REVIEW ARTICLE

Darier disease

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ABSTRACT

Darier disease (DD) is a type of inherited keratinizing disorder that exhibits autosomal dominant inheritance. DD is caused by the mutations of *ATP2A2*, which encodes an endoplasmic reticulum calcium pump, sarco/endoplasmic reticulum ATPase type 2 (SERCA2). DD often develops in childhood, persists through adolescence, and causes small papules predominantly in seborrheic areas such as the face, chest and back. Further, scales and scabs may gradually develop. DD may be accompanied by non-dermal symptoms, including psychiatric symptoms. Histologically, DD is characterized by corps ronds and grains in addition to suprabasal cleavage. There are no currently validated curative treatments available for DD, with the majority of cases treated symptomatically. Despite demonstrating efficacy in the treatment of DD, the use of oral retinoids has been limited due to the association with various adverse effects.

Key words: ATP2A2, Darier disease, pathogenesis, review, sarco/endoplasmic reticulum ATPase type 2.

INTRODUCTION

Darier disease (DD) is a rare autosomal dominant inheritance disease first reported by Darier and White in 1889. The prevalence of DD is reported to range 1/30 000–100 000,[1–3] and there is no sex difference. DD often develops in childhood and persists throughout adolescence, causing small papules to emerge predominantly in seborrheic areas. Further, scales and scabs may gradually develop. DD may be accompanied by non-dermal symptoms, including psychiatric symptoms, such as mental retardation, epilepsy or bipolar disease. Histologically, DD is characterized by dyskeratosis, such as corps ronds and grains, in addition to acantholysis leading to suprabasal cleavage. The causal gene for DD was reported to be present on chromosome 12q23-24.1 in 1993,[4,5] and identified in 1999 as *ATP2A2* encoding sarco/endoplasmic reticulum ATPase type 2 (SERCA2), a calcium pump distributed throughout the endoplasmic reticulum (ER).[6] In this report, we provide a comprehensive review of this disease.

PATHOGENESIS

Darier disease exhibits autosomal dominant inheritance and often arises within families. The occurrence of sporadic cases is reportedly approximately 40–50%, with a high penetrance of greater than 95%.[7]

The *ATP2A2* gene maps to the long arm of chromosome 12 at 12q23-24.1 and encodes SERCA2, a calcium pump classified as a P-type calcium ATPase.[4,5] Mutations in *ATP2A2* have been shown to be responsible for DD.[6] In addition, a subsequent analysis of the *ATP2A2* promoter region demonstrated

that the transcriptional control element, Sp1, plays an important role in the regulation of *ATP2A2*.[8]

According to the Human Gene Mutation Database, approximately 59% and 21% of genetic mutations are missense/nonsense mutations and deletions, respectively. Other mutations, such as splicing and insertion mutations, have also been reported. Mutation sites are scattered throughout genes with no particular hotspots. In a recent report, 66 mutations in *ATP2A2* were identified in 74 out of 95 DD patients, of which 68% were de novo mutations.[9]

There are three paralogs of SERCA, SERCA1–3, encoded by *ATP2A1–3*, respectively. Mutations of SERCA1 cause Brody myopathy, a disorder of skeletal muscle contractions,[10] and SERCA2 mutations cause DD. No disorders caused by SERCA3 mutations have been reported to date.

Sarco/endoplasmic reticulum ATPase type 2 belongs to the P-type Ca^{2+} ATPase2 family[11] and has two isoforms: SERCA2a and 2b. SERCA2a is expressed in cardiomyocytes and slow-twitch skeletal muscles, whereas SERCA2b is expressed in almost all tissues including the epidermis.[12] SERCA2 pumps are predominantly found in the ER. SERCA2 is involved in the transport of Ca^{2+} from the cytosol to the lumen of ER, where Ca^{2+} is stored at a higher concentration.[13,14]

Haploinsufficiency is thought to underlie the autosomal dominant inheritance of DD.[6] It is thought that a mutation in one allele of *ATP2A2* results in half levels of functional SERCA2, and further reductions in mRNA and protein expression from intact *ATP2A2* allele leads to impaired regulation of intracellular calcium concentration and the subsequent development of disease. In addition, cultured keratinocytes exposed to ultraviolet (UV) rays, known to be an exacerbating factor for

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DD, demonstrate suppressed expression of the *ATP2A2* gene, similar to results obtained when the cells were treated with the pro-inflammatory cytokine, interleukin (IL)-6.[15] Further, expression levels of TRPC1, a member of the TRP channel family, are reported to be increased in abnormal keratinocytes of DD.[16] Moreover, Bcl-2 was shown to be an important contributor to the reduced levels of cell apoptosis observed in a DD patient.[17] Based on these results, Savignac *et al.* speculated that reduced Ca^{2+} concentrations in the ER have an influence on Golgi body and calcium signaling at the cell membrane through SECA1 and TRPC1, leading to activation of the ER stress response and cell apoptosis.[14] However, the mechanisms underlying the dissociation of epidermal keratinocytes and dyskeratosis in response to perturbations in calcium homeostasis remain unknown.

CLINICAL SYMPTOMS

In the majority of cases, DD develops from childhood and persists through adolescence. DD is characterized by brown, keratotic papules of sizes varying from pin-head to millet seed which develop in seborrheic areas such as the forehead, central chest, back and scalp margins (Fig. 1). DD papules do not always occur in the hair follicles, but often aggregate to form a verrucous lesion with keratotic crusts (Fig. 2). The lesions are ofte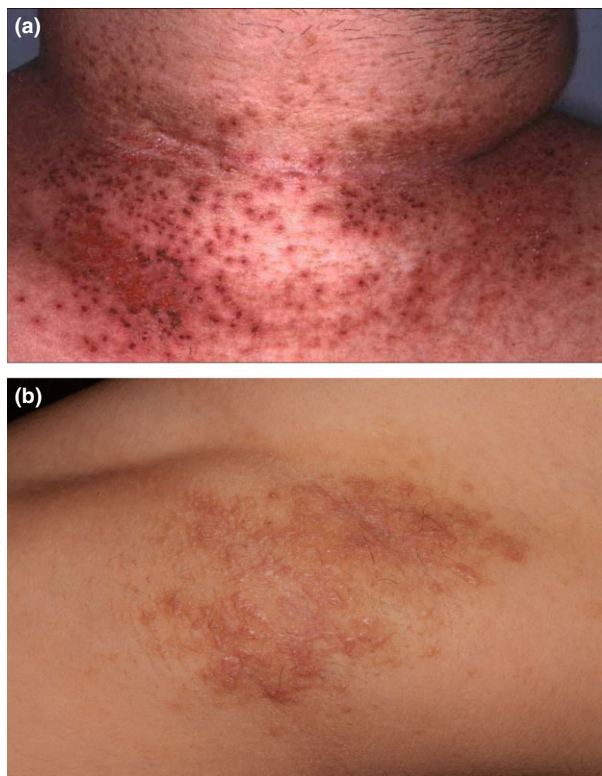n associated with itching and malodor. In particular, papules developing at sites of friction, such as the groin may fuse and become papillary. Additionally, complications such as maceration and secondary infection may result in a strong malodor (Fig. 3). Punctate depressions on the palms and soles may be observed in addition to a keratotic surface and hyperkeratosis (Fig. 4). Acrokeratosis verruciformis may be observed on the backs of the hands and feet. Fingernails and toenails may become brittle and weak. However, no hair-related abnormalities are observed in cases of DD.

Localized cases are thought to be due to genetic mosaicism caused by mutations that occur during zygotic division.[18] Symptoms include a rash with macular or linear patterns in one part of the body, with a distribution similar to epidermal nevus.[19]

Small white papules and nodules are observed in the oral mucosa, forming granular and papillary lesions. Symptoms may extend to the anal or vulvar mucous membranes. DD may be accompanied by non-dermal symptoms including psychiatric symptoms such as mental retardation, epilepsy or bipolar disease.

EXACERBATING FACTORS AND COMPLICATIONS

High temperatures, high humidity, excessive sweating, pregnancy and delivery, surgery, exposure to UV rays and mechanical irritation are known to be exacerbating factors for DD. In some female cases, symptom aggravation is observed during the premenstrual period. It has been reported that some

Figure 1. Keratotic papules with pigmentation on (a) the neck and (b) armpit.

Figure 2. Verrucous lesions with keratotic crusts on the leg.

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medications, such as lithium carbonate, may worsen symptoms. Secondary bacterial or fungal infections may aggravate skin lesions and increase malodor. Kaposi varicelliform eruptions are often observed as complications of viral infection.

Although other complications involving tumorous lesions, such as spinocellular carcinomas, malignant melanomas and epidermoid cysts, have been reported, the association between tumorigenesis and DD remains unclear.

HISTOLOGICAL OBSERVATIONS

In DD, the stratum corneum exhibits irregular proliferation and keratotic plug formation accompanied by parakeratosis. The stratum spinosum thickens and suprabasal cleavage is observed (Fig. 5). With instances of suprabasal cleavage, acantholytic cells and abnormal keratinocytes comprising corps ronds and grains may be observed scattered throughout the area (Fig. 6). Numerous corps ronds are observed in the upper spinous and granular layers adjacent to the site of cleavage formation. Grains may be observed from the upper spinous to granular layer and occasionally in the stratum corneum.

IMMUNOHISTOLOGICAL OBSERVATIONS

In normal-looking skin, no abnormalities are observed in the structure and distribution of adhesive molecules or keratin fibers. However, in affected skin, internalization of adhesive molecules such as desmoglein I/II, desmocollin and plakoglobin may be observed in epidermal keratinocytes that have

undergone acantholysis. Cohesion of keratin fibers may also be observed.[20,21]

DIFFERENTIAL DIAGNOSIS

Seborrheic dermatitis

Erythema with clearly defined borders arising in seborrheic areas and accompanied by fine, sebaceous scales. Moist surfaces are observed at sites of friction.

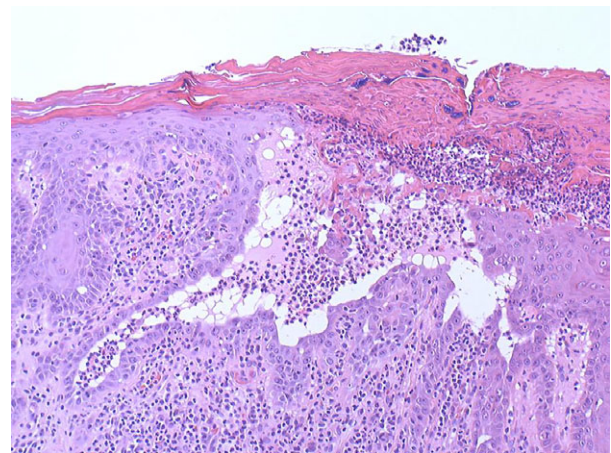**Figure 4.** Pits and keratotic plugs on the sole.

Figure 5. Example of suprabasal cleavage of the epidermis containing acantholytic cells (hematoxylin–eosin, original magnification ×40).

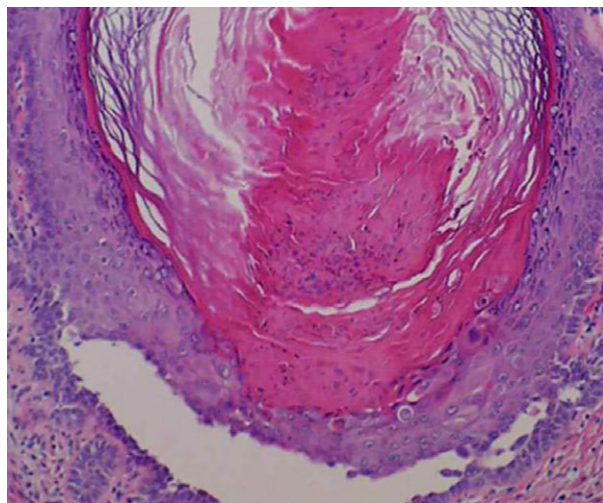**Figure 3.** Papillomatous and macerated lesion in the groin.

Figure 6. Keratotic plug and parakeratotic cells in the horny layer with abnormal keratinocytes comprising corps ronds in the granular layer (hematoxylin–eosin, original magnification ×100).

Hailey–Hailey disease

The responsible gene has been identified as the calcium pump-encoding *ATP2C1* gene,[22] encoding SPCA1 localized Golgi. This disease commonly arises during adolescence, with aggregation of erythema and small blisters at intertriginous areas. Gradually, an ulcerated and macerated surface forms with crusts. The differentiation of Hailey–Hailey disease from DD can be clinically challenging as the latter may exhibit similar symptoms at intertriginous areas.

Acanthosis nigricans

Dark pigmentation, hyperkeratosis and papillary eruptions are observed at intertriginous areas and on the neck. Therefore, differentiation of acanthosis nigricans from DD is frequently required.

Epidermodysplasia verruciformis

Hereditary skin disorder frequently associated with carcinoma resulting from increased susceptibility to human papilloma viruses. Numerous verruca plana are observed over the body from childhood.

TREATMENT

There are currently no validated curative treatments available for DD, with the majority of cases treated symptomatically. Lifestyle advice is important in eliminating exacerbating factors such as high temperatures, high humidity, UV rays and mechanical irritation.

Oral retinoids are often used to treat DD. Although this is highly effective, there are several side-effects, and in many cases patients can only undergo intermittent treatment or require discontinuation of the treatment.[2] It has been reported that cyclosporin has efficacy in the treatment of DD.[23]

However, a further study demonstrated that cyclosporin down-regulates SERCA2 expression,[24] making the effect and mechanism of cyclosporin in DD to remain unclear. Other studies have demonstrated that the p.o. administration of steroids has efficacy in the treatment of particular types of DD, vesiculobullous DD.[25] Furthermore, *in vitro* experiments have demonstrated that treating cultured keratinocytes with the three types of medication described above (prednisolone, cyclosporin and retinoids) ameliorate suppression of *ATP2A2* gene expression in response to UV irradiation, indicating the potential therapeutic efficacy of these drugs.[26]

Topical therapies, such as steroids or vitamin D3 ointment, are widely used for the treatment of DD.[22] In addition, isotretinoin,[27] tazarotene[28] and adapalene (naphthoic acid)[29] have been evaluated as treatments for DD symptoms. For refractory proliferative lesions, surgical dissection using an yttrium–aluminum–garnet laser is sometimes performed.[30]

As secondary bacterial and fungal infections are common in DD, culture tests and microscopic examination should be routinely performed, and antibiotics and/or antifungal agents should be p.o. or topically administrated.

FUTURE TREATMENT OUTLOOK

As described above, exposure of cultured keratinocytes to UV rays suppressed the expression of the *ATP2A2* gene, with similar results obtained with the pro-inflammatory cytokine, IL-6.[15] Based on these results, anti-IL-6 antibodies are expected to be developed for the prevention of DD exacerbations, particularly during the summer.

It has been reported that inhibition of cyclooxygenase-2 (COX2) is increased by UV irradiation and thereby ameliorates suppression of *ATP2A2* gene expression in response to UV irradiation, indicating that UV induces COX2 and prostaglandin E2 suppresses ATP2A2 expression in cultured keratinocytes.[31,32] This result indicates the utility of COX2 inhibitors for the treatment of DD.

Recently, miglustat, a glucosylceramide synthase inhibitor which has been used to treat Gaucher disease type I and Niemann–Pick disease type C, was reported to improve impaired adherens junction and desmosome resulting from the ER stress response in DD,[33] suggesting the benefit of development of miglustat as a new treatment for DD.

CONFLICT OF INTEREST: None declared.

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