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DESMOSOME CELL - CELL CONNECTIVITY - A REVIEW

Malavika Pradeep[1], Archana Santhanam[2], S.Kavitha [3]

Abstract

Desmosomes can be defined as intermediate junctions which tether intermediate filaments to the plasma membrane . When the function of desmosomal protein is altered it can cause tissue fragility which then leads to significant clinical consequences. Desmosomes can be differentiated into 3 morphological identifiable zones namely (i) extracellular core region (ii) outer dense plaque (iii) inner dense plaque . The members of the cadherin superfamily include Desmogleins and Desmocollins. , mediate adhesion at desmosomes . Desmosomes are dynamic structures which are involved in the contribution of cellular processes beyond cell adhesion and are also quite critical when it comes to the maintenance of cell - cell adhesion. Desmosomes are also subject to dynamic regulation and undergo continual turnover. There are four isomers of desmoglein (Dsg 1-4) and three isoforms of desmocollin (Dsc 1-3) , found in humans. Calcium dependent assembly adhesion is seen in desmosomes. Pemphigus is a class of disease where the auto antibodies target desmosomal cadherins - Dsg 1 and Dsg 3. The members of the armadillo gene family , Plakoglobin and Plakophilin are included in the desmosomal plaque. The plakoglobin , plakophilin and desmoplakin associates the cadherin cytoplasmic tails. Alteration in desmosomal protein function leads to tissue fragility with significant clinical consequences.

Keywords:*Desmosome, desmoglein, cell to cell contact.*

Introduction

The term ‘desmosomes’ , desmo means fastening or bonding and soma means body. [1]Desmosomes can be defined as intermediate junctions which tether intermediate filaments to the plasma membrane . [2] Desmosomes were first observed in the spinous layer of the epidermis. [3]Desmosomes can be separated or differentiated into 3 morphological identifiable zones . They are as follows : (i) extracellular core region (ii) outer dense plaque (iii) inner dense plaque . [4]Tissues that experience mechanical stress are conferred with stability by the desmosomes. The presence of desmosomes can be seen in more specialized junctions of the meninges and lymphatic endothelial cell. Keratinocyte terminal differentiation , tissue morphogenesis and epidermal patterning of homeostasis are certain functions of the desmosomes.

The members of the cadherin superfamily include Desmogleins and Desmocollins which mediate adhesion at desmosomes The desmosomal cadherins possess the ability to suppress invasiveness. The desmosomes are highly symmetrical and consist of electron dense plasma domains that intermediate filament networks in the core region of the desmosome in intercellular space- cell-cell adhesion . It is proved that desmosomal cadherin along with its associated proteins play an important role in the instruction of development and differentiation of complex tissues in vertebrates. They are also targeted by bacterial toxins and autoimmune antibodies. Previously our team had conducted numerous original studies [5–11] and surveys [12–19] over the past 5 years. The idea for the present study stemmed from the current interest in our community.

[1] Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India, Mail id: 151901020.sdc@saveetha.com
[2] Assistant Professor, Department of dental anatomy, Saveetha Dental College and Hospitals, Saveetha institute of Medical and Technical Sciences, Saveetha University, Chennai, India, Mail id: drarch.s@gmail.com
[3] Lecturer, Department of Biochemistry, Saveetha Dental College and Hospitals, Saveetha institute of Medical and Technical Sciences, Saveetha University, Chennai, India, Mail id: kavithasankaran87@gmail.com

SALIENT FEATURES

Desmosomes are involved in the regulation of tissue morphogenesis . [20] When the function of desmosomal protein is altered it can cause tissue fragility which then leads to significant clinical consequences. Inherited mutation genes - encoding desmosomal constituents can adversely affect skin. The desmosomes are involved in tumour function - expression of desmosomal components.

STRUCTURE OF DESMOSOMES

Desmosomes consist of desmogleins and desmocollins. The desmogleins or desmocollins , or in other words the desmosomal cadherins is extended upto the extracellular core and outer dense plaque. This is for adhering to neighbouring cells in Calcium dependent manner and for establishing contact. The plakoglobin , plakophilin and desmoplakin associates the cadherin cytoplasmic tails. Within the inner dense plaque , the desmoplakin joins or binds with the keratin intermediate filaments. This serves to tether intermediate filaments towards the plasma membrane. [21]

COMPONENTS OF DESMOSOMES

The cytoplasmic tails of the desmosomal cadherins are found in the outer dense plaque . The cytoplasmic tails bind to the plakin family of linker proteins and the members of the armadillo protein .[22] A member of the armadillo family protein ,plakoglobin , binds directly with the desmogleins and desmocollins cytoplasmic tails. [23] A member of the plakin family , desmoplakin , interacts with plakoglobin and plakophilin , which is another subgroup of armadillo family proteins.[24] The interaction between desmoplakin and keratin filaments forms the inner dense plaque , tethering the cytoskeletal network to adhesion complex.

THE DESMOSOMAL CADHERINS

DESMOGLEINS AND DESMOCOLLINS : STRUCTURE AND FUNCTION

The desmosomal cadherins are divided into two types - (i) desmogleins (ii) desmocollins. There are four isomers of desmoglein (Dsg 1-4) and three isoforms of desmocollin (Dsc 1-3) , found in humans.[25] The three desmocollin gene products undergo alternative splicing, which results in the formation of shorter Dsc “b” form and Dsc”a" forms of the proteins. These forms of proteins differ in the length of respective carboxy - terminal domains.[26] Cadherin mediated adhesion is supported by extracellular calcium, by allowing the cadherin extracellular domain in assuming a rigid and functional confirmation. [27] Intracellular cadherin like sequence is found in desmoglein and desmocollin “a” , that binds plakoglobin. [28]The desmoglein consist of desmoglein terminal domain , variable number of repeat unit domain and additional intracellular proline proline - rich linker. [29] The desmogleins harbour other unique motifs which are specific to this subfamily of cadherins such as glycine - rich desmoglein terminal domain , intracellular proline rich linker and variable number of repeat unit domain. Calcium dependent assembly adhesion is seen in desmosomes. [30]Homophilic interaction is shown by classical cadherins that support cell-cell adhesion and tissue patterning. In human fibrosarcoma cells , heterophilic reactions were observed between Dsg2 and Dsca and also in between Dsg 2 and Dsc2 , by use of recombinant polypeptides. [31]

ROLE OF DESMOSOMAL CADHERINS IN EPITHELIAL DIFFERENTIATION

Dsg 2 and Dsc 2 are widely expressed in all desmosome bearing tissues. Other desmosomal cadherins are predominantly expressed in stratification epithelial. The main distribution of Dsg 2 and Dsg 3 are along the lower layers of epidermis. Dsg 1 is expressed in higher levels of upper layers. Dsg 4 is depressed in the hair follicle and granular layer primarily. Dsc 1 is expressed in a granular layer. The epidermis of the stratified epithelium consists of four distinct layers which is as follows - (i) basal layer (ii) spinal layer (iii)granular layer (ii) stratum corneum. Keratin filaments are shown connecting to hemidesmosomes at basement membrane and shown connection to desmosomes at sites of cell - cell contact. Epidermal hyperproliferation and abnormal

differentiation is the result of misexpression of Dsg 3 with the help of keratin 1 promoter. [20] Hyper proliferation and susceptibility to chemically induced carcinogens is result of misexpression of Dsg2 in differentiated layers of epidermis.[32] In control of keratinocyte proliferation and differentiation and structural integrity of epidermis, a significant role is played by the desmocollins. Perimplantation embryonic lethality is the result of complete loss of expression of Dsc3. [33] Abnormal differentiation and keratinocyte hyperproliferation DSc3 misexpression in suprabasal epidermis. [34]

DESMOSOMAL CADHERINS AND DISEASE

Defective hair follicle differentiation is associated with loss of Dsg4.[35] Striate palmoplantar , an epidermal thickening disease , is caused by Dsg1 haploinsufficiency. Pemphigus is a class of disease where the auto antibodies target desmosomal cadherins - Dsg 1 and Dsg 3. The pemphigus comes from greek word pemphix which means blister. Pemphigus vulgaris and Pemphigus foliaceus are the pathologies included. Pemphigus vulgaris is an autoimmune skin disease that is characterised by circulating autoantibodies against Dsg3 and Dsg1 . [36] It is characterised clinically by membrane erosion blisters and histologically by suprabasal acantholysis.[37] Autoantibodies are directed against desmosomal cadherins in pemphigus foliaceus and pemphigus vulgaris and it causes loss of keratinocyte adhesion. Activation of numerous cell signalling pathways is caused by pemphigus Ig binding. Pemphigus Ig binding interferes with normal turnover - desmoglein. P38 MAPK involved in phosphorylation of Dsg 3 - response - PV IgG. [38]

ARMADILLO FAMILY OF PROTEINS

PLAKOGLOBIN

It is the best characterised armadillo protein in the desmosome. Structurally the protein consists of 12 arm repeats flanked by distinct amino acid and carboxy terminal domains. The central armadillo domain of plakoglobin interacts with desmoplakin and tether at intermediate filaments - desmosomal plaque. Animals null of plakoglobin die because of myocardium fragility. Naxos disease is an autosomal recessive disease. It is characterised by wooly hair and palmoplantar keratoderma , which develops in result of plakoglobin gene mutation that leads to truncation of carboxy terminus of proteins. [39]

PLAKOPHILIN

Plakophilin 1-3 shares approximately 55% sequence similarity within armadillo repeats and approximately 50% sequence similarity P120 of catenin and domain. [40] PKP1 and 2 exist as 2 isoforms . Each generate short “a” form and longer “b” form , that differ in addition of 21 aminoacid in arm repeat three and addition of 44 aminoacids in arm repeat four.Similar to desmosomal cadherins , plakophilins also show tissue differentiation in specific patterns of expression . Conditional ablation of PKP3 in mouse epidermis results in defective hair follicle morphogenesis , increased keratinocyte proliferation and desmoplakin mislocation. [41]

DESMOPLAKIN

It is the most abundant component of desmosome. Desmoplakin contains globular amino and carboxyl terminals that are connected by central alpha helical coiled - coil rod domain . The carboxy tail contains three plakin repeat domains as well as glycine - serine - arginine - rich domain. As a result of alternative RNA splicing , Desmoplakin I and II are produced. Wooly hair , keratoderma and skin fragility is caused by compound heterozygosity in amino terminal missense mutations and carboxy terminal nonsense mutation. [42]

FUTURE SCOPE -

In future , the identification of downstream targets and molecular determinants of desmosomal cadherin signalling will have important implications in understanding of tissue morphogenesis . Further Work to expose interdependent adhesive networks will be important in determining best targets for therapeutic surgeries. In future there can be more studies that aim to define desmosomal cadherin structure and nature of protein that interact with unique cytoplasmic tails , which is needed for better understanding .

CONCLUSION -

Alteration in desmosomal protein function leads to tissue fragility with significant clinical consequences. Desmosomes play the roles of mediators of various signaling pathways. Desmosomes are also subject to dynamic regulation and undergo continual turnover , although desmosomes function as robust adhesive structures.

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AUTHORS CONTRIBUTION -

Malavika Pradeep : Literature search, data collection , analysis , manuscript writing

Dr.Archana S : Study design , data verification , manuscript drafting.

CONFLICT OF INTEREST -

The authors declare that there were no conflicts of interest in the present study.

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