■ REVIEW ARTICLE ■

Dendritic Cells—Importance in Allergy—

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ABSTRACT
In this review we discuss the role of dendritic cells (DC) in the pathogenesis of allergic contact hypersensitivity (ACH) and atopic disorders, such as asthma and atopic eczema. In ACH patients, DC recognize the invasion of simple chemicals such as haptens, and trigger antigen-specific T cell responses leading to the characteristic histological and clinical changes such as spongiosis and papulovesicular eruptions. During atopic disorders, it is well known that the Th2-deviated immune response plays a crucial role in their pathogenesis. DC provide T cells with antigen and costimulatory signals (signals 1 and 2, respectively), as well as with a polarizing signal (signal 3). When studying ACH, it is important to understand how simple chemicals induce the activation of DC and their migration to the draining lymph nodes where they supply signals 1 and 2 to naïve T cells. The mechanisms by which DC induce the Th2-deviated immune response, namely via the Th2-deviated signal 3, are central topics in the pathogenesis of atopic disorders.

KEY WORDS
asthma, atopic dermatitis, contact dermatitis, Th1/Th2

INTRODUCTION

CURRENT VIEWS ON ALLERGIC CONTACT HYPERSENSITIVITY, ASTHMA AND ATOPIC DERMATITIS

During allergic contact hypersensitivity (ACH), chemicals penetrate into the viable layers of the epidermis and into the various cells therein. At these sites, the chemical must react with a carrier protein or peptide to form a T cell epitope, and must also activate epidermal or dermal dendritic cells (DC). The reaction of haptens with proteins is either covalent or non-covalent, such as by forming a coordination complex. In addition, haptens activate DC, although the mechanism by which this occurs is still controversial. Activation of DC induces the augmented expression of various co-stimulatory molecules and increased production of proinflammatory cytokines. Activated DC start to migrate via the afferent lymphatics to the draining lymph nodes where they present haptens to naïve T cells. In the draining lymph nodes, DC stimulate naïve T cells, helper T cells and cytotoxic T cells, in an antigen-dependent manner. Moreover, they may affect the Th1/Th2 deviation of the subsequent T cell response.

On the other hand, the pathogenesis of both asthma and atopic dermatitis (AD) is still not fully understood; however, a central role has been proposed for allergen-specific T cells that produce Th2 cytokines such as IL-4 and IL-5. In addition, mast cells and eosinophils have been shown to exert important effector functions in these diseases. In both diseases, IL-4 and IL-13 induce the expression of cell adhesion molecules in inflamed endothelium and also induce the production of chemokines in the epithelium, thus leading to the recruitment of inflammatory cells and the production of IgE by B cells. IL-5 is important for the growth, differentiation and activation of tissue eosinophils, whereas IL-9 is important for mast cell growth and activation. GM-CSF stimulates the growth of eosinophils and the activation of antigen-presenting cells (APC). Moreover, in asthma, cytokines produced by Th2 cells and inflammatory cells can affect the airway epithelium, subepithelial (myo-) fibroblasts and smooth muscle cells in the lungs, thus leading to structural abnormalities.

ALLERGIC CONTACT DERMATITIS (Fig. 1)

DENDRITIC CELL MATURATION
DC are the most potent antigen presenting cells for

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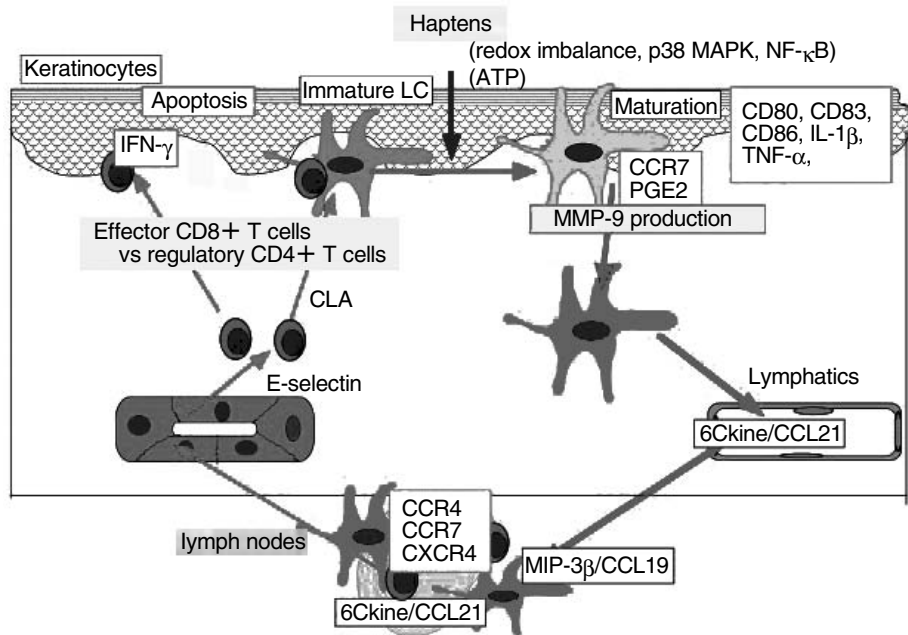Email: aiba@mail.tains.tohoku.ac.jp

Fig. 1 Dendritic cells in allergic contact hypersensitiveity

helper T cells and cytotoxic T cells.[1] They reside in non-lymphoid organs and show extremely active endocytosis and antigen-processing, but weak antigen presenting functions.[2] In response to various stimuli, immature DC mature, and hence become so called mature DC. During maturation, the expression of endocytic receptors decreases, endocytosis is reduced,[3] and the expression of class II-peptide complexes is stabilized.[4,5] In addition, DC undergo significant changes in the expression of many molecules used to interact with T cells, such as several B7-family members (CD80, CD86, PD-L2/B7-DC, ICOS-L), TNF family members (CD137/4-1BBL, CD134/OX40L, CD70), and chemokine receptors (CCR5, CCR7) (reviewed by Steinman).[6]

MATURATION SIGNALS (Fig. 2)

There are many stimuli that induce DC maturation. These stimuli can be classified into danger signals, innate immunity maturation signals, and adaptive immunity maturation signals. Danger signals were first postulated in 1994 as part of a model of immunity that suggests that the immune system responds to substances that cause damage, rather than to those that are simply foreign.[7] They consist of molecules or molecular structures that are released or produced by cells undergoing stress or abnormal cell death. Signals such as TNF-α, IL-1β, type I interferon, intracellular nucleotides such as ATP and UTP, and heat-shock proteins induce activation in resting DC, and thus initiate immune responses.[8] Indeed, certain types of necrotic cells can induce maturation *in vitro*.[9]

Many microbial ligands and synthetic compounds can act as innate immunity maturation signals. These signals act on distinct Toll-like receptors (TLR) to control DC maturation, e.g., viral RNA and poly IC on TLR3, mycobacterial extracts on TLR2 and TLR4, imidazoquinolines on TLR7 and bacterial DNA and CpG deoxyoligonucleotides on TLR 9 (reviewed by Kawai and Akira).[10] In addition, innate cell types such as NK cells,[11,12] γδT cells[13] and NKT cells[14] can induce the maturation of DC.

Adaptive immunity maturation signals are composed of CD40-CD40 ligand interactions, antigen-antibody complexes and Fc receptors. The natural ligand for CD40 is CD154/CD40L, a trimeric TNF-like molecule that is expressed mainly on activated Th cells.[15] Ligation of CD40 on DC induces maturation that is reflected by the production of high levels of IL-12, enhanced T cell stimulatory capacity and improved DC survival.[16-18] The triggering of CD40 on DC empowers these cells to activate naïve CD8+ CTL.[19] It has been shown that CD40L has a number of effects on the different blood DC subsets. For example, plasmacytoid DC activated by CD40L induce Th2 differentiation, whereas myeloid DC activated by CD40L induce Th1 differentiation.[20] CD40 ligation bypasses the need for CD4+ T cell help,[21] although CD40 ligation cannot replace CD4+ T cell help for CD8+ CTL responses under certain conditions.[22] Ag-Ab immune complexes are able to induce DC maturation *in vitro*.[23-25] This enables DC to prime peptide-specific CD8+ CTL *in vivo*, independently of CD4+ Th cells.[25]
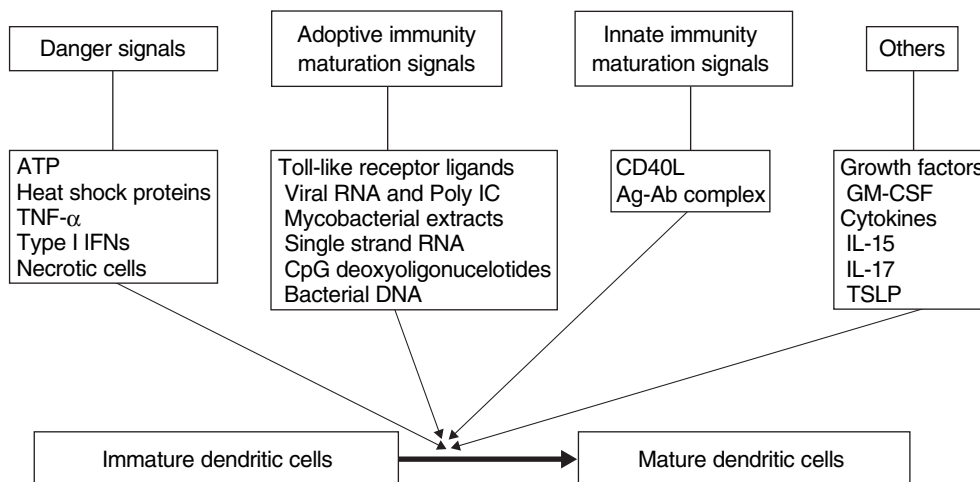
Fig. 2 Dendritic cell maturation signals

HAPTENS AS A MATURATION SIGNAL

We have previously reported that murine LC up-regulate their expression of class II MHC antigen and antigen presenting function after hapten painting to the skin.[26] Indeed, chemicals that simply irritate the skin rather than sensitize animals cannot induce this phenomenon.[26] In addition, we have demonstrated that the application of haptens to murine skin is accompanied by the up-regulation of several co-stimulatory molecules on LC, including CD40, CD54, CD80, and CD86.[27] In a different study, Enk *et al*. demonstrated a crucial role for IL-1β secreted by the LC themselves, after exposure to hapten application.[28]

In addition to these *in vivo* studies, we have demonstrated *in vitro* that purified human monocyte-derived DC (MoDC) respond to haptens such as NiCl$_2$ and dinitrochlorobenzen (DNCB), but not to irritants such as benzalkonium chloride (BC) or sodium lauryl sulfate (SLS).[29] The mechanism by which this occurs involves the increased expression of CD54, CD86, and HLA-DR, and an increased production of proinflammatory cytokines. Furthermore, using Langerhans cell-like DC induced from peripheral blood monocytes in the presence of transforming growth factor β1 (TGF-β1), GM-CSF, and IL-4 (MoLC),[30] we have shown that *in vitro* treatment with haptens can induce the same phenotypic and functional changes in MoLC that are seen in epidermal LC during the initiation phase of contact hypersensitivity reaction *in vivo*,[31] e.g., the down-regulation of E-cadherin[32] and CLA,[33] the induction of MMP-9 expression,[34] and the augmentation of some of β1-integrins,[35,36] CD44 and some of its variants,[37] as well as the expression of CCR7 mRNA that enable LC to respond to MIP-3β.[38-40]

HOW DO HAPTENS INDUCE THE MATURATION OF DC?

A number of studies have addressed the question of how different haptens stimulate MoDC to acquire a mature phenotype. Kuhn *et al*.[41] demonstrated that strong sensitizers could induce the formation of phosphotyrosine in MoDC *in vitro*, suggesting that tyrosine phosphorylation plays an important role in the activation of MoDC by haptens. In addition, Arrighi *et al*. have recently reported that 2,4-dinitrofluorobenzene (DNFB) and NiSO$_4$ induce p38 MAPK phosphorylation, and that the augmentation of CD80 and CD83 induced by NiSO$_4$ is partially suppressed by a p 38 MAPK inhibitor.[42]

We have also examined the role of MAPKs and NF-κB in DC stimulated with two representative haptens, NiCl$_2$ and DNCB.[43] Human MoDC stimulated with DNCB induced the phosphorylation of p38 and SAPK/JNK, while NiCl$_2$ induced that of p44/42 ERKs, p38, and SAPK/JNK. In addition, NiCl$_2$ phosphorylated IκB and activated NF-κB. In contrast, primary irritants such as benzalkonium chloride (BC) and sodium lauryl sulfate (SLS), did not activate these signal transduction pathways. These data indicate that NiCl$_2$ and DNCB stimulate different signal transduction pathways in MoDC, and subsequently induce different phenotypic and functional changes.

P38 MITOGEN-ACTIVATED PROTEIN KINASE IS ACTIVATED BY THE REDOX IMBALANCE INDUCED BY HAPTENS

We examined the mechanism by which p38 MAPK is activated by sensitizers. Changes in the intracellular reduced/oxidized glutathione ratio (GSH/GSSG) are crucial reduction-oxidation (redox) events, which transduce oxidative stress into the modulation of MAPKs and various transcription factors related to growth, differentiation, and death.[44,45] Indeed, p38 has been shown to be phosphorylated by oxidizing

conditions via ASK1 modulation.[46] We therefore measured the ratio of the oxidized (GSSG) *vs.* reduced (GSH) form (GSH/GSSG) of cellular glutathione in MoDC stimulated with various concentrations of haptens, $NiCl_2$, $MnCl_2$, DNCB, thimerosal, and formaldehyde (HCHO), and non-haptens such as $ZnCl_2$, SLS, and BC. The results clearly demonstrated that all the haptens, but none of the non-haptens, reduced the GSH/GSSG ratio in MoDC, accompanied by phosphorylation of p38. In addition, treatment with the antioxidant, N-Acetyl-L-cysteine (NAC), which suppressed the reduction of the GSH/GSSG ratio in MoDC, abrogated both the phosphorylation of p38 and the augmentation of CD86 expression by MoDC. These data suggest that the GSH/GSSG imbalance plays a crucial role in triggering DC maturation by sensitizers.

THE ROLE OF ATP RELEASED BY HAPTEN-TREATED KERATINOCYTES IN THE ACTIVATION OF DC

The release of nucleotides such as ATP or ADP can be triggered by various environmental stimuli including mechanical shear forces, stretch, changes in osmolarity, oxidative stress, and microbial products.[47-53] Indeed, Mizumoto *et al.* have recently reported that various irritant chemicals induce ATP release from keratinocytes.[54] Extracellular nucleotides, in turn, bind to the purinergic type 2 receptors and regulate cell death, growth, differentiation, migration, and cytokine production.[55-58] DC also express a variety of purinergic receptors and respond to ATP by increasing the membrane expression of CD54, CD80, CD86, and CD83. This slightly reduces the endocytic activity of DC, and augments their capacity to promote the proliferation of allogeneic naïve T lymphocytes. Moreover, ATP enhances LPS- and soluble CD40 ligand-induced CD54, CD86, and CD83 expression[59] Conversely, ATP markedly and dose-dependently inhibits LPS- and soluble CD40 ligand-dependent production of IL-1α, IL-1β, TNF-α, IL-6, and IL-12, whereas IL-1 receptor antagonist and IL-10 production is not affected. As a result, T cell lines generated from allogeneic naive CD45RA (+) T cells primed with DC matured in the presence of ATP, produced lower amounts of IFN-γ and higher levels of IL-4, IL-5, and IL-10 compared with T cell lines obtained with LPS-stimulated DC.[59,60] Grabbe *et al.* have previously demonstrated that skin irritation is required for reactive haptens to produce allergic contact hypersensitivity responses.[61] Indeed, Mizumoto *et al.* have demonstrated that dinitrofuorobenzene,a representative hapten, induces ATP release from keratinocytes.[54] Thus, ATP released by keratinocytes treated with haptens may contribute to the activation of LC in the initiation phase of the allergic contact hypersensitivity reaction.

THE MIGRATION OF DC TO THE REGIONAL LYMPH NODES

Activated DC exhibiting augmented expression of various co-stimulatory molecules and increased production of proinflammatory cytokines start to migrate via the afferent lymphatics to the draining lymph nodes where they present haptens to naïve T cells (below). In order to migrate to the lymph nodes, DC down-regulate E-cadherin which functions in anchoring epidermal DC or Langerhans cell (LC),[32,62] produce MMP-9 that is required for passing through the basement membrane,[34,63] and increase their expression of chemokine receptor CCR7 that induces the migration toward CCL-19 (MIP-3β) and CCL-21 (SLC)[39,64] and the consequent lymph node migration of DC is controlled by signals that are usually found at sites of inflammation; these include lipid mediators such as cysteinyl leukotrienes[65] and prostaglandins E2,[66-68] and the ADP-ribosyl cyclase CD38.[69] It has been recently reported that the CCR8 receptor for the chemokine CCL-1 (also known as I-309 in human subjects and TCA-3 in mice) acts in concert with CCR7 during emigration of DCs from the skin and lung.[70]

INDUCTION OF EFFECTOR T CELLS AND REGULATORY T CELLS IN THE DRAINING LYMPH NODES

DC do not only stimulate naïve T cells, but also influence the differentiation of T cells into Th1, Th2, Th3 or T regulatory cells. The signal to skew emerging T cell responses is transmitted as signal 3, and is composed of cytokines and other molecules. Cytokine production by DC is subject to a tight regulation, which is particularly relevant in the case of IL-12, the prototypic Th1-polarizing cytokine. IL-12 production is elicited by most pathogens and is potently boosted by activated Th cells through CD40L;[71] however, it is not induced by some maturation stimuli, such as TNF-α, IL-1β, cholera toxin or FasL. IL-12 production can be modulated by cytokines and mediators present during the induction of maturation.[72] Thus, IFN-γ and even IL-4 enhance IL-12 production induced by the appropriate stimuli, while PGE2 and IL-10 exert an inhibitory effect. Moreover, IL-12 production by DC is restricted to a narrow temporal window after the induction of maturation.[73] The capacity to induce Th2 responses is a property of DC that does not produce Th1-polarizing cytokines. A substantial portion of the CD4+ lymphocytes that are recruited in allergic contact dermatitis (ACD) skin release IFN-γ and belong to the Th1 subset. Hapten-specific Th0 as well as Th2 cells are also represented, and they may effectively cooperate in the amplification of the inflammatory response.[74-76]

DC are also able to stimulate CD8+ T cells. CD8+ T lymphocytes are likely to be the major effector population in response to chemicals during ACD. CD8+ T cells (both type 1 and type 2) can exert direct cytotox-
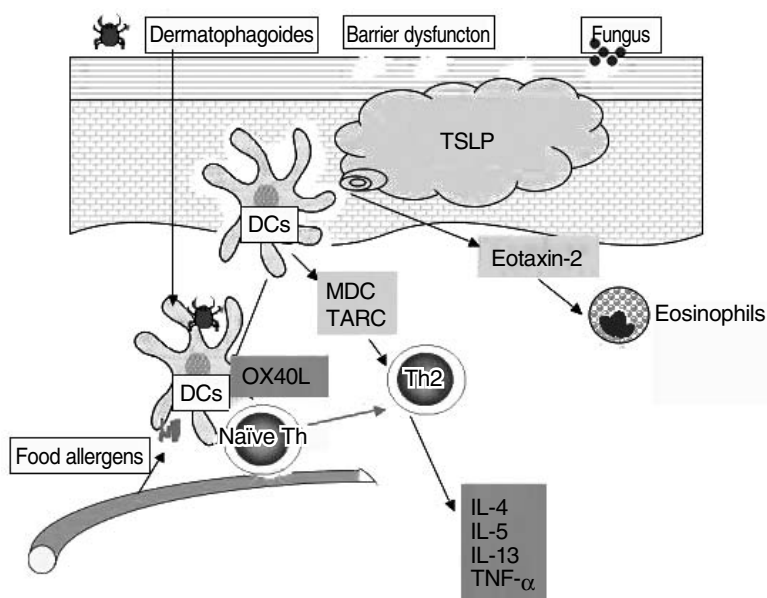
Fig. 3 Dendritic cells in atopic dermatitis

icity against resting resident cell populations, in particular keratinocytes, and release cytokines upon antigen encounter.[77] In contrast, killing by CD4+ Th1 cells requires the prior treatment of keratinocytes with IFN-γ to stimulate the expression of MHC class II molecules and ICAM-1. Moreover, IFN-γ up-regulates Fas expression and renders keratinocytes susceptible to FasL-mediated cytotoxicity, which predominates in Th1 cells.[77,78]

ATOPIC DERMATITIS AND ASTHMA (Fig. 3)
THE ROLE OF DC IN TH1/TH2 DEVIATION
After the activation of T cells, a crucial step in the additional tailoring of adaptive immunity is their differentiation into either Th1 or Th2 cells. DC influence Th1/Th2 deviation depending on not only their lineage, but also the microenvironment of cytokines and/or inflammatory mediators and maturation status. The most important signal responsible for Th differentiation is the cytokine profile present at the time of T-cell stimulation. For example, a Th1-inducing profile is represented by IL-12 family members and IFN-a, whereas a Th2-inducing profile is represented by IL-4 and IL-10.

In humans, myeloid DC and plasmacytoid DC subsets were initially called DC1 and DC2 respectively, referring to their capacity to preferentially induce the differentiation of naïve T cells into Th1 and Th2 effector cells.[20] After CD40 triggering, the subpopulation of DC derived from monocytes in humans and referred to as DC1, would provoke a type 1 response by producing high amounts of IL-12. The other subpopulation, derived from plasmacytoid DC in humans and defined as DC2, produces little IL-12 and could induce a type 2 response.[68] However, plasmacytoid

DC can prime both type 1 and type 2 responses depending on the activation signal they received,[79] demonstrating that the phenotype of a given DC subset cannot be considered as a marker of functionality for the activation of Th1 *vs.* Th2 cells.

THE TH2 RESPONSE INDUCED BY DC IN ATOPIC DISORDERS
Two new mediators have recently been identified that may act on DCs during allergy to induce Th2 responses. The first is histamine, which, when added to monocyte-derived DCs in the presence of lipopolysaccharide, reduces IL-12 production and the induction of Th1 responses while enhancing IL-10 production and Th2 development.[80-82]

A second mediator is human thymic stromal lymphopoietin (TSLP), which is of epithelial origin and is a DC-based inducer of "inflammatory" Th2 responses. TSLP is a novel IL-7-like cytokine,[83] while the TSLP receptor (TSLPR) is heterodimeric, consisting of the IL-7R- chain and a common γ receptor-like chain (TSLPR-γ).[84-86] Surprisingly, TSLP was shown to be highly expressed by keratinocytes in atopic dermatitis lesions and its expression was associated with the migration and activation of Langerhans cells. This suggests for the first time that TSLP might be an early trigger for DC-mediated allergic inflammation.[87] Moreover, TSLP-activated DC induced robust proliferation of naive allogeneic CD4+ T cells, which subsequently differentiated into Th2 cells. These Th2 cells produced the allergy-promoting cytokines IL-4, IL-5, IL-13, and TNF-α, but did not produce IL-10 or interferon-γ.[87] Recently, it has been demonstrated that TSLP induces human myeloid DC to express the TNF superfamily protein OX40L at both the mRNA

and protein level.[88] The expression of OX40L by TSLP-DC was shown to be important for the induction of inflammatory Th2 cells, as blocking OX40L with a neutralizing antibody inhibited the production of Th2 cytokines and TNF-α, and enhanced the production of IL-10, by the CD4+ T cells.[88] In addition to atopic dermatitis, a more recent study showed by *in situ* hybridization that TSLP expression was increased in asthmatic airways and correlated with both the expression of Th2-attracting chemokines and with disease severity,[89] thus providing the first link between TSLP and human asthma.

Finally, Yoo *et al.* demonstrated that mice engineered to overexpress TSLP in their skin developed atopic dermatitis characterized by eczematous skin lesions containing inflammatory cell infiltrates, a dramatic increase in circulating Th2 cells and elevated serum IgE.[90] In addition, Zhou *et al.* showed that lung-specific expression of a TSLP transgene induced allergic airway inflammation (asthma) characterized by a massive infiltration of leukocytes (including Th2 cells), goblet cell hyperplasia, and subepithelial fibrosis, as well as increased serum IgE levels.[91]

CONCLUSION

DC play a key role in the initiation of the immune response. Derived from bone marrow precursors, DC colonize the skin and bronchial mucosa where they form a tight surveillance network for the immune system. Once haptens or allergens enter the epithelia, DC react with these antigens and stimulate the acquired immune response. The magnitude and characteristics of the response is determined during this process. DC therefore play a crucial role in the pathogenesis of allergic diseases.

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