

The role of desmosomes in carcinogenesis

Guangxin Zhou¹
 Linlin Yang²
 Ashley Gray³
 Amit Kumar Srivastava⁴
 Cuiping Li⁵
 Gongwen Zhang⁶
 Tiantian Cui²

¹Department of Oncology, Central Hospital of Binzhou, Binzhou Medical College, Binzhou, People's Republic of China; ²Department of Radiation Oncology, Arthur G James Hospital/Ohio State Comprehensive Cancer Center, ³The Ohio State University, ⁴Division of Radiobiology, Department of Radiology, The Ohio State University Wexner Medical Center, Columbus, OH, USA; ⁵Department of Respiratory Medicine, ⁶Department of Cardiac Surgery, Central Hospital of Binzhou, Binzhou Medical College, Binzhou, People's Republic of China

Abstract: Desmosomes, which are intercellular adhesive complexes, are essential for the maintenance of epithelial homeostasis. They are located at the cell membrane, where they act as anchors for intermediate filaments. Downregulation of desmosome proteins in various cancers promotes tumor progression. However, the role of desmosomes in carcinogenesis is still being elucidated. Recent studies revealed that desmosome family members play a crucial role in tumor suppression or tumor promotion. This review focuses on studies that provide insights into the role of desmosomes in carcinogenesis and address their molecular functions.

Keywords: desmosome, desmosomal cadherin, β -catenin, plakoglobin, plakophilins, desmoplakin

Introduction

Desmosomes are intercellular junctions that, in association with intermediate filaments, mechanically link cells and stabilize tissue architecture.¹ Desmosome structure was first observed in 1864 by Bizzozero, an Italian pathologist; its structure has since been analyzed by techniques such as electron microscopy (EM) to reveal a complex structure and organization. The desmosomal components comprise three main protein families: transmembrane cadherin family (desmogleins [DSGs] and desmocollins [DSCs]), armadillo (ARM) protein family (plakoglobin [PKG], plakophilins [PKPs], and β -catenin), and plakin protein family (desmoplakin [DSP]). Genes encoding desmosomal constituents were found mutated, which can have effects on tissue integrity; but they are not only simple static adhesive structures, increased evidences show that desmosomes also act as tumor suppressors or oncogenes in various cancers, regulating cell proliferation, differentiation, migration, apoptosis, and treatment sensitivity.² The following sections of this review describe the structure of the desmosome family members and functional characteristics of the major desmosomal proteins.

Desmosomal structure

Desmosomal cadherin family

DSGs (Dsg1–4) and DSCs (Dsc1–3) are desmosomal cadherin family members found in humans. DSGs and DSCs are required for strong cell–cell adhesion³ via their interaction with each other across the intercellular space (Figure 1), in a homophilic and/or heterophilic manner; the difference between the two types of interactions remains unclear. These desmosomal cadherins show complex developmental and differentiation patterns of expression.^{1,4} Dsg1/3 and Dsc1/3 are present in stratified epithelia, and Dsg4 is found in stratified epithelia and hair.^{5–7} Dsg2 and Dsc2 are the primary isoforms in simple epithelia and are present at low levels in the basal layer of stratified epithelia.⁶ All three DSC1-3 gene products undergo alternative splicing, resulting in the generation of the Dsc “a” form and a shorter Dsc “b” form of

Correspondence: Tiantian Cui
 Department of Radiation Oncology,
 Arthur G James Hospital/Ohio State
 Comprehensive Cancer Center,
 351 Wisemen Hall, 410W 12th Ave,
 Columbus, OH 43210, USA
 Tel +1 614 312 4765
 Email tiantian.cui@osumc.edu

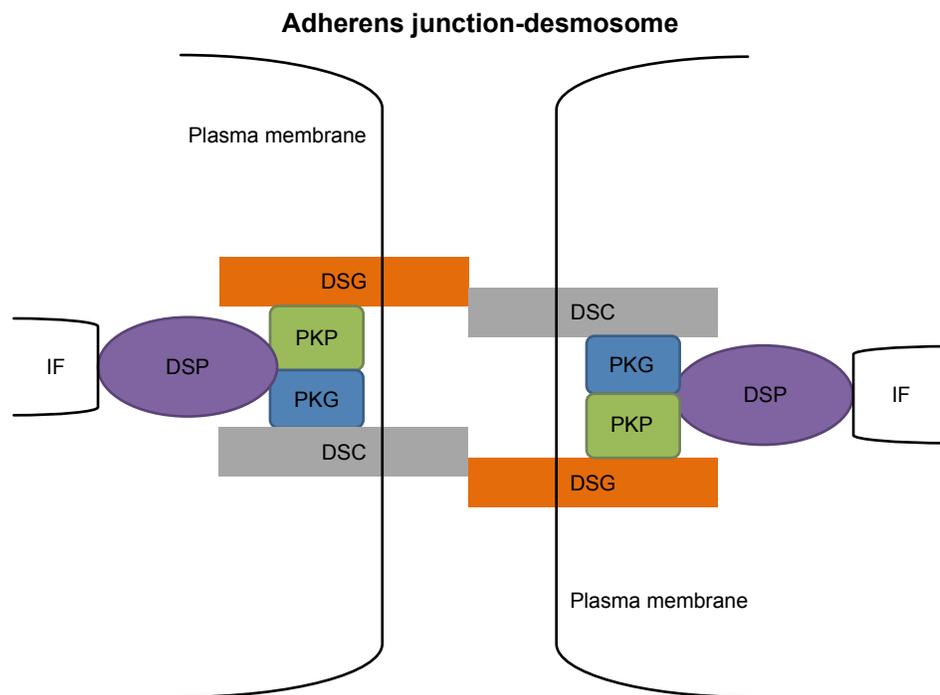


Figure 1 A model for the structure of desmosomes.

Abbreviations: DSC, desmocollin; DSG, desmoglein; DSP, desmoplakin; IF, intermediate filaments; PKG, plakoglobin; PKP, plakophilin.

the proteins, which differ in the length of their respective carboxy-terminal domains.^{8,9} The DSC extracellular (EC) domains can be divided into a number of subdomains, including four cadherin-like EC domains and an extracellular anchor (EA) domain. DSG EC domains are organized in a similar fashion. Within the cell, both DSC “a” and “b” proteins possess an intracellular anchor (IA) domain, but only “a” form proteins have an intracellular cadherin-like sequence (ICS) domain. DSG cytoplasmic tails also have IA and ICS domains. DSC and DSG ICS domains provide binding sites for other desmosomal constituents.¹⁰

ARM family

ARM family members are mainly β -catenin, PKG (or γ -catenin), and PKPs (PKP1–3).¹¹ They are characterized by the presence of a central domain, containing repeating units of a 42 amino acid sequence homology domain,¹² and they mediate the cytoplasmic associations with the cadherins. β -Catenin consists of several very characteristic repeats, each ~40 amino acids long. All these β -catenin elements fold together into a single, rigid protein domain with an elongated shape, called an ARM domain. PKG, which contains 12 arm repeats, exhibits dual localization in desmosomes and adherens junctions. In addition, β -catenin contributes to desmosomes only in PKG-negative organisms. PKPs contain 9 arm repeats with a flexible insert between repeats 5 and 6

that introduces a major bend in the overall structure.¹³ There are two isoforms of PKPs 1 and 2, a shorter “a” form and a longer “b” form, generated by alternative splicing. PKP1a and 1b differ by the insertion of 21 amino acids between arm repeats 3 and 4, whereas PKP2a and 2b differ by the insertion of 44 amino acids between repeats 2 and 3.^{14,15}

Plakin family

There are several plakin proteins, including DSP, plectin, envoplakin, and periplakin. DSP, which is the most abundant component of the plakin family, interacts with other desmosomal family members, such as PKG, PKPs, and intermediate filaments, providing the link in the chain from the plasma membrane to the cytoskeleton.¹⁶ The DSP gene is located on chromosome 6p24.3, containing 24 exons and spanning ~45 kDa of genomic DNA.¹⁷ There are two predominant isoforms; the first, known as “DPI”, has molecular weight 332 kDa (2,871 amino acids) and the second, known as “DPII”, has molecular weight 260 kDa (2,272 amino acids). These isoforms are identical except for the shorter rod domain in DPII. DPI is the predominant isoform expressed in cardiac muscle.¹⁸ Although DPI and DPII are functionally redundant, loss of the C-terminal tail domain from DPI/DPII has devastating consequences on skin integrity and results in early neonatal death in lethal acantholytic epidermolysis bullosa.¹⁹

The role of desmosome in cancer

During the past 15–20 years, studies revealed the role of desmosome in human diseases, especially in heart and skin diseases. Although the role of desmosome proteins in cancer development and progression is not clear, some recent progress has been made.²⁰ Recently, a body of evidence shows that they may influence epithelial cell invasion and metastasis since an important function of desmosomes related to cancer is their ability to inhibit cell motility.²¹

Desmosomal cadherins and cancer

Recently, studies have shown that desmosomal proteins have both tumor-promoting and tumor-suppressive functions in different types of cancers.²² For example, DSG2 is found to be overexpressed in skin cancer,²³ and overexpression of DSG2 promotes lung cancer cell growth through regulation of p27 and CDK2.²⁴ DSG3 was upregulated in head and neck cancer and lung cancer.^{25,26} Brown et al²⁷ showed that DSG3 promotes cancer cell migration and invasion by regulating AP-1 and PKC in head and neck cancer. By contrast, loss of DSC2 contributes to the growth of colorectal cancer cells by regulating Akt/ β -catenin signaling.²⁸ DSC3 ablation increased the incidence of Ras-induced skin tumors in mice;²⁹ furthermore, it is found to be downregulated in breast, lung, and colorectal cancers due to promoter hypermethylation.^{10,30,31} We found that ectopic expression of DSC3 by introducing a DSC3 expression vector into lung cancer cells successfully suppressed lung cancer cell growth and motility through inactivation of the EGFR/ERK signaling pathway.³⁰ Desmosomal cadherin proteins have also been considered as prognostic markers in various cancer types. For example, decreased DSG3 expression was associated with poor prognosis in lung cancer.²⁶ Our studies showed that DSC1 may be a marker for tumor differentiation, DSC3 has a potential diagnostic value in sub-classification of non-small-cell lung cancer (NSCLC) into squamous cell carcinoma (SCC) and adenocarcinoma (ADC), and furthermore, DSC1 and DSC3 may be prognostic markers for lung cancer.³²

ARM proteins and signaling pathway

ARM proteins also mediate important signal transduction pathways in human cancer. β -Catenin, which is widely expressed in many tissues, is involved in regulation and coordination of cell–cell adhesion and gene transcription. Meanwhile, it acts as an intracellular signal transducer in the Wnt signaling pathway. The Wnt signaling pathway plays an essential role in embryonic development and stemness and has also been described in carcinogenesis.³³ When the Wnt

signaling pathway is activated by the binding of Wnt ligands to the Frizzled receptors and the low-density lipoprotein co-receptors, the degradation complex is inactivated, resulting in the stabilization of β -catenin. This leads to the translocation of β -catenin into the nucleus where it associates with the lymphoid enhancer factor/T-cell factor (LEF/TCF) family of transcription factors to activate many downstream target genes.³⁴ More details of the Wnt/ β -catenin signaling pathway can be found elsewhere.³³

PKG, which is closely related to β -catenin, is another important member of ARM family. It interacts with similar molecules, such as β -catenin. Miravet et al³⁵ found that PKG could reduce transcription of Wnt target genes through binding to adjacent sites on Tcf-4 with β -catenin and inhibiting binding of Tcf-4 to DNA. Thus, PKG is a negative regulator of Wnt/ β -catenin signaling and acts as a tumor/metastasis suppressor in various cancers. For example, in ovarian cancer, exogenous expression of PKG or knockdown of N-cadherin is more effective than expression of E-cadherin in inhibiting the growth, migratory, and invasive properties of ES-2 cells.³⁶ PKG-mediated HAI-1 regulation offers a promising novel strategy to inhibit the c-MET signaling pathway in lung cancer.³⁷ Silencing PKG in esophageal cancer cells causes defects in cell–cell adhesion and a concomitant increase in cell migration.³⁸

PKPs, which have been characterized as desmosomal plaque proteins, stabilize desmosomal cadherins at the plasma membrane and interact with the cytoskeletal linker protein DSP. They are predominantly expressed in epithelial cells with distinct expression patterns. PKP 1 is found in suprabasal layers of epithelia, while PKPs 2 and 3 localize to desmosomes from simple epithelia.³⁹ Like β -catenin, PKPs have diverse non-desmosomal functions. Loss of PKPs 1–3 is found in some tumors.^{40–42} Reduced PKP 3 expression is correlated with desmosome instability, increased cell migration, and poor prognoses for patients. Mechanistically, it is transcriptionally repressed by E-cadherin repressor ZEB1 in tumor cells, which suggests a common regulation for adherens junctions and desmosomes during tumor progression.⁴³ Surprisingly, in other tumors, PKP 1 or 3 is overexpressed, such as head and neck tumors,⁴⁴ lung cancer,²⁶ and Ewing sarcoma.⁴⁵

DSP and Wnt signaling pathway

DSP proteins are widely expressed in numerous tissues.^{46,47} Loss of expression of DSP promotes increased local tumor invasion in a mouse model of pancreatic neuroendocrine carcinogenesis.⁴⁸ Interestingly, in keratinocytes, decreased

expression of DSP could increase cell proliferation associated with elevated phospho-ERK1/2 and phospho-Akt levels.⁴⁹ In our studies, we found that DNA methylation contributes to the downregulation of DSP in lung cancer. Additionally, ectopic expression of DSP enhanced expression of PKG (γ -catenin), which is a component modulating the Wnt signaling pathway, resulting in decreased TCF/LEF-dependent transcriptional activity and reduced expression of the Wnt/ β -catenin target genes, Axin2 and matrix metalloproteinase MMP14. The epigenetic regulation of DSP and its ability to increase the sensitivity to anticancer drug-induced apoptosis has potential implications for clinical application.⁵⁰

Conclusion

Although a substantial amount of evidence is available to support the idea that desmosomes are involved in progression of cancer, unlike the role of desmosomes in adherens junctions, our understanding of the role of desmosomes and how they are involved in cancer and metastasis is still evolving. Additional studies are necessary to explore the complete function of desmosomes in human cancer. A better understanding of the regulatory mechanisms of the expression changes of desmosomes and their role as mediators of intracellular signal transduction will be important, especially for personalized therapeutic strategies. Progression on the mechanistic study will lead to a better understanding of the role of desmosomes in malignancy and have implications for cancer treatment.

Disclosure

The authors report no conflicts of interest in this work.

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