

# Fixed Drug Eruption: A Prototypic Disorder Mediated by Effector Memory T Cells

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Effector memory T cells are uniquely specialized to mediate protective immunity. However, their excessive activation may result in the development of organ-specific inflammatory diseases, which have not been extensively studied. Fixed drug eruption (FDE), a localized variant of drug-induced dermatoses characterized by relapse in the same location, is a prototypic disorder mediated by excessive activation of effector memory T cells, which are resident in the lesional epidermis. A variety of clinical and pathologic features uniquely observed in FDE lesions can be explained by the presence of CD8<sup>+</sup> intraepidermal T cells with the effector memory phenotype in the FDE lesion. This review focuses on how these T cells are generated, retained in the epidermis, and activated to cause epidermal damage.

## Introduction

A unique feature of many inflammatory skin diseases is that each preferentially affects distinct sites on the body; the disease-specific distribution patterns of skin lesions can be used to diagnose these skin diseases. Although the patterns theoretically could be observed in other organ-specific inflammatory disorders, it is difficult, unfortunately, to determine the disease-specific distribution patterns in other organs. Thus, the factors that determine the disease-specific distribution patterns of inflammatory lesions can be analyzed only in skin diseases. Among them, fixed drug eruption (FDE) is unique in that lesions recur in the exact same sites when the causative drugs are administered. Another advantage of FDE as a

disease model for gaining insight into the pathomechanism of inflammatory diseases is that the precise sequence of events leading to the destruction of target tissues can be examined from the beginning. This is because reproduced FDE lesions can only start after rechallenging with the causative drug. In contrast, in other inflammatory skin diseases, initiating events occur well before patients become symptomatic, and most changes observed in the lesions reflect downstream events that have occurred as the result of immune activation and skin inflammation. Thus, a critical initial event needed for complete evolution of the FDE lesions could be elucidated only by the sequential investigation of FDE lesions reproduced by a clinical challenge with the causative drug. Based on these findings of biopsy specimens thus sequentially obtained, we have suggested that intraepidermal T cells with the effector memory phenotype resident in FDE lesions have a direct pathogenic role in localized epidermal damage [1,2]. FDE provides an excellent model in which to characterize the factors that regulate the generation and maintenance of effector memory CD8<sup>+</sup> T cells.

## Clinical Manifestations

FDE is a cutaneous drug reaction characterized by a recurrent onset of a solitary or small number of well-circumscribed, round, and/or oval lesions in the same sites with each administration of the causative drug. The appearance of these lesions is often preceded and/or accompanied by itching or burning. FDE lesions flared by administering the causative drug typically present as edematous, dusky-red macules/plaques on the skin and/or mucous membrane. Lesions usually appear within 30 minutes to 8 hours after drug intake (mean time, 2.1 hours) [3]. Some lesions may evolve into bullous and generalized eruptions mimicking Stevens-Johnson syndrome or toxic epidermal necrolysis (TEN), both of which are potentially life-threatening, severe drug eruptions. These FDE lesions become more numerous and more severe with repeated exposure. New lesions often occur at the same sites as the previously traumatized or inflamed skin, such

as insect bite, burn, and venipuncture sites [4]. Systemic symptoms such as fever and malaise are usually absent. Although FDE lesions can occur anywhere on the skin or mucous membrane, the most commonly affected locations are the lip, palms, soles, glans penis, and groin areas. After discontinuation of the causative drugs, these lesions typically resolve over several days, leaving hyperpigmentation. However, in some cases, lesions continue to increase in size and number several days after withdrawal of the causative drug. Thus, the shade of the hyperpigmentation tends to become darker with each succeeding exacerbation. In these patients, hyperpigmented macules/plaques remain at the lesion site for months to years.

Although drugs causing FDE differ from country to country, depending on drug availability, the most common causative drugs are pseudoephedrine, trimethoprim, tetracycline, barbiturates, sulfonamide, mefenamic acid, acetylsalicylic acid, phenolphthalein, ibuprofen, and oxyphenbutazone. Most FDE lesions occur with orally administered rather than injected drugs.

FDE lesions initially appear after susceptible patients are sensitized to a particular drug. Such sensitization is thought to occur more easily in patients intermittently receiving the causative drugs rather than those receiving them continuously. Thus, the period required for sensitization is highly variable, depending on patients, and ranges from a few weeks to several years. After each exacerbation, some FDE lesions fail to recur despite administration of the causative drug, which is known as a *refractory period* [5]. The duration of this period is also variable, lasting from a few weeks to several months.

FDE lesions can be reproduced upon administration of related drugs/agents with chemical structures similar to the inducing, offending drug, which is referred to as *cross-reactivity*. However, in some patients, drugs/agents with totally different chemical structures can activate the FDE lesions at exactly the same sites as the inducing, offending drug, a phenomenon known as *polysensitivity* [6].

Many reports have described patients with typical FDE but no significant history of drug intake preceding the eruptions. Some cases of recurrent exacerbations of the FDE lesions without significant history of drug intake may be attributable to nonspecific exogenous factors. Nonmedical factors, such as food and UV irradiation, have been reported to precipitate exacerbations of FDE lesions [7,8]. The FDE-like lesions precipitated by ingesting a particular food can be termed *fixed food eruption*, although it is unclear whether the agents inducing the lesions are drugs or food in these cases [9,10].

Spontaneous resolution of FDE after several years has been known to occur. In some patients, despite the continued administration of the causative drug, the pigmented lesions eventually disappear. This may indicate that such patients have been spontaneously desensitized to the causative drug. In this regard, Kelso and Keating [11]

reported successful desensitization for treatment of FDE to allopurinol. After a desensitization schedule, beginning with very low doses of the drug with gradual increases in the dose, together with low-dose prednisolone, the patient had the drug successfully reintroduced without recurrence of the FDE lesions.

## Variants of Fixed Drug Eruption

Several less common clinical types of FDE have been reported. Although bullous lesions usually can be seen at an advanced stage in a mild to severe form of FDE in which erythematous patches/plaques are associated with central erosions or bullae, some patients develop multiple bullous lesions involving the entire body. This extensive form of FDE is often associated with systemic manifestations, such as malaise, high fever, nausea, and arthralgia. Because most of these extensive variants do not leave typical hyperpigmentation, Shelley and Shelley [12] described a distinctive nonpigmenting variant of FDE consisting of symmetric, tender, large, erythematous plaques often associated with systemic symptoms. In typical nonpigmenting FDE, large, erythematous, well-circumscribed plaques are symmetrically located in the axillae, groin, pubis, flanks, and intergluteal fold. The clinical features of the nonpigmenting variants of multiple FDE closely resemble those of Stevens-Johnson syndrome or TEN.

## Histology

Histologic examination of biopsy specimens obtained from FDE lesions before rechallenge showed a small number of lymphocytes aligned along the epidermal side of the dermoepidermal junction and minimal perivascular lymphocytic infiltrates (Fig. 1A) [1]. The epidermis appeared normal except for the presence of lymphocytes. Two to 3 hours after rechallenge, at which time irritation and slight erythema appeared in the previously involved sites, lymphocytes originally adhering to the basal layer moved upward to the lower half of the epidermis while preserving the epidermal architectures (Fig. 1B) [1]. A perivascular lymphoid infiltrate remained confined to immediately surrounding blood vessels in the upper dermis. Typical changes of FDE lesions consisting of hydropic degeneration of the basal layer and the extensive exocytosis of lymphoid cells were seen at 24 to 48 hours. The extent of epidermal damage seen at the peak in FDE lesions is highly variable, depending on the lesion examined, and ranges from confluent epidermal necrosis resembling TEN to spongiotic epidermis. Thus, confluent epidermal necrosis—said to be specific for TEN but not FDE—occasionally can be seen in FDE lesions and is largely a function of the site of lesions biopsied. Biopsy specimens obtained from the FDE lesions at 5 days or later after onset showed irregularly thickened epidermis

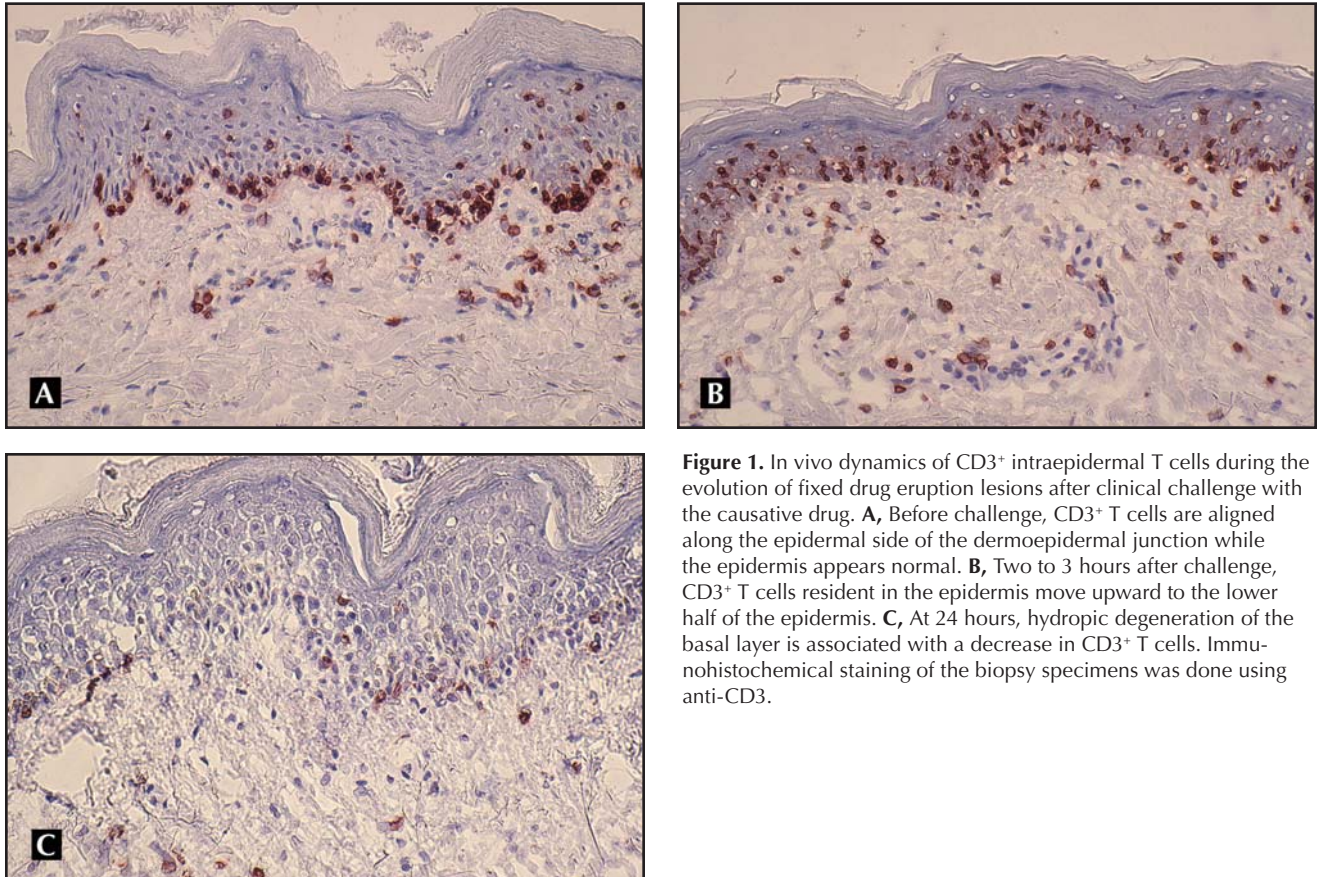


**Figure 1.** In vivo dynamics of CD3<sup>+</sup> intraepidermal T cells during the evolution of fixed drug eruption lesions after clinical challenge with the causative drug. **A**, Before challenge, CD3<sup>+</sup> T cells are aligned along the epidermal side of the dermoepidermal junction while the epidermis appears normal. **B**, Two to three hours after challenge, CD3<sup>+</sup> T cells resident in the epidermis move upward to the lower half of the epidermis. **C**, At 24 hours, hydropic degeneration of the basal layer is associated with a decrease in CD3<sup>+</sup> T cells. Immunohistochemical staining of the biopsy specimens was done using anti-CD3.

and multiple individual or grouped necrotic keratinocytes at all levels of the epidermis with a sparse upper dermal lymphocytic infiltrate, indicating the restoration phase of the FDE reaction.

## Pathomechanisms

### Effector cells in the lesional skin

A potential role for T cells recruited from peripheral blood is well recognized from the histopathology of various inflammatory diseases. In FDE, T cells abundantly detected along the dermoepidermal junction in the established lesions have been implicated in the pathogenesis. The prevailing dogma, shaped by the histopathologic observations of established FDE lesions, that the infiltrating T cells under observation are directly involved in epidermal injury should be viewed with some caution, because an alternative possibility is that these T cells would be nonspecifically recruited from the circulation only late in the course of an ongoing immune response. If this is true, these T cells alternatively may serve to alleviate excessive immune responses. In this regard, observations that the lesional epidermis harbors significant numbers of lymphocytes without causing epidermal damage before clinical challenge may offer an important clue as to T cells' role in FDE pathogenesis. Significant numbers of CD8<sup>+</sup> T cells are aligned along the epidermal side of

the dermoepidermal junction in the FDE lesion (Fig. 1A) [1]. This cell's role was overlooked in the past, probably because histopathologic and immunohistochemical studies of FDE largely have been undertaken using specimens prepared from the fully developed lesions when early biologic events largely have been passed. The abundance of T cells subsequently recruited from the circulation into the site of inflammation would make these intraepidermal T cells resident in the lesion less readily identified by routine histology. Rather, intraepidermal T cells that have participated in the early phase of the inflammatory cascade may have been decreased in number in the fully developed lesions (Fig. 1C) [1]. These considerations led us to investigate intraepidermal T cells detected in the lesional skin that clinically have returned to normal over a prolonged period of time after clinical resolution. This is called a *resting FDE lesion*, because these T cells would persist in a quiescent state in the lesion unless the causative drug was administered.

### Characterization of intraepidermal T cells

Intraepidermal T cells identified in the resting FDE lesions were composed of a phenotypically homogeneous population that expresses T-cell receptor (TCR)- $\alpha\beta$ , CD3, CD8, CD45RA, and CD11b but not CD27 and CD56 [1]. In contrast, T-cell populations isolated from normal epidermis consisted of a variable ratio of CD4<sup>+</sup>, CD8 $\alpha\alpha$ <sup>+</sup>

(homodimeric  $\alpha\alpha$  form of CD8), and CD4<sup>+</sup> CD8<sup>+</sup> T cells [13]. This phenotype of T cells most closely resembles that of effector memory T cells [14,15,16••], although some differences were found in both populations. CD8<sup>+</sup> intraepidermal T cells constitutively express cutaneous lymphocyte-associated antigen (CLA) and  $\alpha_E\beta_7$ , whereas effector memory T cells are negative for CLA expression. CLA expression is usually detected in most infiltrating T cells in the dermis, whereas  $\alpha_E\beta_7$  expression is confined to CD8<sup>+</sup> intraepidermal T cells [2]. The concomitant expression of CLA and  $\alpha_E\beta_7$  is an essential property necessary for skin homing and selective retention within the epidermis, respectively. Thus, the predominance of CD8<sup>+</sup> intraepidermal T cells with the skin-homing phenotype is a unique feature of resting FDE lesions.

Our quantitative polymerase chain reaction analysis of intraepidermal T cells isolated from resting FDE lesions demonstrated that they use a very limited range of TCR V $\alpha$  and V $\beta$  gene families compared with peripheral blood T cells isolated from the same patients [17]. These results indicate that these intraepidermal T cells can recognize a limited set of antigens. However, antigens/ligands to which intraepidermal T cells are directed have not been fully characterized.

Our previous study demonstrated that CD8<sup>+</sup> intraepidermal T cells expanded *in vitro* displayed a cytolytic activity against natural killer (NK)-sensitive or NK-resistant tumor cells and cultured keratinocytes when activated via the CD3/TCR complex, although they were not constitutively cytolytic, unlike murine  $\gamma\delta$ <sup>+</sup> intraepidermal T cells [17]. This finding is consistent with clinical observations that significant epidermal damage can be seen only in the lesion harboring these intraepidermal T cells when the causative drug is given [1,2]. Our intracellular cytokine assay showed that the vast majority (> 80%) of CD8<sup>+</sup> intraepidermal T cells freshly prepared from the resting FDE lesions produced interferon (IFN)- $\gamma$  upon stimulation with phorbol myristyl acetate/ionomycin, whereas less than 1% of T cells produced interleukin (IL)-4 [1]. The proportion of CD8<sup>+</sup> T cells capable of producing IFN- $\gamma$  was much higher in intraepidermal T cells than in peripheral blood counterparts from the same patients [1]. To further confirm that CD8<sup>+</sup> intraepidermal T cells produce IFN- $\gamma$  in the FDE lesion upon stimulation, we performed *in vivo* reverse transcriptase polymerase chain reaction studies using sequentially obtained biopsy specimens. This study clearly demonstrated that CD8<sup>+</sup> intraepidermal T cells resident in the FDE lesions were induced to produce IFN- $\gamma$  mRNA and protein with much faster kinetics than their dermal and peripheral counterparts [1]. The rapid (3 hours after challenge) and strong induction of IFN- $\gamma$  mRNA and protein was confined to CD8<sup>+</sup> intraepidermal T cells and preceded the epidermal invasion of recruited T cells. These results indicate that CD8<sup>+</sup> intraepidermal T cells are the major effector cells

for epidermal injury seen in the established FDE lesions. The lack of an antigen-induced proliferative response by intraepidermal T cells but with the retention of a strong effector cytokine or cytotoxic response is consistent with these T cells having a role in mediating epidermal injury. Although this type of effector memory T cell also has been demonstrated in other inflammatory lesions, such as the lung in animals [18,19], the dynamics of intraepidermal T cells in the course of disease and the balance among various cell types changing with time in humans can be investigated only in the evolution of FDE lesions. Therefore, we address in sequence a series of questions concerning the inflammatory process mediated by intraepidermal T cells that leads to epidermal damage, based on the knowledge obtained from studies of evolving FDE lesions.

### How do intraepidermal T cells migrate to the lesional skin?

In this regard, we previously demonstrated that FDE lesions initially appeared at exactly the same site of a previous trauma, such as burn scars, insect bites, previous venipuncture sites, or viral infection sites [4]. Migration of innate immune cells and/or T cells to sites of microbial infections or trauma is particularly valuable in mediating protective immune responses (Fig. 2). Dendritic cells or  $\gamma\delta$ <sup>+</sup> T cells are recruited into the airway epithelium during the inflammatory response to a broad spectrum of stimuli (eg, viral infections). Antigen-specific CD8<sup>+</sup> T cells with the effector memory phenotype also persist in the upper respiratory tract after influenza virus infection [20]. These findings suggest that viruses are perhaps the most likely infective candidates for a role in the emergence and activation of these intraepidermal T cells. In support of this possibility, CD8<sup>+</sup> T cells persist in association with CD68<sup>+</sup> macrophages in the healed herpes simplex lesions for a prolonged period [21,22]. These virus-specific CD8<sup>+</sup> memory T cells constitutively express high levels of the early activation marker CD69 despite the absence of detectable viral protein [23], a finding observed in CD8<sup>+</sup> intraepidermal T cells [1]. Another important property of these T cells with the effector memory phenotype is their inherent ability to cross-react with other antigens, such as allogeneic major histocompatibility complex antigens [24], and to respond to nonspecific stimuli, such as cytokines, in a bystander manner in the absence of TCR ligation. Effector memory T cells retained in peripheral tissues are also characterized by the expression of lymphocyte function-associated antigen-1 (LFA-1). A murine study of the *in vivo* migration and localization of adoptively transferred CD8<sup>+</sup> T cells demonstrated that the migration and subsequent retention of the T cells in the lungs depends on their expression of LFA-1 [25•].

Consistent with this finding, we previously demonstrated that drug-induced upregulation of intercellular

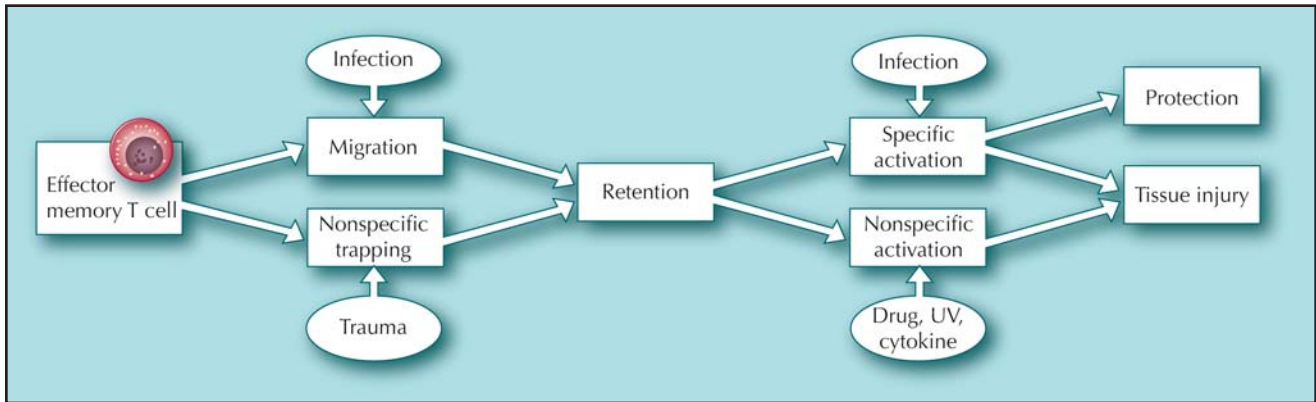


**Figure 2.** The protective or deleterious role of effector memory CD8<sup>+</sup> T cells resident in epithelial tissues. Effector memory T cells expressing epithelial tissue-homing receptors initially migrate to the infection site and subsequently are retained in the tissue. Some activated effector memory T cells are also nonspecifically trapped within inflamed sites and retained there. Upon re-exposure to pathogens, they serve to protect epithelial tissues from the pathogens. However, once they are cross-reacted with drugs or nonspecifically activated, they display a deleterious effect on the tissue.

adhesion molecule-1 expression on the lesional keratinocytes may be part of an essential pathway that facilitates the recruitment of additional CD8<sup>+</sup> T cells into the epidermis [26]. In support of this possibility, adherence of these T cells in the lung is significantly reduced by neutralization of LFA-1 or by intercellular adhesion molecule-1 deficiency [27•,28]. These findings could be interpreted such that effector memory T cells specifically retained in epithelial tissues persist in an activation state so that they can immediately acquire effector functions in response to a variety of stimuli. Thus, we hypothesize that CD8<sup>+</sup> effector memory T cells retained in the healed sites of viral infections or a previous trauma could have originally evolved to protect epithelial tissues from additional insults but once cross-reacted with drug antigens or accidentally activated with nonspecific stimuli would cause localized injury (Fig. 2). If this hypothesis is valid, one could argue that virus-specific T cells activated elsewhere may be nonspecifically trapped in the inflamed skin and retained in the lesions; this provides an explanation for why FDE lesions often appear at exactly the same site of a previous trauma.

#### How are intraepidermal T cells retained in the lesions?

Our previous study demonstrated that CD8<sup>+</sup> intraepidermal T cells persist in a stable population of effector memory T cells for at least 4 years in the absence of an encounter with cognate drug antigen in the FDE lesions [29]. Such selective, long-term retention of effector memory T cells within the lesional skin may depend on factors that can not only maintain CD8<sup>+</sup> intraepidermal T cells in a primed memory state that enables their subsequent activation but also prevent activation-induced death of these cells. In view of the fact that IL-15 is a growth factor for memory T cells and NK cells and protects T cells from IL-2-induced apoptosis [30•], IL-15 is the most likely candidate for such survival factors. Our recent study demonstrated that IL-15 immunoreactivity is observed in the

epidermis and particularly localized to the basal layer, at which CD8<sup>+</sup> intraepidermal T cells expressing CD122 (IL-2/15R $\beta$ ) are preferentially detected [29]. IL-15 has been shown to induce NK-associated molecules on these CD8<sup>+</sup> T cells [31]; consistent with this finding, our studies of the evolution of FDE lesions showed that some CD8<sup>+</sup> intraepidermal T cells acquire an NK-like phenotype after clinical challenge with the causative drug [29]. These results indicate that CD8<sup>+</sup> intraepidermal T cells can be maintained in the lesional epidermis containing high levels of survival factors—IL-15—by being prevented from undergoing apoptosis. Also in the lung environment, IL-15 expressed in bronchial epithelial cells plays an important role in T-cell- and NK-cell-mediated inflammation [32], and loss of IL-7R and IL-15R expression is associated with disappearance of CD8<sup>+</sup> memory T cells in the respiratory tract after influenza infection [33].

Because we empirically know that intermittent rather than continuous administration of the causative drug can have a positive impact on the development of FDE lesions, the persistence of effector memory T cells in the lesions may depend on the factors that enable these cells to rest in a quiescent state permitting subsequent reactivation. Thus, the ability of IL-15 and other factors present in the evolving FDE lesions to induce these intraepidermal T cells to rest may be an essential mechanism that enables their subsequent reactivation and expansion upon re-exposure to the causative drug. If these intraepidermal T cells were continuously activated via TCR ligation, they would be prone to death, resulting in desensitization or spontaneous resolution of FDE lesions.

#### How is extensive epidermal damage prevented in fixed drug eruption?

Although the clinical and histologic features of a bullous variant of multiple FDE closely resemble those of TEN, the subsequent evolution of the two diseases is quite different.

Many FDE lesions resolve spontaneously upon discontinuation of the causative drug, whereas extensive epidermal necrosis rapidly extends to involve the whole body in TEN. Thus, it is important to investigate how disease progression to TEN is prevented in FDE. Investigations into the difference in histologic changes of the evolving lesions and in serum cytokine levels between the two diseases may provide an important clue to factors that determine whether lesions spontaneously resolve or progress to TEN.

Our recent study of biopsy specimens sequentially obtained from FDE lesions has demonstrated that in the fully evolved FDE lesions (at 24 hours after challenge), the presence of CD8<sup>+</sup> intraepidermal T cells resident in the lesions is diluted by the prominent influx of CD4<sup>+</sup> T cells and that an inverse relationship exists between the frequency of CD4<sup>+</sup> T cells in the fully evolved lesions and the extent of epidermal injury [29]. In particular, CD4<sup>+</sup>CD25<sup>+</sup>forkhead box P3<sup>+</sup> T-regulatory cells (Tregs) are detected exclusively in the fully evolved FDE lesions [29]. Although Tregs were also found in TEN lesions, the ratio of Tregs to CD8<sup>+</sup> T cells within the epidermis of the fully evolved FDE lesions was higher than that observed in TEN lesions. These results indicate that Tregs could exert their suppressive functions by inhibiting excessive activation of the CD8<sup>+</sup> T cells and limiting further migration of pathogenic T cells. Our flow cytometric analysis of CD4<sup>+</sup> T cells freshly isolated from the fully evolved FDE lesion showed that greater than 70% of CD4<sup>+</sup> T cells expressed CD25 and that they have the capacity to produce IL-10 upon in vitro stimulation [34]. Although it remains to be determined whether their suppressive function is mediated by cytokines such as IL-10 and transforming growth factor- $\beta$  or through a contact-dependent mechanism, the influx of Tregs into the epidermis during the evolution could reflect an appropriate response that may contribute to homeostatic control of potentially harmful immune reactions mediated by CD8<sup>+</sup> intraepidermal T cells. In TEN, the defective function of Tregs in the peripheral blood has proven to be of greater importance in the pathology, irrespective of whether the Tregs are increased or decreased in number in the lesions (Takahashi, unpublished data).

This finding was also confirmed by our analysis of serum cytokine levels sequentially obtained from a patient with a severe form of nonpigmenting FDE before and after clinical challenge. Although tumor necrosis factor- $\alpha$  levels reached their maximum at 5.5 hours and remained elevated at 5.5 to 9 hours, IL-8 levels were decreased at 5.5 and 7 hours and were associated with a gradual increase in IL-6 and IL-10 levels. IFN- $\gamma$  levels were also gradually increased at 3 to 9 hours, but it was not possible to continue a time-course study without systemic prednisolone because the eruption became generalized and the temperature rose. IL-10 levels detected in reported TEN cases (mean, 6.8 pg/mL) were much lower than those detected in our patient with nonpigmenting FDE (138.0 pg/mL)

(Mizukawa et al., unpublished data). Thus, the timing of migration of Tregs to the inflammatory sites and of IL-10 production would be a crucial factor in determining whether the inflammation becomes resolved or progresses to the fatal outcome. Further studies are needed to determine factors that promote the appearance of Tregs and restore their defective function.

## Conclusions

The clinical and histologic features of FDE are more than curiosities because FDE is the prototypic disorder mediated by effector memory CD8<sup>+</sup> T cells resident in epithelial tissues. Future studies of FDE lesions will establish whether targeting of molecular pathways involved in the selective recruitment, retention, and long-term survival may help to control disease progression in a variety of organ-specific inflammatory disorders. Characterization of the mechanisms thus involved will provide a new perspective on the control of chronic inflammation in different tissue microenvironments under physiologic and pathologic conditions. It also should be appreciated, however, that this T-cell population may have originally evolved to protect epithelial tissues from invading pathogens. We do not even know whether the same T-cell population causes severe epithelial damage in some conditions of excessive antigenic stimulation while serving to protect tissue integrity under normal conditions.

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## Disclosures

No potential conflicts of interest relevant to this article were reported.

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