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A REVIEW ON DESMOGLEINS, DESMOCOLLINS AND ASSOCIATED DISEASES

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Abstract:
In most epithelia, desmosomes are important adhesion structures which have a key role in linking the intermediate filament network of one cell to its neighbor, thus forming a strong bond. These junctions are essential for retaining the integrity of organs, subject to mechanical stress, particularly the heart and skin. Desmogleins and desmocollins belong to super family of cadherin, which mediate adhesion at desmosomes. Through a series of protein interactions, desmosomal cadherin tails get associated with Cytoplasmic components of the desmosome, the sites of desmosome assemblage are employed with intermediate filaments. There are four types of desmogleins (Dsg1, Dsg2, Dsg3 and Dsg4) and three types of desmocollins (Dsc 1, Dsc 2, and Dsc 3). These types of desmosomal cadherins are involved in various defects. This review outlines the structure, function and associated diseases of cadherin superfamily. I believe that this review will assist researchers to enhance their basic knowledge regarding desmogleins, desmocollins and their major associated diseases.

Key words: *Desmosomes, desmogleins, desmocollins, diseases.*

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INTRODUCTION:

The tissues and organs such as skin and heart that have to withstand significant mechanical stress are abundant in desmosomes which are cell–cell adhesion structures (junctions). Desmosomes are disc-like structures and their diameter varies from 0.1to 0.5 mm. Furthermore, these structures are chiefly located in epithelial cells and their chief functions include, cell communication & cell-cell adhesion [1-3]. When these structures are visualized through standard transmission electron microscopy they have ultra structure having of two main domains. The first, called as ‘‘desmoglea’’which is separated by an electron-dense mid line area is approximately 30 nm in width. The cellular adhesion to neighboring cells is provided by such extracellular core domain that comprises of extracellular heads of this superfamily [4]. An electron dense cytoplasmic plaque, the second domain which can be further divided into an inner dense plaque and outer dense plaque, which are separated from one another by an electron lucent zone. The desmosomal plaque proteins: desmoplakin, plakoglobin, plakophilins and the amino terminal domains of the intermediate filament protein constitutes the cytoplasmic plaque. Based on previous research and evidences it has been identified that a group of glycoproteins identified by desmosomes play a significant recognition and adhesion functions of desmosomes [5]. When these glycoproteins were isolated and characterized, after that the researchers revealed that they were associated to calcium dependent class of single pass transmembrane cell adhesion molecules called cadherins [6] which were later on named as desmocollins and desmogleins. The desmocollins and desmogleins have five extracellular domains which consist of a carboxy-terminal cytoplasmic tail, a single transmembrane on both sides of domain and putative calcium-binding sites [7]. The major building of desmosomes includes three protein families, which are desmogleins, desmosomal cadherins; armadillo proteins (JUP; plakophilins, PKP1-PKP3, plakoglobin) and plakins (desmoplakin, DSP). PERP and desmosomal cadherins [8-10], collectively core of the transmembrane desmosome is responsible for their formation. Within the core, the direct heterophilic interactions between DSG and DSC proteins have major input in cell adhesion **[**11]. Through JUP, DSP is linked to the intermediate filament (IF) cytoskeletons while at least one member of the PKP family has association with desmogleins and desmocollins proteins. Giulio Bizzozero, a pathologist, was first to observe desmosome in the spinous layer of epidermis (1846–1901). These small dense nodules of Bizzozero’s observations were later on termed as “nodes of Bizzozero,” which further helped in explaining role of such structures as adhesive cell–cell contact points. Basically “desmo” is a Greek word meaning bond or fastening, and “soma,” means body, which was termed by Josef Schaffer in 1920 [12, 13]. The desmosomes organization at the ultrastructural level resulted with the discovery of electron microscopy accompanied by the hectic efforts of Porter, Odland, and Kelly. On the basis of these findings and other evidences, the three morphologically exclusive zones of desmosomes are: the inner dense plaque (IDP), the dense plaque (ODP) at outer side and the extracellular core region (desmoglea) [14-15, 3, 4, 16]. Furthermore, the field of isolation of desmosomes was advanced by using biochemical techniques [17-19]. The view that how desmosomal components are organized was further made clear through other various findings. Desmogleins and desmocollins (transmembrane glycoproteins) which belong to cadherin super family of calcium dependent adhesion molecules symbolize a distinct subfamily [16]. The cytoplasmic tails of desmogleins and desmocollins associate with the desmosomal plaque proteins, while the extracellular domains of these cadherins mediate adhesion. The cytoplasm tails of the desmosomal cadherins makes the outer dense plaque that connects plakin family of linker proteins and members of the armadillo and [16]. The upcoming portions of this review will explain the main structural and functional properties of desmocollins and desmogleins. Furthermore, this review shall also through some light on the differences in desmosomal proteins tissue expression patterns and their part in human diseases.

STRUCTURE AND FUNCTION OF DESMOCOLLINS AND DESMOGLEINS:

Desmosomes are multi protein complexes, which connect neighboring cells & intermediate filament cytoskeleton. They provide attaching points, as these structures assemble at the plasma membrane [20]. It is worth mentioning that maintenance of cohesion of tissues especially skin, heart and appendages depend upon these cell junctions. It has been reported that the subfamily of cadherins namely desmocollin (Dsc) and desmoglein (Dsg) are parts of transmembrane glycoproteins, through their heterophilic interactions, cell-cell adhesion occurs. Furthermore, a protein complex that comprises of Plakophilin(s) (Pkp), Plakoglobin (Pg) and Desmoplakin (p) connects desmosomal cadherins are connected to intermediary filament**.** Desmosomal cadherins have two main types which include desmocollins (Dscs) and desmogleins (Dsgs) [21]. There are three isoforms desmocollins (Dsc 1–3) while desmogleins have four isoforms of (Dsg 1–4) in humans [22]. Through alternative splicing of all three desmocollin genes it results in the formation of desmocollin “a” form and a shorter desmocollin “b” type of proteins, whose carboxy-terminal domains differ in their length [20, 25]. On the long arm of human chromosme number 18 (18q12.1), the three desmocollin & four desmoglein genes are present neighboring to one another [21, 26]. Moreover, four extracellular cadherin homology repeats are present in desmogleins and desmocollins along with extracellular anchor as the fifth domain**.** The length of each repeat is approximately 110 amino acids, and functional conformation of this

cadherin extracellular domain is achieved through adhesion [27]. The mouse chromosome number 18 has two additional desmoglein genes (dsg1b, dsg1g) with similar arrangement of desmosomal cadherins as in case of humans. From structural as well as evolutionary point of view, there is a resemblance between the genes of E- and N-cadherin (i.e., classical cadherins) and desmocollin than desmogleins [28]. At the cytoplasmic face of the plasma membrane, an intracellular anchor (IA) along with a single pass transmembrane domain is present [28, 10, 22]. An intracellular cadherin-like sequence (ICS) is possessed by desmogleins and the longer Dsc "a" that combines plakoglobin [29-31]**.** The unique motifs of cadherins includes: an uneven number of repeat domain (RUD), Intracellular proline-rich linker (IPL) domain, and a glycine-rich desmoglein terminal domain (DTD), such that are also possessed by desmogleins [10, 16]. Even though the exact system of desmosomal adhesion and desmosomal cadherin specificity is not completely implicit, but desmosomes demonstrate adhesion and Ca2þ-dependent assembly. For supporting cell–cell adhesion and tissue patterning, the classical cadherins typically show homophilic interactions. As for as most recent studies are concerned, desmosomal cadherins are needed for powerful cell to cell association [32, 33, 34]. Regarding desmosome adhesion, it is still not clear whether heterophilic or hemophilic interactions are mainly responsible for it. In addition to it, human fibrosarcoma cells (HT-1080) have shown heterophilic interactions between Dsg2 and Dsc1a [11]. Homophilic interactions mediated by the desmogleins have been revealed through atomic force microscopy studies [35, 36]. In the case of mature desmosomes; further studies are needed in order to understand specifically that what is the main reason that these cadherins assemble and associate in a very structured adhesive line [37].

ROLE OF DESMOGLEINS AND DESMOCOLLINS IN EPITHELIAL:

Differentiation:

Differentiation patterns of expression and complex development have been shown by desmosomal cadherins [10]. All those tissues in which desmosome is present, Dsg2 and Dsc2 are extensively expressed. In the context of stratifying epithelia, the desmosomal cadherins are chiefly expressed in epidermis of tissues of all types of desmogleins and desmocollins **(**Desmosomal cadherins). In addition, these genes go through terminal differentiation and are differentially expressed as keratinocytes [40, 10]. In the upper layers Dsg1 is expressed while Dsg2 and Dsg3 are present everywhere on lower layers of the epidermis. Hair follicle and the granular layer primarily contain Dsg4. In the case of desmocollins, the site of expression of Dsc1is in the granular layer while Dsc2 and Dsc3 are present in the basal and spinous layers. Desmosomes are biochemically and presumably function differently within various tissues, which have been confirmed via differential expression pattern of the desmosomal cadherins. Its main function is not completely clear in the tissue-specific pattern of expression of desmosomal cadherins, but tight regulation of their model of expression is significant to tissue homeostasis due to the handling of desmosomal cadherin expression. It has also been come forwarded that epidermal hyper proliferation and abnormal differentiation due to the usage of keratin 1 promoter which results into the misexpression of Dsg3, expresses in the supra basal epidermal layers of transgenic mice [39]. In recent times, hyperproliferation and susceptibility to chemically induced carcinogenesis is caused as result of misexpression of Dsg2 in epidermis differentiated layers [41]. It has been discovered in further studies that gene ablation studies play a significant job for desmosomal cadherins in adult tissue function and development. As an instance, with separation of keratinocytes and weaken desmosomal adhesion, the compromised cell– cell adhesion in the oral mucosa is due to the loss of mouse Dsg3 in animals [42]. In further studies, embryonic lethality is caused shortly after implantation due to the ablation of Dsg2 [43]. Interestingly, these studies also suggest the main roles of Dsg2 that excel adhesive functions of desmosme, and subsequently resulted in decreased embryonic stem cell proliferation due to the loss of Dsg2. A key role is also being played by Desmocollins in the control of keratinocyte proliferationand differentiation and structural integrity of the epidermis. Gene namely Dsc1, that is expressed on the epidermal t\layers of mice. In the absence this gene greater expression of injury keratins, six and sixteen, hyperproliferation, and hair follicle degeneration is caused [44]. More interestingly, preimplantation embryonic lethality (E2.5) is due to the non-desmosomal roles of Dsc3 during development [45]. Finally, keratinocytes hyperproliferation and abnormal differentiation has been caused due to the misexpression of Dsc3. The main features of this defect include epithelial proliferation, increased stability of b-catenin and the protein that regulates expression of gene [46]. Desmosomal cadherins in epithelial cells expedite cell–cell adhesion, proliferation and differentiation which is needed for the integrity of tissue. These findings have successfully been illustrated in reported studies by using mouse genetic models. These findings have also been confirmed by several numbers of human diseases (both inherited and acquired).

ASSOCIATED DISEASES OF CADHERINS:

In last two decades several studies have reported that disorders due to desmosomal cadherins have affected different human organs such as the skin & heart. Majority of the inherited disorders that affect the skin and appendages are linked with desmosomal genes, which comprise of mutations in plakophilin (PKP1 (MIM 601975), that causes ectodermal dysplasia with skin fragility & sparse hair [47]. Plakoglobin (PG (MIM 173325) & Desmoplakin (DSP (MIM 125647),

characterized by sparse wooly hair and cardiomypathy underlay Naxos disease (MIM 601214) [48- 49]. Mutations that cause inherited disorders are due to the involvement of three of the desmoglein isoforms. Function of Desmoglein seems critical throughout differentiation of layers of hair follicle when it is expressed in the inner epithelial layers of the hair follicle. Several human disorders that result from mutations in adhesion plaque genes assist in understanding the importance of properly arranged adhesion during hair follicle development. In recent times by using the candidate gene approach several congenital disorders involving desmosomal components have been recognized [50]. There are two desmosomal genes namely desmoglein 1 and desmoplakin which are associated with rare autosomal dominant disorder known as Striate Palmoplantar Keratoderma [51-53]. Desmoglein-1, which is a transmembrane member of the cadherin family, plays a significant role in homo typic cell adhesion. In addition, due to desmogleins-1 amino terminal deletion in the extracellular domain negative effect on dimer formation and disruption of desmoglein 1 cell binding has occurred. The prominent symptoms of this disease include linear and focal hyperkeratosis of the palms and soles.

Desmoglein 3 in transgenic mice:

Oral blistering which is caused due to the knockout of Desmoglein 3 in mice reflects its main function in cell-cell adhesion [54]. Due to these findings the significance of desmoglein 3 in maintenance of cell-cell adhesion and in oral epithelium of patients with the disease pemphigus vulgaris becomes more vivid [55, 56].

DESMOSOMAL MOLECULES AND ASSOCIATED DISORDERS:

Auto immune disorders:

The loss of epidermal cell-cell adhesion becomes more evident due to the occurrence of life risking blistering skin diseases like pemphigus foliaceus and pemphigus vulgaris [56, 57]. The autoantigen in pemphigus foliaceus, which is expressed in all the epidermal layers is desmoglein 1 (a transmembrane glycoprotein) [58, 59]. Desmoglein 3 (a transmembrane glycoprotein that is expressed in the epidermis and oral epithelia) is the antigen in pemphigus vulgaris [58, 60]. Eosinophilic spongiosis and autoantibody binding to desmoglein 1 and/or desmoglein 3 are the main characteristics of Herpetiform pemphigus, which is one of the numerous subtypes of pemphigus that has been identified up till now. It has also been supported by various evidences that in intercellular IgA pemphigus desmocollin 1 is the target antigen [61]. Moreover, autoantibodies react with a variety of plakin family of proteins, including desmoplakin 1 and 2, the 230 kD bullous pemphigoid antigen, plectin, desmoglein 3, and a 170 kD protein which have still not been characterized [61]. Defective hair-follicle differentiation is caused due to the loss of DSG4 [62]. Palmoplantar keratoderma which is an epidermal-thickening disease is marked when DSG1 haploinsufficiency goes further [51]. Moreover, when the tissue expression patterns of such genes results it prompts the impact of these restricted mutations in DSG1 and DSG4 on the skin. On the other end, arrhythmogenic right ventricular cardiomyopathy (ARVC) results with the mutations in DSG2 [63, 64]. In order to resist mechanical stresses associated with cardiac contraction, Dsg2 function is necessary for the manifestation of heart disease. Up till now, several mutations related to DSG3 have been reported. The examples of DSG3 mutations have not been reported up till now. Nonetheless, in recent times, Simpson and colleagues have reported the association of autosomal recessive ARVC with desmocollin (DSC2) in which first ever mutation has been found [65].

By studying human disorders some roles of desmocollins and desmogleins in both differentiation and strength of tissue have been revealed. As in the case of mouse genetic models such functions have already been reported. Desmosomal cadherins are also involved in autoimmune diseases apart from inherited disorders. Desmosomal cadherins, such as Dsg1 and Dsg3 are targeted by auto antibodies in Pemphigus class of diseases. The word “pemphigus” has been taken from a Greek word “pemphix,” meaning blister. Such pathologies comprise pemphigus and vulgaris [66]. Auto antibodies (IgG) against Dsg3 and sometimes against Dsg1 are the main characteristics of autoimmune skin disease PV [57, 67-70]. Mucous membrane wearing away and epidermal blisters are the clinical symptoms of PV while suprabasal acantholysis (loss of cell–cell adhesion) is it’s histological sign [71]. On the other end, antibodies are shown by PF patients against Dsg1 and they also show clinical symptoms without mucous membrane involvement and superficial blisters of the epidermis. In the clinical appearance of PV and PF, there is dissimilarity due to tissue distribution of Dsg1 and Dsg3 [72]. Nevertheless, loss of keratinocytes adhesion is caused as a result of auto antibodies directed against tdesmosomal cadherins in both the cases [73]. Although, Pemphigus is comparatively an uncommon disease, such disorders have confirmed significant in illuminating the process through which desmosome role is synchronized and roles of desmogleins too. Stanley and Amagai rightly envisage that a common infection namely bullous impetigo is caused by staphylococcal bacterium. This infection further results in epidermal blistering after targeting Dsg1. All such predictions became possible after understanding the molecular mechanisms of pemphigus. Dsg1 extracellular domain is cleaved by a serine protease bacterium which produces exfoliative toxin. Due to this cleavage, acantholysis is caused by Dsg1. Moreover, autoantibodies in PF patients are very similar to the blistering in the granular layer [4, 71]. Due to autoantibodies or bacterial toxins that target desmogleins, the epidermal strength is

compromised. It is still not clear that what is the main reason of loss of adhesion, even though; a lot of research has been done in this regard for recognizing pemphigus antigens. It could be one of the elaborations of fact that due to steric obstruction the adhesion is blocked as a result antibody binding to desmoglein extracellular domain. Nevertheless, more than a few observations, such hypothesis is called into query. It has also been discovered through other various studies that PV-induced acantholysis mediated due to signal transduction. Activation of several cell signaling pathways has also been due to the binding of Pemphigus IgG. It has been further explained that due to the binding of PV IgG, the phosphorylation of heat shock protein 27 (HSP27) via p38 mitogen-activating protein kinase (p38MAPK) has been induced [75-77]. In response to PV IgG, p38MAPK has been found to participate in the phosphorylation of Desmoglien-3 [78]. Moreover, keratin retraction, formation of epidermal blisters in mouse model and actin reorganization has been prevented as a result of inhibition of p38MAPK activity [79, 75]. In the same way, c-myc pathway is helpful in PV pathogenesis [80]. Such findings further make the things clear that either due to binding with the desmosomal cadherins, activation of signaling pathways occur, which may result in decrease of adhesion. It has been observed that the normal turnover of the desmogleins is due to the interference of pemphigus IgG binding. In previous studies it has been reported that after binding to the surface of keratinocytes, PV IgG were internalized [81-83]. Furthermore, PV IgG binding is responsible for endocytosis of Dsg3, clathrin self-regulating and subsequent routing of the cadherin for degradation in a lysosomal compartment [84, 85]. Moreover, Dsg3 endocytosis is blocked or Dsg3 biosynthesis up-regulation and keratinocytes loss of adhesion in response to PV IgG is prevented by exogenously expressing Dsg3 [85]. The internalization of newly synthesized pools of Dsg3 is caused by PV IgG [83, 86], therefore, the work of Payne and Kitajima has also supported that the desmosomal assembly is being affected by PV IgG. Overall, these studies propose that the normal turnover and assembly of desmosomes is disrupted by pemphigus IgG. The key mechanisms due to which regulation of cell adhesion during development and disease is due to the regulation of post Golgi trafficking of cadherins which has been supported via various evidences [87, 88].

Heart diseases and their Targeted Desmosomal molecules:

Desmoglien-2 and Desmocollin-2 are the main targeted desmosomal molecules in the case of Arrhythmogenic right ventricular cardiomyopathy (ARVC). This disease results in the thinning of the right ventricular wall and sudden cardiac death due to the substitution of right ventricular myocardium with fibro fatty tissue [89-90]. Furthermore, Dilated cardiomyopathy (DC) results in ventricular dilation that damages myocardial role and subsequently results in heart failure. In this disease the main desmosomal molecule is desmoglien-2 [91].

Defects associated with Skin and their targeted desmosomal molecules:

Several diseases have been resulted due to the defect in one or two of the many desmosomal molecules. Desmoglien-1 is the target desmosomal molecule in Pemphigus vulgaris (PV). The symptoms of this defect include acantholysis and/or oral mucosa [67]. Bullous impetigo is another skin disease which results in numerous symptoms likewise, bacterial exfoliative toxin which results in the appearance of localized blisters, usually on the trunk, arms or legs. The targeted desmosomal molecule responsible for Bullous impetigo is Desmoglien-1 [74]. Prevalent surface skin blistering and exfoliation that result in general form of bullous impetigo is the main sign of Staphylococcal scalded-skin syndrome (SSSS) and the targeted desmosomal molecule in this case is Desmoglien-1 [74]. Defect in desmocollin-2 results in a condition called as woolly hair. This disease is accompanied with and without cardiomyopathy. The main symptoms of the disease are: syndrome of the scalp hair characterized by frizzy and wiry hair giving it wool-like appearance [92]. Moreover, epidermal thickening of the palms and soles are the symptoms of Striate palmoplantar keratoderma (SPPK). In this condition Desmoglien-1 and Desmocollin-2 are responsible [51, 52]. In the subsequent researches it has been revealed that desmoglien-4 is responsible for hypotrichosis, which results in Sparse, fragile hair with abnormal hair follicles, impaired hair keratinization and epidermal hyperproliferation [62]. Hypotrichosis with skin vesicles results from Desmocollin-3. Sparse, fragile hairs with normal follicles are the main symptoms which help researchers to identify such cases [93].

CONCLUSION:

This review focused on the structure, function and some associated diseases of Desmosomal cadherins. Basically, desmosomal cadherins (Desmogleins and Desmocollins) are the main targeted desmosomal molecules. The growing knowledge regarding desmogleins and desmocollins has revealed many innovative findings in the field of genetics. The basic information pertaining to various types of desmosomal cadherins (DSG1, DSG2, DSG3, DSG4, DSC1, DSC2, DSC3) help in understanding the types of diseases or defects that are associated with them. Moreover, every disorder such as heart and skin are associated with one of the many types of desmosomal cadherins.

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