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Darier's disease: a calcium-signaling perspective

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Abstract. Ca^{2+} influx evoked across the plasma membrane upon internal store depletion is essential for a myriad of cellular functions including gene expression, cell proliferation, differentiation and even apoptosis. Darier's disease (DD), an autosomal dominant inherited disorder of the skin, arising due to mutations in the isoform 2 of the sarco (endo) plasmic reticulum Ca^{2+} ATPase (SERCA2), exemplifies an anomaly of Ca^{2+} signaling disturbances. Owing to loss of function mutations in SERCA2, keratinocytes in DD patients have a reduced pool of endoplasmic reticulum (ER) Ca^{2+}. Importantly, the status of ER Ca^{2+} is critical for the activation of a class of plasma membrane Ca^{2+} channels referred to as store operated Ca^{2+} channels (SOCs). The widely expressed transient receptor potential (TRP) family of channels is proposed to be SOCs. In this review we discuss DD from the viewpoint of Ca^{2+} signaling and present a potential role for TRPC1 in the disease pathogenesis.

Keywords. Darier's disease, SERCA, calcium signaling, SOCE, TRPC channel, cell proliferation, apoptosis.

Introduction

The skin is the largest organ in the human body and functions as a primary barrier of defense against physical, chemical, and pathogenic insults [1, 2]. The external layer of the skin (epidermis) is highly differentiated and is regenerated by the mitotic activity of the stratum basale, which is lined by a single layer of keratinocytes that are held to each other and to the underlying dermis by desmosomes. These keratinocytes divide and undergo major biochemical and morphological remodeling as they make their way up to the top cornified layer (stratum corneum) before being eventually removed from the skin surface by shedding [2, 3]. Ca^{2+} plays a prominent role in all of the cutaneous strata. Ca^{2+} is crucial for normal cell division and is also integral to the expression of junctional complexes [4–7] that hold the keratinocytes in position and regulate their proliferation, thereby synchronizing the epidermal stratification and giving the appropriate texture to the skin [3–5]. Apart from providing epidermal integrity, keratinocytes also provide a cellular type of immunity against whole pathogens or their associated products and are thus dubbed as 'non-professional immune cells' [8]. Thus, pathological alteration of any kind to the Ca^{2+} signaling axis in these cells will result in severe biological consequences.

Darier's disease

Clinical perspective

Darier's (Darier-White) disease (DD), alternatively referred to as 'keratosis follicularis', was initially

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described independently by Darier and White in the year 1889 [1, 9, 10]. DD is a devastating form of blistering anomaly of the skin typified by warty papules, plaques and an intolerable stench arising from them. The warty papules and plaques predominately occur at the seborrheic sites involving scalp, forehead, retroauricular folds, flexures and front and back of the central trunk. Major histopathological findings include, but are not limited to, skin fragility, a distinct form of dyskeratosis (abnormal keratinization of keratinocytes) with corps ronds (apoptotic hallmark), acantholysis (focal areas of separation between suprabasal epidermal cells), and distinctive nail abnormalities [1, 9–12]. Additionally, ultrastructural studies demonstrate separation of keratin filaments from the desmosomal complex so that the skin cells not only lose their ability to adhere, but also have increased proliferation (hyperkeratosis) leading to abnormal keratinization [1, 4, 6, 7].

Genetics perspective

The autosomal dominant inheritable trait of DD was not identified until 1993, when the gene associated with DD was mapped to chromosome 12q23–24.1 by linkage analysis [13, 14]. Later, in 1999, a group led by Alain Hovnanian and colleagues identified the *ATP2A2* gene, which encodes the type 2 sarco(endo)-plasmic reticulum Ca^{2+}-ATPase (SERCA2), as the causative gene for DD [12]. The *ATP2A2* gene is alternatively spliced to three variants – SERCA2a, SERCA2b, and SERCA2c. These isoforms have differential tissue distribution, with SERCA2b being the major skin isoform [1, 7]. SERCA pumps facilitate the sequestration of cytosolic Ca^{2+} into the endoplasmic reticulum (ER) lumen. Mutations in the SERCA protein are widespread and constitute a variety of missense mutations, frameshift mutations, and even deletions. Since the identification of the gene responsible for DD, about 140 different mutations of SERCA2 have been evaluated with different degrees of phenotypic severity associated with the levels of expression and function of the pump. However, mutations rendering a state of SERCA2 haploinsufficiency are congruent with the classical DD phenotype [12, 15–20].

Genotype to phenotype perspective

DD is a kind of genodermatosis that does not seem to have a gender bias, although onset of the phenotypic abnormalities occurs around puberty and before the third decade. The disease has a high rate of penetrance, with a worldwide prevalence of 1 in 30 000–55 000 [1, 9–12]. Although DD has been genetically linked to dominant mutations in SERCA2, the phenotypic manifestations are, surprisingly, restricted to skin. Extra-cutaneous manifestations of DD remain largely enigmatic; however, certain neurophyschiatric disorders such as schizophrenia, epilepsy, and depression have been associated with the disease, albeit with no prominent genotype-to-phenotype correlation [17, 18, 21]. Sporadic salivary gland abnormalities, indicated by gland obstruction and metaplastic histology, have been reported [17, 22], but a lack of studies demonstrating glandular dysfunction in larger patient population fails to corroborate these findings. Cellular transformations and tumorigenesis associated with DD have been much debated. There are a number of isolated reports suggesting the co-existence of DD and carcinogenesis [23–25], but whether DD is a cause or effect of any associated carcinogenesis still remains to be determined. Interestingly, a murine model of DD, heterozygous (+/-) for SERCA2, overexpresses the *H-ras* oncogene and does develop papilloma and squamous cell carcinoma at a later stage, but does not exhibit a DD-like phenotype [26, 27]. The same mouse model has been reported to have impaired cardiac performance [28] without any apparent clinical features. However, in DD patients the differential expression pattern and/or compensatory activity of alternate SERCA isoforms may explain why pathological manifestations are restricted to skin lesions. For example, in cardiac tissues, SERCA2a seems to be the major isoform and hence can potentially compensate for the SERCA2b deficiency which is why DD patients have normal cardiovascular function [1, 7, 18, 21]. With respect to the disease pathophysiology, it would certainly be intriguing to identify why the genotype versus phenotype correlations are not faithfully translated between DD and its murine counterpart. Nonetheless, at present aberrant Ca^{2+} signaling arising due to impaired SERCA performance is the subject of much discussion.

Darier's disease and Ca^{2+} signaling

A steady-state of the ER Ca^{2+} pool is important for post-translational modifications, protein sorting, and the protein-folding machinery, because the function of many ER chaperones is dependant on local Ca^{2+} changes within the ER. SERCA pumps perform the crucial function of replenishing the depleted ER Ca^{2+} stores and hence constitute an integral component of the cellular Ca^{2+} homeostasis circuitry [29]. The potential role of Ca^{2+} in the growth and differentiation of epithelial cells as well as keratinocytes is recognized [3, 5, 30]. Interestingly, the majority of SERCA2 mutations associated with classical DD reveal a reduction in the expression and activity of the pump [15–20]. Hence, an imbalance in cellular Ca^{2+} signal-

ing is an obvious readout of DD. In an elaborate study on Ca^{2+} transport kinetics of 10 DD-related SERCA2 mutants, the group of Alain Hovnanian provided a mechanistic explanation for the reduced efficiency of the pump activity [15]. Furthermore, analyses of 12 DD-associated mutations of SERCA2b by the group led by Shmuel Muallem provide evidence for its reduced activity and expression. The difference in expression level of different mutants in this study was attributable to their proteasome mediated turnover. Additionally, a dominant, interfering effect of the mutants that cause a severe DD phenotype over the activity of the wild-type pump was also suggested [19]. In yet another interesting study, the same group working on a murine model of the disease (SERCA+/- heterozygous mice) demonstrated the effect of defective SERCA pumps on exocytosis. Secretion of amylase was about ten-fold more sensitive to Ca^{2+} in SERCA2+/- mice compared to the wild type [31]. More recently in 2006, Hiroshi Suzuki and colleagues reported a comprehensive analysis of 51 SERCA mutants associated with DD. In their study, 48 of 51 mutants showed severe disruption of Ca^{2+} homeostasis [20]. Although the skewed function of SERCA remains widely accepted disease etiology, the pathophysiological outcomes are quite pleiotropic. As a consequence of perturbed Ca^{2+} signaling, the trafficking of junctional complexes in DD keratinocytes is adversely affected leading to acantholysis, a distinct histological feature of the disease [1, 6, 7]. Furthermore, the involvement of the ER Ca^{2+} store in junctional biogenesis has been demonstrated in primary keratinocytes from normal and DD patients [7] and in MDCK cell lines [32], where inhibition of the SERCA pump was shown to inhibit the formation of tight junctions and desmosome assembly. Similarly, in *Drosophila* S2 cells, reduced SERCA activity has been shown to impair Notch receptor processing and trafficking to the plasma membrane [33]. These findings provide explicit evidence for the compromised SERCA pump activity associated with DD pathophysiology.

Store-operated calcium entry

Activation of the plasma membrane G-protein-coupled receptors (GPCRs) mobilizes Ca^{2+} from the ER stores through a series of signaling events [29, 34] and accounts for a transient increase in the cytosolic Ca^{2+} levels. Elevated cytosolic Ca^{2+} in turn activates the plasma membrane Ca^{2+} channel, which adds to the overall concentration of Ca^{2+} in the cytosol. This phenomenon of ER Ca^{2+}-mediated activation of plasma membrane Ca^{2+} channels is referred to as store-operated Ca^{2+} entry (SOCE) [35–37]. A group of specialized channels known as transient receptor potential (TRP) channels have been identified as store-operated calcium channels (SOCs) [35, 36, 38]. More recently, stromal interaction molecule (STIM) and ORAI [also known as calcium-release-activated calcium (CRAC) channels] proteins have been suggested as integral components of SOCE [39, 40]. Predominantly in immune cells, ORAI1 constitutes the plasma membrane component of SOCs, whereas STIM1 functions as the ER Ca^{2+} sensor which has a rather ubiquitous role in facilitation of SOCE by activating ORAI1 and/or TRPC (TRP canonical) components of SOCs [37, 39–41]. Although, the molecular identity of SOCs in keratinocytes remains elusive, increasing evidence suggests a profound involvement of TRPC channels in the skin system [42–44]. Elevating the cytosolic levels of Ca^{2+} via the activation of plasma membrane SOCs not only aids replenishment of ER stores but also maintains cellular functions. The build up of Ca^{2+} facilitates a variety of local effects like protein phosphorylation, neurotransmitter release, and global physiological changes like cell proliferation and differentiation [34]. In this scenario, the proper functioning of the SERCA pump is also imperative for restoring ER Ca^{2+} and thus continuing with an effective SOCE circuit.

Darier's disease – TRPC1 perspective

TRPC1, which is typically activated by ER store depletion, has been reported to be a critical component of SOCs in many cell types including endothelial, neuronal, smooth muscle and salivary gland cells, platelets, and keratinocytes [30, 35, 36, 38, 44, 45]. Its interactions with the newly identified SOCE components, STIM1 and ORAI1, as a dynamic complex further amplify the physiological significance of TRPC1 as a SOC [41, 46, 47]. It is the status of the ER Ca^{2+} store that regulates the activation of plasma membrane SOCs. Since DD keratinocytes cannot fully replenish the ER stores, due to deficient SERCA2 activity, a compensatory activation and/or expression of Ca^{2+} signaling components can be reasonably speculated. Our recent study on the involvement of TRPC1 in DD was based on the hypothesis that in SERCA2-compromised keratinocytes, expression and function of TRPC1 would be augmented to compensate for the prolonged state of depleted stores [44]. Interestingly, in DD, similar upregulation of Ca^{2+} signaling elements has been envisioned and reported [31, 48]. In a mouse model of DD, the expression and activity of a plasma membrane isoform of Ca^{2+} ATPase (PMCA) was significantly higher [31], perhaps as a compensatory adaptation toward SERCA2 haploinsufficiency. A similar upregulation of the human Golgi secretory Ca^{2+} ATPase 1 (hSPCA1) has been demonstrated in

keratinocytes of DD patients [48]. This study also provides evidence for an enhanced capacitative Ca^{2+} entry and discusses the potential involvement of non-selective Ca^{2+} channels in DD keratinocytes [48]. Our recent results indicated an upregulation of TRPC1 in skin tissues of DD patients. Increased expression of TRPC1 was accompanied by an enhanced Ca^{2+} influx activity [44]. Interestingly, keratinocytes obtained from Darier's patients have been shown to preserve Ca^{2+}-mediated signaling; however, they have lower levels of resting free cytoplasmic Ca^{2+}, which can be explained by the increased activities of PMCA and/or hSPCA1 [31, 48]. Furthermore, silencing of the hSPCA1 activity has been proven to restore the reduced resting Ca^{2+} to normal levels [48]. Despite the increased Ca^{2+} transient upon TRPC1 upregulation, which can potentially account for a transformed state of the keratinocytes, DD patients do not develop cancer, unlike their murine counterpart. This can be explained by the increased activities of PMCA and hSPCA1, which are responsible in part for balancing the elevated cytosolic Ca^{2+}. This integration of 'ER-plasma membrane-Golgi' compartments in DD further indicates a higher order of molecular 'cross-talk' between the Ca^{2+}-signaling components.

For many years, the mechanism linking intracellular Ca^{2+} regulation and the DD-associated hyperkeratinization was unknown. To investigate the consequence of SERCA2 suppression, we applied an siRNA strategy in HaCaT cells (a human epidermal keratinocyte cell line) to silence SERCA2 and to essentially mimic a DD-like state. SERCA2 silencing replicated our findings obtained from DD patient samples. The expression and function of TRPC1, but not TRPC3, was enhanced. The TRPC1-mediated increase in cytosolic Ca^{2+} stimulated keratinocytes to proliferate more, as a result of which, a decrease in ER stress-induced apoptosis was observed [44]. In a pathological context, this hyperproliferative phenotype may associate with and synergize the hyperkeratinization effect. Interestingly, silencing of SERCA2 gene expression in neonatal rat cardiac myocytes has been shown to trigger transcriptional remodeling, as demonstrated by a compensatory upregulation of TRPC4, TRPC5, and Na^{+}/Ca^{2+} exchangers (NCXs) [49]. Furthermore, TRPC isoforms have been suggested to assemble into homo- or heteromeric complexes so as to function as native SOCs [45, 50]. Additionally, STIM1 has been shown to interact with TRPC1/C4 and C5 channels and has been proposed to activate SOCE by facilitating TRPC channel heteromultimerization [41]. Hence, for attaining enhanced Ca^{2+} influxes in DD keratinocytes, a compositely organized TRPC-SOC, comprising 'TRPC1-C4/C5-STIM1' seems to be a logical possibility. The augmented activity of TRPC-SOCs would lead to an increased magnitude of the cytosolic Ca^{2+} oscillations, which would eventually precipitate into activating Ca^{2+}-responsive transcription factors like NFκB and NFAT [44, 49, 51–54]. Although an elaborate study of Ca^{2+}-dependant regulation of gene expression still needs to be done in DD, it is plausible that the elevated cytosolic Ca^{2+} levels can engage pro-survival/proliferative transcriptional paradigms. In support of this, upon SERCA2 silencing, our findings show upregulation of TRPC1 as a consequence of NFκB activation [44]. Alternatively, in DD keratinocytes, a constant state of low ER Ca^{2+} might potentially mediate a sub-optimal stress-induced sustained activation of the NFκB pathway, which in turn can potentiate a constitutive expression of TRPC1. Following its activation, TRPC1 can stimulate a Ca^{2+}-dependant feed-forward loop to reinforce NFκB-mediated regulation of anti-apoptotic genes like BclxL, thereby antagonizing cell death [44, 51, 55, 56]. Interestingly, activation of NFκB has been reported as a pro-survival/proliferative strategy of cells to evade ER stress [57]. Similarly, increased expression of TRPC channels in DD points toward one of the probable facets of epidermal plasticity for adapting to the impaired SERCA activity. Nevertheless, our study suggests that the enhanced function of TRPC1 in DD leads to a hyper-proliferative state of keratinocytes and hence accounts for disease exacerbation. The causal link between TRPC1 and cell proliferation remains to be investigated; however, considering the fact that TRP channels are associated with vital cellular physiologies such as survival, proliferation, differentiation, and death [42–44, 54], it can be reasoned that in DD, TRPC1 would participate in enhancing Ca^{2+}-responsive gene regulation that would eventually feed into an anti-apoptotic/pro-proliferative axis. Supporting evidence for keratinocyte hyper-proliferation in a canine model of genodermatosis was reported earlier by Müller and colleagues. Their investigation provides interesting findings on terminal differentiation and proliferation of keratinocytes from wild-type, lesional and non-lesional tissues [58]. Immunostaining for Ki67 (a proliferation marker) and cell cycle analysis by bromodeoxyuridine incorporation revealed enhanced proliferation in lesional keratinocytes. Analogous to DD and its murine model [23–26], the canine lesional tissues also correlated with hyperplastic histology [58].

DD has a genetic predisposition, but it is intriguing that the phenotypic manifestation is not a whole-body one, rather, it is concentrated in certain cutaneous 'hot spots', such as seborrheic sites. Exacerbation of these cutaneous lesions has been reported in certain stress

conditions such as UVB radiation, mechanical stress, and microbial infestation. Analogous evidence for stress-induced activation of TRP channels has also been documented [35, 59]. This underscores the participation of TRPC1 in DD progression. Moreover, the adhesion defects found in DD patients that are attributable to desmosomal disruption and internalization have been linked to decreased intracellular Ca^{2+} stores. Although the role of TRPC1 in desmosomal disruption/internalization was not examined in our study, the biogenesis and trafficking of the desmosomes are more directly influenced by the status of the ER Ca^{2+} store. Hence, it could be speculated that as a secondary effect of SERCA2b haploinsufficiency, the turnover of junctional components might be enhanced and Ca^{2+} influx by TRPC1 might not be sufficient to maintain a steady-state of their expression. The SERCA2 pump also influences the formation of Ca^{2+} oscillations, regulates resting cytoplasmic Ca^{2+} concentrations after signal-induced ER Ca^{2+} mobilization, and maintains the Ca^{2+}-rich environment of the ER lumen. Although involvment of TRPC1 in maintaining some of these functions cannot be ruled out, the defects in SERCA pump activity may additionally affect post-translational protein processing and chaperone-mediated trafficking of essential proteins in keratinocytes. Nevertheless, these findings strongly suggest a profound role for TRPC1 in DD pathogenesis.

Mitigation perspective

Due to the pleotropic nature of DD, there is no single way to manage this complex disease. Use of oral and topical retinoid therapy seems to be promising at present, albeit with a modest rate of success. Use of accutane/isotretinoin, a 13-*cis* retinoic acid formulation, commonly prescribed for the treatment of nodular acne, has proven to provide temporary symptomatic relief in DD [1, 10, 60]. Withdrawal from an accutane regimen has been reported to cause the return of DD symptoms [10, 60]. Although, it is not known how accutane functions in DD, our results indicate that in DD keratinocytes, isotretinoin suppresses cell proliferation and perhaps promotes apoptotic cell death as a result of a reduction in TRPC1-mediated Ca^{2+} influx [44]. A similar report of accutane treatment in adult mice has shown a reduction in proliferation and hippocampal neurogenesis, leading to defects in learning ablility [61]. In humans, neurophyschiatric disorders have also been documented with the use of accutane [1, 9, 21, 62] and it has been contra-indicated for use by pregnant women, because of its propensity to cause severe birth defects [10, 63].

Concluding remarks and future perspectives

It is evident from the findings of a number of research groups including ours that the dysfunction of Ca^{2+} homeostasis in DD is associated with a complex remodeling of Ca^{2+} signaling [1, 7, 15, 31, 44, 48, 49]. Although, the identification of the *ATP2A2* gene as the causative factor provided a major scientific breakthrough, a comprehensive analysis of alterations in Ca^{2+} signaling secondary to SERCA2 dysfunction is warranted. Elucidating the intricacies of organelle cross-talk with respect to perturbations in Ca^{2+} homeostasis and regulation of Ca^{2+} handling components would provide remarkable opportunities for future research endeavors. The precise mechanism of TRPC1 overexpression and enhanced proliferation of DD keratinocytes with respect to disease exacerbation need to be further evaluated. Appealing in this context would be to investigate if other isoforms of the TRPC family are also upregulated and whether or not TRPC1 tends to multimerize with them to be functional. This would help identify if the TRPC isoforms have any precise role in disease progression or whether their function is redundant. Furthermore, with the identification of STIM and ORAI proteins as critical components of SOCs, it would be interesting to study their role in the onset and progression of DD. Considering the fact that the molecular identity of SOCs in keratinocytes remains to be determined, it would be worthwhile to address issues of whether in skin cells, 'TRPC1-STIM1-ORAI1' work in concert or exhibit disparity. Addressing these questions will help us understand the precise molecular makeup of SOCs in the epidermal system and hence would pave ways to delineate Ca^{2+}-dependant regulation of gene expression in DD.

It has been several decades since DD was first described and a plethora of scientific findings about the disease have enriched our understanding of its pathophysiology. However, the search for an effective remedy has been a daunting task. The debate linking DD and carcinogenesis needs to be resolved in order to embark on developing new therapeutic strategies. The age-specific (at the onset of puberty) manifestation of the disease and its focal nature (cutaneous specific) pose major challenges toward developing safe and effective therapy. Additionally, it is a puzzling fact that the SERCA2+/- mice model of DD does not mimic ideally the disease phenotype. Moreover, the relatedness of the canine model to DD is debatable. Hence, it will be necessary to unravel the complex discrepancies existing with the use of the murine model in understanding DD. Nevertheless, this model provides ample opportunities for studying SERCA2 dysfunction and is definitely an invaluable resource

for the success of many testable hypotheses. Furthermore, whether retinoids can modulate the expression and functioning of Ca^{2+} handling components in keratinocytes remains to be explored. Because of the adverse side effects of isotretinoin, it would be prudent to understand the molecular targets and mode of action of the drug in DD. This would provide novel information for improving the existing therapy and/or formulating alternative and safer medication. As a combinatorial approach for topical emolument therapy, inclusion of small-molecule channel modulators that can rheostat Ca^{2+} fluxes may hold promise as future drugs for management of the disease.

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