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Mini Review

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Spongiosis: A Short Review

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ABSTRACT

Spongiosis is the hallmark of eczematous dermatitis. The mechanism underlying it is somewhat complex and is not fully understood up till now. Many factors interplay to produce spongiosis. One of these factors is Fas receptor/Fas ligand interaction.

KEY WORDS: Spongiosis; Dermatitis; Fas.

ABBREVIATIONS: DSC: Desmocollins; DSG: Desmogleins; ECAD: E-cadherin; EPLIN: Epithelial Protein Lost in Neoplasm; IC: Intercellular; KCs: Keratinocytes; RCM: Reflectance Confocal Microscopy.

DEFINITION

Spongiosis is a process in which intercellular edema between the squamous cells of the epidermis causes an increase in the width of the spaces between them, separating the malphigian cells with stretching and eventually rupture of the intercellular prickles, and accentuation of honeycombed morphology of the upper epidermal layers appears accentuated, resulting in a sponge like appearance of the tissue (hence the name spongiosis).[1,2]

Another feature frequently observed is vesicle formation, which—either focal or widespread in extent—is seen on reflectance confocal microscopy (RCM) as well-demarcated that appear as dark hollow spaces between granular and spinous keratinocytes (KCs). Often small round, weakly refractile cells may be seen in the center of vesicles and microvesicles, these may correspond to apoptotic KCs or inflammatory cells.[1]

Exocytosis is regularly associated with spongiotic dermatitis, whereby the inflammatory cells are seen on RCM as bright, round highly refractile structures of about 8-10 mm, interspersed between KCs. Inflammatory cells may also be observed to various extents in perifollicular, perivascular or interstitial dermal distribution.[1]

MECHANISM

Spongiosis is a characteristic histopathologic appearance in eczematous dermatitis.[3,4] It entails condensation of KCs with widening of the intercellular (IC) spaces, IC edema and distention of the remaining IC contacts which give the epidermis a 'sponge-like' appearance. IC adhesion is normally anchored by desmosomes and adherens junctions.[5]

Fluid Accumulation

The two reasonable possibilities for the source of accumulated fluid in the intercellular space: (1) from the epidermal cells or (2) from the dermal fluids which arise, in turn, from the vessels. The epidermal cells alone cannot account for all the fluid, which is obvious in that an extremely spongiotic epidermis (e.g., a blister of contact dermatitis) often assumes a greater volume than the initial epidermis. If we accept that most of the fluid comes from the dermis, then why does that fluid accumulate in the epidermis.[6]

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There are two hypotheses for epidermal spongiosis fluid accumulation: (1) the fluid is pushed there by dermal hydrostatic pressure (due to decrease in the osmotic pressure of the dermis), or (2) the fluid is pulled there by epidermal osmotic pressure (due to increase in the osmotic pressure of inter-KCs space). In both cases a permissive basement membrane is assumed. The first possibility is clearly not operative; for under conditions in which there is massive dermal edema (increased dermal hydrostatic pressure), such as in urticaria or erythema multiforme, bullous formations often result in the upper dermis before any spongiosis is appreciable in the epidermis.[7]

While this mechanism may play a role in some situations, it is easier to visualize the epidermal cell as the agent influencing this process. The KC may respond to injury actively, for example, by altering its membrane cation pump, favoring an outflow of ions. A review of the cell physiology literature yields some experimental data from frog skin studies, suggesting that stratum spinosum cells may pump sodium ions into the epithelial interspaces,[8] and enough sodium salt may be transported into the interspaces to keep them expanded.[9]

In one report when sodium transport was stimulated, the IC spaces widened, and when sodium transport was inhibited by ouabain or dinitrophenol, the intercellular spaces closed.[10] A passive mechanism can also be hypothesized. Permeability of the KC plasma membrane could increase (e.g., from cell death), with leakage of cytoplasmic protein. This in turn would pull fluids to the inter-KC area.[6]

Detachment of Cells

Specific adhesiveness of KCs is provided by homophilic interactions of the cadherin superfamily.[11,12] Adherens junctions anchor actin microfilaments and contain E-cadherin (ECAD) as their transmembrane glycoprotein. The intracellular segment of ECAD associates with α-catenin, β-catenin, and ɤ-catenin (plakoglobin) .[12] Although, central to cellular adhesion, cadherins display physiologic functions beyond the mechanical interconnection of cells. It has been suggested that cadherins play a crucial role in regulatory pathways involved in various aspects of cell fate including developmental decisions, cell differentiation, and cell survival.[13]

CADHERINS

Cadherins are a superfamily of adhesion molecules that mediate Ca^{2+} dependent cell-cell adhesion in all tissues of that determine tissue architecture and control cell contact formation and dissociation during development, tissue homeostasis of all metazoans.[14]

This superfamily involves: Classical cadherins that are the major component of cell-cell adhesive junctions, desmogleins (DSG), desmocollins (DSC), protocadherins and some other cadherin-related molecules (e.g., The Fatprotein of Drosophila). Expression of particular cadherins often correlates with formation of discrete tissue structures, and in mature tissues discrete cell layers or other cell assemblies are often demarcated by particular cadherins.[15]

The majority of members of the cadherin superfamily are transmembrane glycoproteins that pass the membrane only once. The N- and C-termini of the cadherin protein chain are located outside and inside the cell, respectively.[16]

Classical cadherins contain five cadherin domains that are commonly designated as extracellular1 (EC1)-extracellular5 (EC5) (beginning with the N-terminus of the molecule). The conformation of the cadherin molecule is stable only in the presence of Ca^{2+}, whose binding with the EC portion of the polypeptide chain is prerequisite for cadherin-mediated cell-cell adhesion.[17] Removal of Ca^{2+} leads to a disordering of interdomain orientations, as can be seen by electron microscopy,[18] increased sensitivity to proteolysis, and increased motion between successive domains.[19]

THE EXTRACELLULAR DOMAIN (EC)

EC portion of the cadherin molecule consists of a varying number of so-called cadherin domains that are highly homologous to each other. Each domain is comprised of approximately 110 amino acid residues. EC cadherin domains per seared capable of hemophilic recognition and binding. It was shown that cells that express mutant cadherins lacking the cytoplasmic domains can bind with substrate covered with purified cadherin ectodomains. However, in this case adhesion is much weaker than in the case of cells bearing full-size cadherins.[17,20]

The Cytoplasmic Domain

The cytoplasmic region of classical cadherins, roughly 150 amino acids long, is the most highly conserved portion of these proteins. The juxta-membrane region binds to p120, and the carboxy-terminal ca. Hundred amino acids bind to β-catenin and to plakoglobin. Sequences homologous to the β-catenin/plakoglobin-binding region are also present in the desmosomes. The cytoplasmic domain of classical cadherins is associated with the cytoplasmic proteins catenins, which, in turn, serve as intermediate linkers between the cadherins and actin filaments**.** These data indicate that the formation of stable cell-cell junctions depends on the presence of functionally active cytoplasmic domain in the cadherin molecule and association of the latter with the cytoskeleton. Deletion of the cytoplasmic domain or the catenin-binding site suppresses stable cadherin-mediated adhesion of cultured cells.[17] Alternatively, over expression of the catenin-binding site also entails disruption of cell-cell junctions. This could be explained by competition of the expressed catenin-binding site with the endogenous cadherin for catenin binding.[21]

The Role of Cadherins in Mechanotransduction

Cadherins require anchoring to the cytoskeleton for properad-

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hesive function and junction organization. This is mediated by the catenins, a class of cytosolic proteins that were identified as cadherin-associated proteins necessary for cell adhesion.[22] Catenins form a protein family that is characterized by the armadillo repeat. Cadherins bind with their C-termini to β-catenin that in turn binds to α-catenin. The cadherin-catenin complex is connected *via* α-catenin with actin filaments, an interaction that may not be direct,[23] and might require further bridging proteins such as epithelial protein lost in neoplasm (EPLIN) or vinculin.[24]

Regulation of Cadherin Activity

Cadherin-mediated adhesion can be regulated by a variety of extracellular signals, including growth factors,[25] peptide hormones[26] signals from gap junctions and cholinergic receptor agonists.[27]

In response to these external stimuli, different signals are generated in the cell, of which protein phosphorylation is apparently, the most important for the regulation of cadherin function.[28]

Another mechanism of regulation of cadherin activity is changing the extent of clustering of cadherin molecules in the junction area which can significantly affect the strength of cell-cell interaction.[29]

Implications and Indications of Cadherins in Diseases

1) Cancer: Mutations that lead to a loss of ECAD, may play a role in cancer as found in laryngeal squamous cell carcinoma.[30] Down-regulation or loss of cadherins correlates with an increased metastatic potential of the affected cells due to the loss of their adhesive properties.[31]
2) Renal fibrosis is associated with downregulation of ECAD in kidney fibrosis.[32]
3) Cerebral cavernous malformation may be accompanied by irregular distribution of vascular endothelial-cadherin (VE-cad) and upregulation of N-cadherin in endothelial cells.[33]
4) Pemphigus vulgaris is associated with autoimmune disease directed against DSG1 and DSG3.[34]
5) Arrhythmogenic cardiomyopathy is associated with mutations in DSG2 and DSC2 in humans.[35]
6) Cognitive disorders and neurosensory diseases may be associated with protocadherin dysfunction.[36]

Loss of Cell Cohesion in Eczematous Dermatitis

Recently, it has been found that T-cell-mediated KC apoptosis plays a key pathogenic role in the formation of eczematous dermatitis. Spongiosis, the histologic hallmark of eczematous dermatitis, is characterized by impairment of cohesion between epidermal KCs. It is conceivable that the intercellular junction of KCs is an early target of apoptosis-inducing T-cells. It has been demonstrated that the induction of KC apoptosis is accompanied by a rapid cleavage of E-cad and loss of β-catenin. In situ examination of ECAD expression and cellular distribution in acute eczematous dermatitis revealed a reduction in KC membrane ECAD in areas of spongiosis. In contrast, the *in vitro* and *in vivo* expression of desmosomes during early apoptosis remained unchanged. Therefore, induction of KC apoptosis by skin-infiltrating T-cells, subsequent cleavage of ECAD, and resisting desmosomes suggests a mechanism for spongiosis formation in eczematous dermatitis.[5]

The development of spongiosis is initiated by early KC apoptosis due to cell shrinkage and cleavage of ECAD, which is essential in mediating KC cohesion. It has been found that impairment and loss of KC cohesion constitute the primary event in spongiosis formation. Therefore, despite being the obvious driving force of spongiosis formation, fluid influx into the skin is apparently not the primary step, but rather the end result of a sequence of pathogenic events. Accordingly, dermal inflammation and intense fluid influx into the dermis in urticaria leave skin coherence totally intact.[37]

In contrast, in early lesions of bullous autoimmune skin diseases in which desmosomes are targeted by auto-antibodies, spongiosis is visible. It should be noted here that spongiosis is a nonspecific sign of cutaneous inflammation involving the epidermis. It is found in all kinds of eczemas, in bullous skin diseases, and in some viral and superficial fungal infections as well.[38]

Spongiosis takes place mainly in the spinous layer of the epidermis. The heterogeneous basal layer contains stem cells, transit amplifying cells, and postmitotic differentiating cells with high expression of integrins.[39] It seems that in the basal layer at least stem cells exhibit strong anti-apoptotic defenses.[40] In contrast to adherens junctions that may contain only ECAD, desmosomes always include cadherins from two subfamilies, Dsg and Dsc.[41]

It has been demonstrated that apoptosis-induced protein cleavage in KCs is selective for certain adherens junction and desmosomal proteins. E-cad was cleaved, whereas β-catenin and desmosomal cadherins were not. The functional properties of ECAD and desmosomal cadherins are distinct despite their overall structural homology.[5]

The most striking sequence difference between Dsc, Dsg, and ECAD lies in their cytoplasmic tails.[42] This may contribute to the selectivity of the cytoplasmic tails for different plaque proteins connecting them with different cytoskeletal filaments. These differences may also account for the differential behavior of desmosomal cadherins and E-cad in KC apoptosis. In the spongiotic epidermis of eczematous dermatitis, not all KCs go into apoptosis. Therefore, it is likely that in areas of intense spongiosis there is additional cleavage of cadherins on by standing KCs without ongoing apoptosis possibly due to proteinases released from secondary necrotic KCs.[5]

E-cad acts as a substrate for activated caspases during KC apoptosis and its cleavage was inhibited by caspase inhibi-

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tors. These caspase inhibitors were also able to abrogate T-cell-induced KC apoptosis at the same concentration that blocked caspase-mediated cleavage events. Because of high levels of glycosylation of cadherins, several potential caspase cleavage sites, and different antibody epitopes.[5]

It was demonstrated that the cleavage site of ECAD during apoptosis is proximal to the transmembrane domain in the cytoplasm. At the 24 h time point the 85 kDa cleavage product was not consistently detectable, suggesting that further degradation may also occur.[43]

CONCLUSION

To summarize; T-cells infiltrating the skin in eczematous dermatitis induce KC apoptosis.[44] The early apoptotic response of KCs is characterized by cleavage of ECAD, whereas desmosomal cadherins remain intact. Hydrostatic pressure, which is an important factor in the development of spongiosis, and the portions of the epidermal cell surface that still retain desmosomes may explain the elongation and distortion of remaining IC contacts observed in histopathology.[5]

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