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Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

The possible role of TRPC6 in atopic dermatitis

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ARTICLE INFO

Article history:

Received 23 February 2011

Accepted 19 September 2011

Available online xxxxx

ABSTRACT

Skin barrier dysfunction is involved in the pathogenesis of atopic dermatitis (AD). The impaired barrier function is related to disturbed keratinocyte differentiation through improper Ca^{2+} -regulated pathway in AD. Transient receptor potential canonical (subtype) 6 (TRPC6) is a Ca^{2+} -permeable nonselective cation channel expressed in keratinocytes. TRPC6 contributes to the process of keratinocyte differentiation by regulating Ca^{2+} influx. Furthermore, TRPC6 alone is considered to be sufficient for nearly full physiological response of keratinocyte differentiation. Until now, the correlation between TRPC6 and AD has not been investigated. We hypothesize that dysfunction of TRPC6 may trigger the process of AD, and that restoring or enhancing the activity of TRPC6 may serve as a new modality in treating AD.

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Introduction

Atopic dermatitis (AD) by definition is an allergic disease characterized by pruritus, dry skin, and history of atopy (e.g. asthma and allergic rhinitis). Though the exact pathophysiological mechanism remains elusive, impaired skin barrier function is blamed to be a major player. Studies showed that the strictly regulated differentiation of keratinocytes was disturbed in AD, leading to defective epidermal barrier function [1]. The dysregulated differentiation is also coupled with aberrant expression of some differentiation-specific markers [2]. Abnormal differentiation of keratinocytes in the pathogenesis of AD is an interesting topic to study.

In the process of epidermal differentiation, some distinct biochemical markers are expressed and they contribute to the formation of skin barrier. Keratin 5 (K5) and keratin 14 (K14) are the specific proteins in basal keratinocytes, while K1 and K10 as the early differentiation markers are specific in spinous cells [3–5]; the late differentiation markers, such as involucrin [6], loricrin [7] and filaggrin [8] are expressed in the granular layers and/or stratum corneum. It has been found that abnormal changes of K5, K10, involucrin, loricrin and filaggrin are present in lesional and/or non-lesional skin of AD [2]. Furthermore, it has been proved that there is a close association between AD and filaggrin expression [9–11].

Calcium (Ca^{2+}) is assumed to take a pivotal role in keratinocyte differentiation [12]. Cultured keratinocytes proliferate rapidly at extracellular calcium concentration ($[\text{Ca}^{2+}]_o$) between 0.02 and 0.1 mM, while differentiate as Ca^{2+} influx at a $[\text{Ca}^{2+}]_o$ above 0.1 mM [13–15]. In vivo, there is a distinct Ca^{2+} gradient in epidermis, which decides keratinocyte differentiation [16]. Ca^{2+} gradient is also important for the expression of differentiation-specific markers and the formation of skin barrier, a fact proved by the results that the fluctuations of the Ca^{2+} in epidermis induce changes in the expression of loricrin, involucrin, and profilaggrin (the precursor of filaggrin) [17]. In fact, the abnormal epidermal barrier is accompanied by a loss of the Ca^{2+} gradient in AD [18].

Transient receptor potential canonical (subtype) 6 (TRPC6) is a Ca^{2+} -permeable nonselective cation channel belonging to the mammalian transient receptor potential (TRP) family of ion channels. The TRP family is subdivided into seven subfamilies: TRPC (“Canonical”), TRPV (“Vanilloid”), TRPM (“Melastatin”), TRPA (“Ankyrin”), TRPN (“NOMPC”), TRPP (“Polycystin”), and TRPML (“Mucolipin”) [19,20]. TRPC subfamily is further divided as follows: TRPC1, TRPC2, TRPC3/6/7 and TRPC4/5 [21]. TRPC is expressed in various tissues and implicated in some diseases, such as diabetic nephropathy [22] and hereditary focal segmental glomerulosclerosis (FSGS) [23]. Some TRPC channels are expressed in keratinocytes and they are involved in differentiation. For example, store-operated Ca^{2+} channels represent the primordial Ca^{2+} entry pathway and play a pivotal role in initiating Ca^{2+} -induced keratinocyte differentiation [24–26]. Tu et al. [27] showed that TRPC1 and TRPC4 were the subunits of the endogenous store-operated channel (SOC) and the major mediators of SOC activity in keratinocytes. Some other researches found that TRPC1 and TRPC6

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were expressed in gingival epithelium; moreover, TRPC1 was considered to be involved in inducing differentiation of human gingival keratinocytes (HGKs) [28,29]. In epidermis, TRPC6 is primarily expressed in keratinocytes of stratum spinosum and stratum granulosum, but not in basal layer, suggesting that Ca^{2+} -induced differentiation of keratinocytes is predominantly mediated by TRPC6 channels [30]. Further investigations showed that calcium homeostasis was impaired in psoriatic keratinocytes in association with reduced expression of TRPC channels. The defect of epidermal calcium homeostasis might lead to a disturbed balance between proliferation and differentiation in psoriatic keratinocytes. Hyperforin, a TRPC6 activator, could partly restore the impaired differentiation of psoriatic keratinocytes [31]. It is interesting to note that topical application of hyperforin-containing cream could improve AD clinically [32]. Thus we postulate that dysfunction of TRPC6 might be involved in the pathogenesis of AD.

Hypothesis

The hypothesis is that dysfunction of TRPC6 in keratinocytes triggers the pathogenesis of AD through inhibiting Ca^{2+} influx, perturbing keratinocyte differentiation and impairing the epidermal barrier functions. TRPC6 may serve as a potential target for the treatment of AD.

The rationale for the possible role of TRPC6 in the pathogenesis of AD

Our hypothesis is supported by a couple of facts. Firstly, dysfunction of TRPC6 results in the inhibition of Ca^{2+} influx and the failure of increase in intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$). It has been proved that TRPC6 channel is involved in high $[\text{Ca}^{2+}]_o$ -mediated Ca^{2+} influx. Specific activation of TRPC6 alone is sufficient to induce keratinocyte differentiation, similar to the physiological stimulus of $[\text{Ca}^{2+}]_o$ [30]. Secondly, it is well established that the increase in $[\text{Ca}^{2+}]_i$ is essential for differentiation response of keratinocytes, and the inhibition of Ca^{2+} influx impedes the process of keratinocyte differentiation [33]. The mechanistic correlation between the rise in $[\text{Ca}^{2+}]_i$ and the subsequent keratinocyte differentiation is not fully clear. So far, several molecules have been implicated in this process and a tentative pathway is proposed: calcium-sensing receptor (CaR) can sense $[\text{Ca}^{2+}]_o$ [34]; the increase in $[\text{Ca}^{2+}]_i$ produces the second messengers, i.e. inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) by activating the phospholipase C (PLC) pathway. IP3 is believed to account for calcium signaling in the keratinocytes [34,35]. The increase of $[\text{Ca}^{2+}]_o$ and DAG can activate protein kinase C (PKC), the alpha isozyme of which can induce keratinocyte differentiation [36,37]. Thirdly, as described above, proper differentiation of keratinocytes leads to the normal expression of differentiation markers and the formation of epidermal barrier, while the abnormal process of keratinocyte differentiation might result in AD. Knockdown of TRPC6 with siRNA can inhibit the expression of K10, correlating with dry skin and disturbed barrier function of AD [2,38]. In addition, in a randomized, placebo-controlled, double-blind half-side comparison trial, a hyperforin-containing cream, as a specific activator of TRPC6 channel [39], showed a significant superiority compared to the vehicle in treating mild to moderate AD [32].

Conclusion

Skin barrier dysfunction is related to disturbed differentiation of keratinocytes via abnormal Ca^{2+} -regulated pathway in AD. The key role of TRPC6 in Ca^{2+} influx and keratinocyte differentiation sug-

gests its pivotal involvement in the pathogenesis of AD. Once validated, TRPC6 may serve as a target molecule in AD management.

Conflict of interest

None declared.

Acknowledgment

This work was supported by the Program for Innovative Research Team in Universities, Ministry of Education (grant IRT0760) and Liaoning provincial Bureau of Education (2007T186, 2009T105). The sponsors play no role in the collection, analysis, interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

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