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Review article

Could tight junctions regulate the barrier function of the aged skin?

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ABSTRACT

The skin is known to be the largest organ in human organism creating interface with outer environment. The skin provides protective barrier against pathogens, physical and chemical insults, and against uncontrolled loss of water. The barrier function was primarily attributed to the stratum corneum (SC) but recent studies confirmed that epidermal tight junctions (TJs) also play important role in maintaining barrier properties of the skin. Independent observations indicate that barrier function and its recovery is impaired in aged skin. However, trans-epidermal water loss (TEWL) values remains rather unchanged in elderly population. UV radiation as major factor of photoageing impairs TJ proteins, but TJs have great self-regenerative potential. Since it may be possible that TJs can compensate TEWL in elderly due to its regenerative and compensatory capabilities, important question remains to be answered: how are TJs regulated during skin ageing? This review provides an insight into TJs functioning as epidermal barrier and summarizes current knowledge about the impact of ageing on the barrier function of the skin and epidermal TJs.

Contents

1. Introduction

The skin consists of three individual compartments: hypodermis, dermis and epidermis. The barrier function of the skin is exclusively fulfiled by the epidermis, which is a cellular layer composed mainly by keratinocytes stratified into sub-layers including stratum corneum, stratum granulosum (SG), stratum spinosum and stratum basale, by their stage of differentiation [1]. Until recent years the SC was thought to be the only barrier in the

Abbreviations: aPKC, atypical protein kinase; ECL, extracellular loop; FD4, 4 kDa FITC-dextran; FD10, 10 kDa FITC-dextran; FD40, 40 kDa FITC-dextran; JAM, junctional adhesion molecules; Par, partitioning defective; SC, stratum corneum; SG, stratum granulosum; TER, trans epithelial resistance; TEWL, trans epidermal water loss; TJ, tight junction.

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epidermis. However, epidermal TJs have also been shown to maintain barrier properties of the skin, and act not only as a physical barrier but also as a regulatory element [2]. Human skin is constantly exposed to UV radiation causing photoageing over time. Skin ageing is a complex process affecting cells and molecules throughout the whole skin [3,4]. Besides aesthetic impact, ageing impairs barrier function of the skin. However, TEWL is not affected in aged skin. One possible, but not sufficient explanation is that elderly people have different hydration, pH and sebum of the skin than younger people. Epidermal TJs contributing to the barrier and regulatory function of the skin could therefore provide missing link in the barrier function of elderly individuals.

2. Composition of tight junction

Cell junctions are cellular structures created by protein complexes connecting cells to each other or connecting cells with extracellular matrix [5,6]. TJs are type of cell–cell junctions sealing an intercellular space between adjacent cells [7] that in transmission electron microscopy appear as fused contacts between adjacent cells, also known as “kissing points” [8]. TJs are complex structures comprised of various transmembrane, scaffolding and cell polarity proteins, see Fig. 1 [9,10]. While TJ structures are strictly formed only within one cell layer, localization pattern of individual TJ proteins is more complex [11].

Claudins, occludin, and tricellulin are tetraspan transmembrane proteins with two extracellular loops which act mainly as physical barrier in TJ complexes [12–16]. Claudin-1 and claudin-7 are expressed in all living epidermal layers, while occludin and claudin-4 is only present at the SG [17–19]. Tricellulin is predominantly expressed in the SG at tricellular contacts but can be also found in lower layers of the epidermis [20]. Junctional adhesion molecules (JAMs) have two extracellular Ig-like domains and also create physical barrier in the intercellular space. JAM-A is present in all living epidermal layers [19].

Scaffolding proteins are localized peripherally to the cell membranes. They are tightly associated with transmembrane proteins, and anchor the whole protein complex to actin component of the cytoskeleton [21]. ZO-1, ZO-2, cingullin and symplekin belong to the scaffolding proteins and reside at the SG with faint expression pattern into the lower layers [17,18,22].

Functional TJ structure is formed where all TJ proteins co-localize, which is between uppermost living cell layers of the epidermis [23,24]. Recent studies demonstrated that TJ barrier is single layered and formed by the second SG layer in rodent [25,26] as well as in human epidermis [11].

3. Functions of tight junction complex in the skin

Skin TJs represent multifunctional elements, which are involved in the barrier function of the skin, regulation of epidermal homeostasis and differentiation of the epidermis. TJs are associated with establishment of epithelial polarity that helps to facilitate these functions. It was demonstrated that only the second SG layer containing TJs exhibited cellular polarity [11]. Polarity in mammalian epithelial tissues is maintained by Par3/Par6/aPKC protein complex [27,28], which is also responsible for the correct assembly of the whole TJ structure [29–33].

3.1. Regulation of epidermal barrier components

Growing evidence suggests that TJs might have modulating effects on other structural units of epidermal barrier system. Knockdown experiments of individual TJ proteins changed localization pattern of other TJ proteins [34,35], and altered either ceramide composition or structural proteins of the SC [34,36]. It seems that regulation of TJs and the SC is closely associated as previously suggested [37].

3.2. Barrier capabilities

Recently, the most discussed function of epidermal TJs is the barrier function for endogenous as well as exogenous molecules. The first observations of its barrier capabilities was described by Furuse et al. [26]. TJs create a selective paracellular barrier that regulates both inside-out and outside-in movement of various molecules such as water, ions (Na^+, Cl^-, Ca^{2+}), intermediate sized molecules (fluorescein, 336 Da) and macromolecules (FITC-

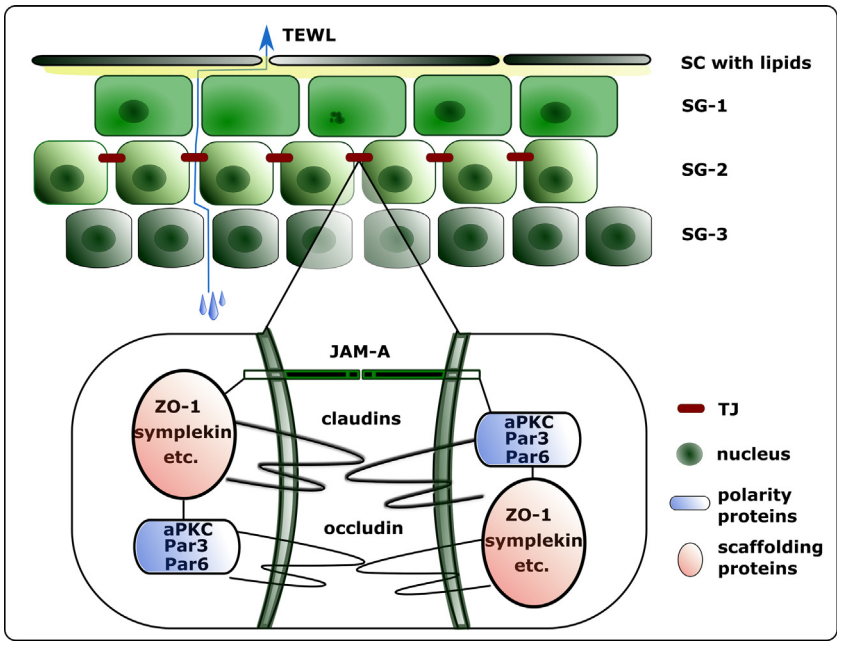

Fig. 1. Localization, structure and protein composition of epidermal TJ. JAM, junctional adhesion molecules; Par, partitioning defective; aPKC, atypical protein kinase; SC, stratum corneum; SG, stratum granulosum; TEWL, trans epidermal water loss; TJ, tight junction.