Review Article

Role of desmosomal components in the initiation and metastasis of oral cancer—A review

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Abstract

Desmosomes are composed of a number of proteins, including cadherins, armadillo proteins and plakoplilins, which are responsible for mediating cell–cell adhesion. Cadherins are transmembrane proteins that bind to each other on adjacent cells, forming a strong adhesive bond between the cells. In normal tissues, desmosomes help to maintain the structural integrity of the tissue by holding the cells together. During carcinogenesis, the structure and function of desmosomes may be altered. For example, in oral cancer, the expression of certain cadherins may be increased, leading to increased cell–cell adhesion and a more cohesive tumour mass. This may contribute to the ability of cancer cells to evade the immune system and resist chemotherapy. In addition to their role in cell adhesion, desmosomes also play a role in cell signaling. The proteins that make up desmosomes can interact with signaling pathways that regulate cell proliferation, migration and survival. Dysregulation of these pathways may contribute to the development and progression of oral cancer. There is also evidence that desmosomes may be involved in the process of invasion and metastasis, which is the spread of cancer cells from the primary tumour to other parts of the body. Cancer cells that have disrupted or abnormal desmosomes may be more likely to migrate and invade other tissues. Overall, desmosomes appear to be important in the development and progression of oral cancer. Further research is needed to fully understand the role of these cell–cell junctions in the disease and to identify potential therapeutic targets.

Keywords: Armadillo proteins, desmosomal cadherins, desmosomes, head and neck cancer, plakins

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INTRODUCTION

Cancer remains one of the leading cause of death worldwide and even if treated can lead to an altered lifestyle for the rest of the years. Increased understanding of this disease has left researchers and clinicians with more questions unanswered than actual solutions. Cancers involving head and neck are the sixth most common type worldwide and oral cancer is the most common type among them. Oral cancer is the most common type of cancer in India accounting for 50–70% of the total cancer mortality rate. More than 90% of oral cancers are squamous cell carcinomas.[1] However, it remains the most common type of cancer among men in India due

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to various factors like the population genetics, low incomes, lack of cancer awareness, environment and lifestyle leading to a heterogeneous distribution of disease burden and health loss. One of the important aspects of cancer management still remains an early detection and timely interventional management for prolonged survival. The five-year survival rates post-treatment have been encouraging but better understanding of the etiopathogenesis of cancer can help the clinicians and researchers to look into specific targeted therapies for different types of malignancies.

Carcinogenesis is a complex process and the disease itself is a result of interplay of multiple factors. An individual's food habits, lifestyle, environmental factors, tobacco, alcohol usage and viruses though are contributory to pathogenesis but the core reason still remains the mutations, at both genetic and epigenetic levels thus resulting in accumulation of multiple mutations leading to cancer.[2]

One of the important aspects of cancer progression is invasion and metastasis, and are indeed the biological hallmarks of malignant tumours and are a major cause of cancer-related morbidity and mortality. In fact, the structural integrity of the normal tissue depends on various factors that help maintain cellular adhesion including the intercellular adhesion structures or the desmosomes.

Structure of desmosomes and their role in cell adhesion

Desmosomes are intercellular junctions that provide strong adhesion between cells. They also link intracellularly to the intermediate filament (IF) cytoskeleton so that they form the adhesive bonds in a network that gives mechanical strength to tissues.[3] Thus, desmosomes are particularly abundant in tissues such as epidermis and myocardium, and are continually abused by mechanical forces.[4]

The core components of desmosomes are three protein subfamilies, namely the desmosomal cadherins, armadillo proteins and plakin proteins.[5] Desmosomal cadherins are a class of transmembrane proteins composed of desmoglein (DSG) and desmocollin (DSC), which not only mediate cell adhesion and desmosome assembly but also act as signalling scaffolds for cell movement.[6] The armadillo family consists of plakophilins (PKP) and plakoglobin (PG), which bind to an intracellular fragment of desmosomal cadherins. The plakin family is composed of desmoplakin (DSP), which is connected to IF through the C-terminal domain.[7]

Desmosomal components in cancers

Tumourigenesis and its progression is often accompanied by loss of intercellular adhesion.[8,9] Studies have shown that due to tumour development, there is an associated reduction in the desmosomal components.[10–12] Desmosomal loss is attributed to the changes that are seen in adherens junction of epithelial tissues due to the loss of E-cadherin based cell-to-cell adhesion, which is commonly seen during the progression of many types of cancers.[12] It has been shown that DSG1, DSC2, DSC3, DSG3, PG, PKP1-3 and DSP expression is reduced and this in turn is associated with poor prognosis in patients with different types of cancer like head and neck cancers, oesophageal cancers, lung cancers, skin cancer and gastric cancer.[13–15] Several desmosomal components including DSG2, DSG3, PKP3 and PKP1 have also shown an upregulation in the development of various cancers like skin cancer, lung cancer, head and neck cancers, breast and oesophagus cancer, correlating with increased proliferation, metastasis and thus leading to poor prognosis.[16,17] Thus, these studies have shown that the desmosomal components can work paradoxically and hence, the underlying mechanisms of cancer progression are complex and two-sided. Other than the desmosomal component expression, factors such as the interacting proteins, post-translational modification may also affect the role of desmosomes in cancer.[18,19] This could be due to the difference in the function which is specific to the tumour microenvironment. In head and neck cancers including Oral squamous cell carcinoma (OSCC), the altered expression of these desmosomal components plays a vital role.[20]

Desmosomal loss in oral cancers

Multiple histopathological changes are seen during the progression of the lesion from Oral potentially malignant disorders (OPMDs) to cancer and these changes are pathognomic and are critical for clinical diagnosis. During oral tumourigenesis, the number of desmosomes in altered premalignant epithelial cells reduces, resulting in loose cell-to-cell adhesion and this reduction in desmosomal number within infiltrating carcinomas leads to loss of cellular adhesion.[21,22] Following radiotherapy, it was found that there has been an increase in the desmosome abundance in tissues of head and neck carcinomas.[23,24] In addition, there is a significant correlation between desmosome loss and tumour metastasis. Desmosome loss occurs before the loss of adhesion connections, and desmosome loss drives early tumour invasion before the downregulation of adhesion connections. The loss of cell-to-cell adhesion occurs due to alterations in desmosome localisation. Desmosomal molecules detach from the membrane and accumulate in the cytoplasm leading to increased intercellular space.[25] Alterations in desmosomal expression and localisation are important parts of tumourigenesis and can be used as a molecular indicator for early diagnosis and treatment.

Desmosomal components expression and their significance

In head and neck cancers, the expression of different desmosomal components vary and so as their significance. Desmocollin 1 and PKP2 levels are significantly higher and their higher expression predicts poor outcomes and hence, these components play a potentially oncogenic role.[26,27] Alternately, significantly lower levels of expression of DSC2, DSC3, DSG1, PKP3 and DSP indicate good clinical outcomes thus these components act as tumour suppressors in head and neck carcinomas.[13,27,28] Immuno-histochemical study for the detection of desmosomes in oral squamous cell carcinoma and its correlation with differentiation, mode of invasion and metastatic potential showed that the weaker expression of DSG1 was observed in poorly differentiated and more invasive OSCC.[14] Desmosomal immune-histochemical studies also revealed contradictory roles for desmosome members like DSG2, DSG3, PKP1 and PG in head and neck carcinomas suggesting that the role of these components may be affected by modification of tumour microenvironment or other signal transduction molecules.[17,29]

Desmosomal cadherins

Desmosomal cadherins are calcium-dependent adherence proteins and consist of DSG1-4 and DSC1-3 in humans. The exact roles of these desmosomal cadherins in head and neck carcinomas are complicated as well as contradictory.[30]

Desmosomal cadherins act as a suppressor in head and neck carcinomas by the upregulation of cadherin proteins like DSC3 and mRNA in TP53-mutated maxillary carcinomas by increasing membrane localisation, indicating enhanced cell adhesion. In addition, OSCC cells exhibited DSG1 cleavage, which was related to the loss of cell–cell adhesion function. Desmoglein 1, through its interaction with Erbin (ErbB2 Interacting Protein) downregulates invadopodia signalling by decreasing Epidermal Growth Factor Receptor (EGFR)/Erk activation, which ultimately leads to a decrease in invadopodia formation and matrix degradation, thus suggesting that the expression of DSC3 and DSG1 has an inhibitory effect on head and neck carcinomas.[31]

The low expression of DSG2 is in line with the result of its functional study, in which DSG2 may act as a tumour suppressor to enhance intercellular adhesion. The level of DSG2 is reduced, and the cell–cell mechanical adhesion is decreased when OSCC cells are treated with the proteasome inhibitor bortezomib.[32] Studies have shown a potential link between DSG3 and EGFR in OSCC as the expression of DSG3 was increased after the treatment with cetuximab, an inhibitor of EGFR.[33]

Contrastingly, desmosomal cadherins can act as an oncogene in head and neck carcinomas. The low expression of DSC1 reduced the proliferation and invasion by decreased levels of β-catenin, c-myc and cyclin D1 proteins.[26] Desmoglein 2 is highly expressed and overexpression leads to the release of extracellular vesicles and promotes the progression of tumours. Desmoglein 3 also promoted invasion and migration of OSCC cells by regulation of c-Jun/activator protein 1 (AP c-Jun/activator protein 1 (AP-1) activity -1) activity.[34]

Metastasis is an important aspect of cancer-related deaths and not the primary tumour itself, and head and neck carcinomas are known to metastasise quite commonly. Despite the advanced treatment modalities available, the five-year survival rates are still low. The need of the hour are the essential biomarkers for diagnosis, prognosis and detection of tumour response to therapies. Desmoglein 3 is upregulated in head and neck squamous cell carcinoma[17,35] and it's potential as a diagnostic and prognostic marker has been studied. Diagnosing cervical lymph node metastasis is one of the important aspects of clinical staging and management and is always challenging. Lymph node biopsy may not be accurate and clinically negative lymph nodes still tend to have higher recurrence rates.[36] Sentinel node biopsy can be a feasible measure for the identification of negative nodes and DSG3 has been identified as a precise biomarker for the identification of head and neck lymph node metastasis and can distinguish between positive and negative nodes. 3D-printed microfluidic immunoassay can detect low concentrations of DSG3, which can be used as a reliable biomarker for head and neck lymph node metastasis and hence, can help accurately diagnose false negative treatment and can improve treatment strategies in head and neck carcinomas.[37]

Plakophilins

Plakophilins PKP1, 2 and 3 are the armadillo proteins, and PKP4 association as part of desmosomes is still controversial.[38] However, the exact function of PKPs in cancer remains unknown. Plakophilin expression though has been related to many disorders including cancers, it is still unclear. Plakophilin 1 expression is associated with aggressiveness of head and neck cancers and PKP3 loss is associated with tumour progression and metastasis, and hence, PKP 1 and 3 play tumour suppressor roles in head and neck carcinomas.[28]

Plakophilin plays a crucial role in desmosome stabilisation and downregulation of PKP1 and 3 and its loss can promote cancer progression. In oral cancers PKP1 is known to cause redistribution of DSP from cell membranes to cytoplasm,

thus decreasing the desmosome assembly and altered adhesion between the cells causing tumour motility and invasion[39] Snail family of zinc-finger transcription factors, including slugs have been shown to play an essential role in epithelial–mesenchymal transformation in various tissues, and slug expression is associated with increased metastatic behaviour of tumour cells.[40] Hence, PKP 1 and 3 can provide new therapeutic strategies in head and neck carcinoma metastasis. The role of PKP2 as an oncogene in head and neck carcinoma is still being studied as its expression was more in metastatic tumours than the non-metastatic ones.[27]

Plakoglobin

The other armadillo member of desmosome assembly is the PG, which is a homolog of β-catenin. Plakoglobin also exists in cytoplasm and the nucleus like PKP and it has some known nuclear functions, such as transcriptional regulation and inhibition of Wnt/β-catenin signalling.[11,41] PG also is known to act as a suppressor gene as well as an oncogene in head and neck carcinoma. Plakoglobin overexpression was associated with poor prognosis in OSCC and can act as an independent prognostic factor. The localisation of PG mediates cell-to-cell adhesion. Plakoglobin is shown to exhibit β-catenin-like activity and modulate Wnt/β-catenin signalling.

Desmoplakin

Desmoplakin is a necessary structure connecting desmosome core protein and IF skeleton, and is also the most abundant component in desmosomes. Alterations in the expression or function of DSP may affect desmosome assembly and signal transduction of cancer cells, which may promote tumourigenesis. Desmoplakin is downregulated in human oral squamous cell carcinoma and the decrease in DSP staining is associated with loss of differentiation, degree of invasion, and the presence of lymph node metastasis.[28] Findings from studies suggest that DSP may serve as a biomarker to assess prognosis and metastatic risk of head and neck carcinoma.

CONCLUSION

Desmosomal components play diversified roles in head and neck cancer and development, and their expression of the function of desmosomal cadherins, armadillo proteins and plakin proteins are not consistent. These inconsistencies could be due to multiple factors like physiological factors, pathological factors, interacting proteins, tumour environment, molecular modifications, etc. However, their role cannot be denied in head and neck carcinogenesis, and with the limited evidence of the specific roles of these desmosomal components currently, there seems to be only limited evidence of specific roles of desmosome proteins in certain features. Characterisation of new participants, the role of post-translational modifications, and identification of novel signalling pathways can contribute to a better understanding of the role of desmosomes head and neck cancers in the future.

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Conflicts of interest

There are no conflicts of interest.

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