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The Key Role of Aquaporin 3 and Aquaporin 10 in the Pathogenesis of Pompholyx

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Abstract

Pompholyx remains a chronic skin affliction without a compelling pathophysiological explanation. The disease is characterized by the sudden onset of vesicles exclusively in the palms and soles which generally resolves. However, the disease may progress and the vesicles may expand and fuse; with chronicity there is deep fissuring. Multiple therapeutic approaches are available, but the disease is often resistant to conventional treatments. Currently, oral alitretinoin is used for patients with resistant chronic disease; however, this therapy is only approved for use in the UK, Europe and Canada.

In this paper we wish to put forward a hypothesis: exposure to water and the subsequent steep osmotic gradient imbalance are key factors driving skin dehydration seen in pompholyx patients once the disease becomes chronic. The mechanistic explanation for the epidermal fissuring might lie in the over-expression across the mid and upper epidermis, including the stratum corneum, of two water/glycerol channel proteins aquaporin 3 and aquaporin 10, expressed in the keratinocytes of afflicted pompholyx patients. The over-expression of these two aquaporins may bridge the abundantly hydrated dermis and basal epidermis to the outer environment allowing cutaneous water and glycerol to flow outward.

The beneficial effects reported in alitretinoin-treated patients with chronic hand eczemas may be due potential regulation of aquaporin 3 and aquaporin 10 by alitretinoin.

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Keywords

Pompholyx; Dishydrotic Eczema; Aquaporin 3; Aquaporin 10; skin

Introduction

Pompholyx, or dyshidrotic eczema, is a chronic vesicobullous disorder of the palms and soles characterized by many deep-seated pruritic, painful, clear vesicles (1) (Figure 1A). The small vesicles can fuse and may then create scaling and painful fissures which ultimately incapacitate the patient for work and activities of daily living. Many factors are suspected to trigger pompholyx, including allergens, stress or seasonal changes but the exact immunological mechanism(s) remains elusive. The condition has been associated with allergies to metals, foods or drugs or left undiagnosed as “idiopathic” (1, 2). Importantly, the factors that maintain the disease once it has become chronic are even more elusive. As pompholyx becomes increasingly recurrent and resistant, patient quality of life is generally compromised.

The exact prevalence of pompholyx has been difficult to establish due to a lack of specific biomarkers. Current studies estimate its prevalence between 0.05–10.6% in the adult population (3, 4). The large range may be due to its inclusion as a form of Atopic Dermatitis (AD) by some clinicians. Pompholyx has a particularly high incidence in nursing (4), where hand washing is frequent. Interestingly, the prevalence of this disease seems to decrease with age (5).

There are several treatments that have been reported to manage pompholyx. Topical emolliation and corticosteroids constitute the first line of treatment. Other topical treatments include calcineurin inhibitors (6) and retinoids, including bexarotene (7). Interestingly, bexarotene is a synthetic retinoid specifically selective for the retinoid X receptors (RXR) (8), similar to alitretinoin’s specificity (see below). For treatment-resistant disease, systemic corticosteroids (9), immunosuppressants (10, 11), selective UVB phototherapy (12), Botulinum toxin A (13), anti-histaminics (14) biologics(15), radiotherapy (16) and tap water iontophoresis(17) have been used to treat refractory hand eczemas with varying degrees of success(18).

Currently, one new therapeutic for pompholyx has reached the market: alitretinoin or 9-cis retinoic acid. This treatment has been efficacious in double-blind randomized studies, leading to 75% improvement in patients with recalcitrant chronic hand eczemas, with an impressive 50% remission rate (19). Alitretinoin differs from other retinoic acids such as all-trans retinoic acid (ATRA) or isotretinoin because it acts through RXR receptors in addition to retinoic acid receptors (RAR). The RXR/RAR dual specificity is also shared by bexarotene, another retinoic acid that is able to improve pompholyx (8). This dual specificity may account for the unique beneficial effects of alitretinoin and bexarotene regarding pompholyx compared to other retinoic acid isomers such as ATRA or Isotretinoin. However, like all retinoids, alitretinoin is teratogenic, and strict pregnancy prevention measures must be observed before, during and after treatment. Alitretinoin is currently approved only in the UK, Europe and Canada, and in addition, it is generally cost-prohibitive at this point.

Alitretinoin however doesn't provide an irreversible cure, since recurrence of the disease following discontinuation of therapy has been described (20), although tachyphylaxis in subsequent treatments is not observed (20). Side-effects associated with alitretinoin treatment are considerable, including benign intracranial hypertension prompting headaches and nausea among other adverse reactions, in which cases patients must discontinue treatment immediately (21). Alitretinoin has also been described to induce dryness of the mucosa, increase plasma cholesterol and triglyceride levels in patients (19, 21), necessitating the need for serum monitoring on a regular basis.

Aquaporins

Aquaporins are channel proteins that increase the permeability of cell membranes to the bi-directional, osmotically-driven passage of small uncharged molecules, including water, glycerol and urea (22). Currently, thirteen members have been identified in mammals and they are subdivided into three categories: aquaporins, aquaglyceroporins and super-aquaporins for their ability to transport strictly water, water and glycerol or their restricted intracellular expression respectively. Interestingly, recent publications have shown that aquaporin-3 (AQP3) and aquaporin-10 (AQP10) are the main aquaglyceroporins expressed in human keratinocytes (23, 24). AQP3 has been found to be ectopically expressed in the stratum spinosum of atopic dermatitis (AD) patients (23), potentially contributing to the increase of Trans Epidermal Water Loss (TEWL) seen in AD patients. We present evidence that in pompholyx patients AQP3 is also expressed ectopically in the stratum spinosum of involved skin lesions (Figure 2A) while upregulated in the stratum basale of uninvolved skin lesions (Figure 2B). However, in healthy controls, AQP3 is confined to the stratum basale of the skin (Figure 2C) (23). AQP3 over-expression in keratinocytes has also been shown to promote proliferation (25) and interestingly, UVB-treated skin exhibits a decrease in AQP3 expression (26).

As members of the aquaglyceroporin subfamily, AQP3 and AQP10 transport both water and glycerol. Glycerol or glycerin is a natural humectant known for its property of retaining water in the stratum corneum. Glycerol also constitutes one of the key components involved in creating the lipid-based water-proof barrier that surrounds corneocytes in the SC of the skin (27). Last but not least, AQP3 conducting properties are inhibited in an acidic environment ($\text{pH} < 7$), with water transport being inhibited at a pK value of 6.4, and glycerol at pK 6.1 (28).

Given its known ability to augment water loss, we hypothesize that AQP3 and AQP10 may play a central role in exacerbating the intensity and chronicity of pompholyx. We believe the pathology stems from an increased water transport mechanism that contributes to the epithelial dehydration. Chronic dehydration may result in greater inflammation and poorer response to injury due to a weakened and compromised skin barrier.

Hypothesis

We hypothesize that AQP3 and AQP10 are overexpressed across all layers of the epidermis thereby facilitating dehydration of the affected palms and soles of pompholyx patients.

Therefore, minimizing wet to dry cycles concomitantly with the usage of AQP3 and AQP10 topical or systemic inhibitors might be the key to successful treatment of pompholyx.

Evidence that AQP3 and AQP10 are over-expressed in the hands of Pompholyx patients

Immunohistochemical staining was used to demonstrate the expression of AQP3 and AQP10 in hand skin biopsies obtained from three individuals diagnosed with pompholyx (Figure 1). AQP3 and AQP10 expression can be observed across all layers of the epidermis in the palm lesions of pompholyx patients (Figures 2A and 3A, respectively). However, in non-lesional skin from pompholyx patients, AQP3 and AQP10 expression remained confined to the stratum basale although expression appeared to still be higher than in skin from a healthy donor (Figures 2B and 3B and Figure 2C and Figure 3C, respectively). AQP3 was expressed more strongly than AQP10, in agreement with previous studies (24, 38). Control isotype staining for AQP3 and AQP10 staining is shown in Figures 2D and 3D, respectively.

Mechanistic explanation for the increased dehydration in lesional palms of Pompholyx patients

Stratum Corneum Hydration Decreases Following Exposure to Water

One of the puzzling characteristics of skin is that the stratum corneum (SC) tends to become dehydrated after water exposure (29). This is a known phenomenon, and it happens in a matter of seconds after water exposure, with skin dehydration being one of the main mechanisms increasing the extent of pompholyx blisters (30). However, why does exposure to water lead to a net decrease in the ability of the skin to retain water? Shouldn't the opposite be the case, since the skin tissue has received water? Dermatologists are aware that water exposure is actually detrimental (31) and routinely advise pompholyx patients to reduce water contact while using hand lotions to keep the skin hydrated. Thus, water's detrimental effects on pompholyx has been described as an aggravating factor (31), not as the main cause driving the disease.

However, skin dehydration triggered by water is a paradox. The presence of water should help hydrate skin tissue, not dehydrate it, unless there is a mechanism in the skin that allows endogenous water to be lost upon contact with exogenous water.

The Water Loss Mechanism for Pompholyx Skin Dehydration

Aquaporins are water and glycerol transporting proteins that don't require energy and their function is driven by osmotic gradients. As shown in Figure 4A, water will flow through an aquaporin channel from the higher to the lower water gradient between cell membranes. However, the acidic pH in healthy skin inhibits AQP3 transport and thus helps to maintain water retention (Figure 4B).

This suggests that under physiological conditions the water channels in the stratum lucidum close to the SC (Figure 4C) remain inhibited by the low pH of normal skin, thus helping the skin retain water. For example, soaps that have low pH are known to promote skin

hydration, perhaps by inhibiting the outermost AQP3 channels of the skin. However, the major barrier for water in healthy skin is the thick SC (29), which is normally devoid of AQP3 and AQP10 expression (Fig 2 &3B and Fig 2 &3C).

However, under pathological conditions such as pompholyx or AD, the pH of the upper SC is increased (32). Therefore, as shown in Figure 4D, one could reasonably assume that the higher pH favors activity of AQP3 and AQP10 in the lesional palms, keeping the water pores leaky, and prone to be open for longer periods of time.

In addition, in lesions of pompholyx there is continuous expression of AQP3 and AQP10 across all layers of the skin, (Figure 2A and Figure 3A, respectively), connecting the dermis and all its layers with the outer environment (Figure 4D).

Under resting conditions, the multi-stratification of the epidermis in pompholyx lesions may maintain TEWL through AQP3 and AQP10 channels relatively low due to the multiple layers of keratinocytes and corneocytes, albeit not close to zero as in healthy skin. However when the skin is exposed to exogenous water (Figure 4E), during hand washing, for example, the osmotic gradient strongly favors outside water to permeate inward and the osmotically-regulated AQP3 and AQP10 in the SC help conduct water from the outside to the inside of the epidermis. However, after this initial water exposure, hands are usually dried in seconds and this triggers another quick change: a sudden reversal of the very same osmotic gradient. Now the osmotic gradient is opposite: high in the tissue and low in the outside (Figure 4F), and AQP3 and AQP10 allow all water absorbed during the wash to be lost through their pathological presence across all skin layers (Figure 4F). At this point, tissue-derived water flows outward and, due to the increased pH observed in pompholyx skin, for longer periods of time. Glycerol is also lost in this process since AQP3 and AQP10 are aquaglyceroporins, and glycerol's humectant properties may help carry out additional water (Figure 4F). Additionally, loss of glycerol may carry a more detrimental impact on the skin than water loss itself in the long term, since depleting one of the key biosynthetic components that help create the water-proof lipid-lamelae surrounding the corneocytes may stall the ability of skin to heal properly.

If we take into account that hands are washed an average of eight times a day, this dynamic is repeated multiple times and thus the tissue water content keeps getting lower and lower relentlessly. The chronic lack of water may help crack the skin and destabilize the lesional hand tissue homeostasis (Figure 1A) contributing to barrier disruption by provoking stress to structural integrity. In this regard, pompholyx blisters might over-hydrate the epidermis causing exaggerated damage from rapid drying of very hydrated skin. With tissue water lost, several molecular changes described in the literature might take place, including imbalance of proteases that degrade desmosome anchoring (27, 30), increased intracellular concentration of Ca^{2+} in keratinocytes disturbing their differentiation (33, 34), and activation of Ca^{2+} -dependent transglutaminases involved in corneocyte envelope maturation (35). We also want to emphasize that this water-loss mechanism is in place only in the chronic stages of the disease when the over-expression of AQP3 and AQP10 reach all supra-epidermal layers of the skin. During the initiation of the disease, aquaporin expression might be less critical as a trigger such as skin damage might hold more weight in initiating the

blisters typical of a pompholyx flare. Thus, initiation of blisters might not be related to aquaporin over-expression. The hypothesis advanced herein is that aquaporin over-expression may play a role in increasing skin dehydration, facilitating blister rupture after they have been created and accelerating the expansion of the diseased skin, and thus increasing its chronicity.

Evaluation of the hypothesis

If the hypothesis put forward in this paper is valid, the therapeutic power of alitretinoin resides in its unique ability to down regulate AQP3 and AQP10 expression on keratinocytes in the skin of pompholyx patients. The episodes where the disease is recurrent might be due to the residual presence of AQP3 and AQP10 or an incomplete return to their basal expression levels across the very same layers where it was once over-expressed. This residual AQP presence might be enough to initiate the water loss mechanism explained above.

Could the ability of alitretinoin to down regulate other aquaporins also explain the dryness of mucosa, the benign intracranial hypertension and increase in cholesterol and tryglycerides that some patients experience as side effects? We performed a bioinformatic comparison of the human genome and it revealed that the RXR consensus promoter sequence PuG(G/T)TCAnPuG(G/T)TCAn, which alitretinoin binds to specifically, is present in the promoters of aquaporins 3,5,7,8, 10 and 11. According to published records, human aquaporin 5 has been identified within cells of the airways, salivary glands, eyes and brain (36) while human AQP7 and AQP8 are expressed in the proximal tubule epithelium (36), being potentially related to obesity (37). Although aquaporin 11 is expressed at low levels in virtually any tissue, it's main function is suggested to be involved with kidney development (38).

However, more in-depth studies will be required to conclusively link alitretinoin's benefit to its ability to down-regulate specific aquaporin protein channels.

Another approach that might shed light on the hypothesis advanced in this paper is the development of safe topical treatment(s) that include specific inhibitors of AQP3 and AQP10. If such treatments would be successful in healing pompholyx lesions *regardless* of lesional skin being exposed to water, it might prove that inhibiting AQP3 and AQP10 are key to successfully reversing pompholyx pathology (Figure 4G).

Clinical Implications

If the hypothesis is correct, water exposure should be regarded as the primary factor responsible for maintaining pompholyx. Therefore, patients should avoid prolonged water exposure to afflicted areas of the skin as often as possible. Patients may benefit from wearing double gloves whenever taking showers. The double glove should consist of an inner cotton glove within a water-proof glove made tight using a rubber band around the wrist. There is a strong rationale behind this approach (39). The cotton glove stops the inner glove condensation from occurring while the water glove protects the hands from water exposure. The rubber band avoids water getting inside the gloves once the hand is beneath the water shower. In addition to this measure, whenever washing their hands, patients should

be advised to apply emollients prior to drying the hands to avoid completely drying the skin. We hypothesize that behavior modifications will improve the skin conditions through more water retention.

Discussion

Although several treatments are available, pompholyx remains a chronic skin condition that if left unchecked can seriously impact the quality of life of those suffering. The condition is never fatal, but is a serious ailment mediating depression or social isolation. In this prospectus we wished to put forward a compelling hypothesis to explain the underlying pathophysiology of this disease and preliminary data to support the hypothesis. We hypothesize that over-expression of AQP3 and AQP10 concomitantly to water exposure is the main reason for exacerbation of the disease in patients with increased aquaporin expression. The fissures of pomphoyx may exacerbate during winter conditions, which establish a steep humidity gradient (40) potentially contributing to rapid wet and dry cycles. The only effective treatment currently available in Europe and Canada to reverse the chronic and refractory stage of this disease is oral alitretinoin, a 9-cis stereoisomer of retinoic acid. Although the ultimate mechanism responsible for alitretinoin healing properties is not known, its beneficial effects compared to other retinoics such as ATRA or Isotretinoin, could stem from the dual specificity for RAR and RXR receptors.

Interestingly, this disease also seems to be less prevalent with increased age (5), which may be related to the decrease of AQP3 in aged skin (41). This could imply that AQP3 is a double-edge sword for the skin. Its high-expression may provide the skin with superior flexibility, appearance and hydrated nature, but if it goes beyond a certain threshold it may expose the body to develop chronic dehydrated conditions such pompholyx or AD.

Materials and Methods

Human skin biopsies

All studies involving human subjects were approved by the Institutional Review Boards of Case Western Reserve University and University Hospitals Case Medical Center. 3-mm punch biopsies were obtained from two pompholyx patients diagnosed by a certified dermatologist and one healthy adult volunteer following informed consent. The biopsies were immediately snap frozen in liquid nitrogen and stored at -80C until further use.

Immunohistochemistry

For IHC analysis, 7µm sections were prepared and stored at -80°C until fixation in ice-cold acetone for 10' at 4°C, rinsed with PBS and blocked overnight at 4° C with 5% chicken serum (Jackson ImmunoResearch, West Grove, PA). Samples were stained using primary rabbit polyclonal antibodies against human AQP3 and AQP10 or corresponding isotypes (Abcam, Cambridge, MA) for 3 hours at RT. An Alexafluor® 647-conjugated chicken anti-rabbit secondary antibody was applied for 1 hour at RT (Life technologies, Grand Island, NY). Slides were rinsed in PBS, mounted with Fluoromount G (Southern Biotech, Birmingham, AL). All images were acquired using the UltraVIEW VoX spinning disk confocal system (PerkinElmer, Waltham, MA) mounted on a Leica DMI6000B microscope

(Leica Microsystems, Inc., Bannockburn, IL,) equipped with a HCX PL APO 20x objective. All confocal images were analyzed using Metamorph™ (MDS Analytical Technologies, Sunnyvale, CA)

Bioinformatic analysis

The upstream 5000 sequences for human genes in the hg19 release were obtained from UCSC genome browser. RXR motif search was conducted using fuzznuc program in EMBOSS package for the pattern of 5'-RGKTCAN(1,5)RGKTCAN-3'.

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Figure 1. Pompholyx afflicted palms

A) Pompholyx patient lesional skin. B) Pompholyx patient uninvolved skin. C) Healthy volunteer. The white circles denote the area where the 3-mm biopsy was obtained.

Figure 2. AQP3 is increased in Pompholyx

A) Palm lesion of a pompholyx patient stained for expression of AQP3. B) Uninvolved skin from a pompholyx patient stained for expression of AQP3. C) Palm from a healthy volunteer stained for expression of AQP3. D) Isotype control for AQP3 antibody. AQP3 expression is denoted in red (647nm) and the skin is counterstained with the nuclear marker DAPI (blue,UV) and a membrane lectin stain (Green, WGA-488). The arrow denotes the range where AQP3 expression is found.

Figure 3. AQP10 is increased in Pompholyx

A) Palm lesion of a pompholyx patient stained for expression of AQP10. B) Uninvolved skin from a pompholyx patient stained for expression of AQP10. C) Palm from a healthy volunteer stained for expression of AQP10. D) Isotype control for AQP10 antibody. AQP10 expression is denoted in red (647nm) counterstained with the nuclear marker DAPI (blue,UV) and a membrane lectin stain (Green, WGA-488). The arrow denotes the range where AQP10 expression is found.

Figure 4. The water-activated water loss mechanism

A) Aquaporins are bidirectional passive water/glycerol transporters. B) The AQP3 pore is inhibited in an acidic environment ($\text{pH} < 7$). C) Healthy skin retains water efficiency through low AQP3 and AQP10 expression in the SS, the SC's acidic pH and a SC devoid of aquaporins, even though the osmotic gradient favors aquaporin function. D) In pompholyx, the SC's basic pH along with over-expression of AQP3 and AQP10 across all layers of the epidermis allows exogenous water to permeate the skin. E) Upon drying, the osmotic gradient is reversed and over-expression of AQP3 and AQP10 allows endogenous water to be lost along with glycerol. F) Potential AQP3 and AQP10 inhibitors would turn the lesional upper SS and SC water-proof, preventing exogenous water to permeate inwards and endogenous water to be lost after hands are dried.