatory cytokine in AD patients. HDM extract elevate the production of TNFα and IFNγ from T cells and production of TARC also increases. Increased TARC production recruit T cells to inflammatory sites of skin and helping in T cell migration (Jang et al., 2016).

Self-allergens:

IgE and T cell mediated autoreactivity also associated with AD. Autoreactivity may be the result of scratching which in turn releases intracellular antigens and associated with innate and adaptive immune system. Human antigen α-NAC (α chain of the human nascent polypeptide associated complex) induces autoreactive IgE sensitization and proliferate T cells. α-NAC specific T cells produce IL-4 and IFNγ which are involved in sensitization in AD patients (Heratizadeh, 2016).

(viii) Environmental risks factors:

Climate:

It is found that in US, a lower prevalence of AD is found with high quartile temperature. Higher relative humidity improves skin barrier function and thereby protect an individual against AD. Higher UV level is important for decrease prevalence of AD. Increased stratospheric ozone filters UVB and UVC radiation and also involved in photo immunosuppression of AD. Higher precipitation may be responsible for lowering UV levels and more time spent indoors and exposed to indoor heating is associated with increased prevalence of AD (Silverberg et al., 2013).

Urban vs rural life:

The risk of AD increases with urbanization.
Urban living may be linked with factors like high stress, higher exposure to environmental pollutants. So, prevalence of AD is higher in urban areas than in rural areas (Kantor and Silverberg, 2016).

**Diet:**

Consuming western diet (i.e., high intake of cereals, red meat, and saturated and unsaturated fatty acid) can contribute in increasing the risk of AD. Higher fish intake during pregnancy can decrease the risk of AD in the offspring for the first 5 years of its life by 25-43%. Fish contain high amount of ω-3 polyunsaturated fatty acid (PUFA) which has anti-inflammatory activity. Western diets lack ω-3 PUFA and contains ω-6 PUFA thus increase the risk for the development of AD (Flohr and Mann, 2013).

**Breast feeding:**

Breast feeding has role in preventing the AD (Flohr and Mann, 2013).

**Tobacco smoke:**

In a meta-analysis, it is found that active smoking and exposure to passive smoking is associated with increased AD in adults and children but maternal smoking during pregnancy has no role in AD (Kantor et al., 2016).

**Conclusion**

Atopic Dermatitis is a multifactorial, heterogenous skin disease which severely affects the patients’ quality of life. AD is characterized by skin barrier abnormalities and skin inflammation and pruritus caused due to immune dysregulation, microbial colonization, allergic reactions and various environmental factors (Fig. 1). All these factors are interconnected and involved in developing the clinical signs and symptoms in AD patients.

The knowledge on the underlying mechanism and key mediators leading to skin barrier disruption, immune reactions, *S. aureas* colonization may be helpful for the development of a precise medicinal approach for preventing or treating Atopic Dermatitis.

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