A brief overview of clinical implications of desmoglein 3 in lung cancer

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ABSTRACT

Lung cancer is the leading cause of cancer death in the world. Despite developments in personalized treatment, lung cancer is still problematic for therapy due to resistance and metastasis. Moreover, heterogeneity of lung cancers makes treatment difficult. Therefore, there is an urgent need to find novel prognostic and diagnostic markers. Desmosomal proteins seem to be a good candidate to be acknowledged due to their function in the cell. Desmosomal proteins are known to be responsible for accurate cell–to–cell adhesion in physiological conditions. In cancer cells, the destabilization of desmosomes by the loss of proteins promotes the process of epithelial-mesenchymal transition, which is strongly connected to metastasis. Desmoglein 3 is one of the desmosomal proteins often deregulated in cancer, including lung cancer. Taking the above, our goal was to analyze the results on DSG3 function and its clinical implications in lung cancer.

Keywords: Non-small cell lung cancer, desmoglein 3

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INTRODUCTION

Lung cancer is one of the deadliest malignancies worldwide, and more than half of all lung cancers are non-small cell lung cancer (NSCLC). Despite developments in personalized treatment, lung cancer is still problematic for therapy due to resistance and metastasis. Moreover, heterogeneity of lung cancers makes treatment difficult [1, 2]. Therefore, it is worth focusing on molecules that play pivotal functions in tumorigenesis and may be good biomarkers for distinguishing between lung cancer subtypes.

Desmosomal proteins are known to be responsible for accurate cell–to–cell adhesion in physiological conditions. For example, Desmoglein 3 (DSG3) is a 130-kDa surface calcium-dependent adhesion molecule that belongs to a desmosomal protein of the cadherin family (Figure 1). Moreover, DSG3 is the serologic target in the autoimmune skin disease called pemphigus vulgaris [3,4].

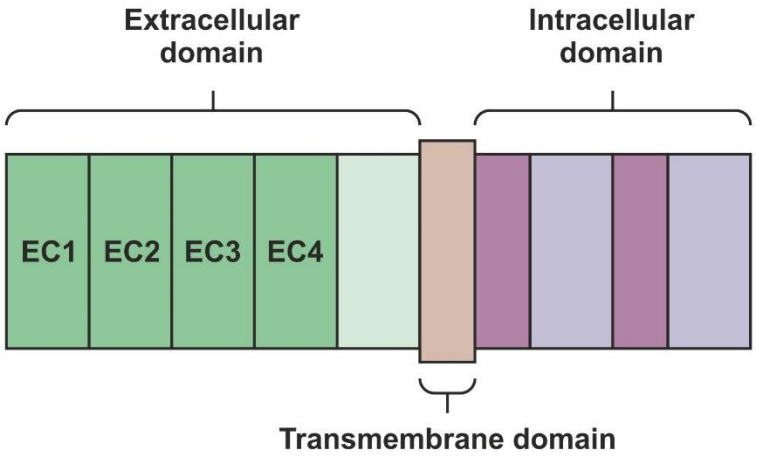

Figure 1. The scheme of Desmoglein 3

In cancer cells, the destabilization of desmosomes by the loss of proteins promotes the process of epithelial-mesenchymal transition, which is strongly connected to metastasis. Moreover, DSG3 has been recognized as a good predictor for clinical staging of malignancy [3]. According to available literature, the upregulation of several desmosomal components in cancer, including DSG3 has been related to the prognosis and has been described as potential diagnostic and prognostic markers [5].

Significance of desmoglein 3 expression in lung cancer

Recent observations regarding the role of DSG3 in lung cancer have been made based on its expression profile. For instance, Fukuoka et al. detected that the molecule mentioned above was most greatly expressed in SCC (squamous cell carcinoma) lung cancers. However, less expression was indicated in ADs (adenocarcinomas) and normal lungs among all tested desmoglein-related genes. The immunohistochemical analyses showed that DSG3 was positive in nearly 80% of SCC, but as far as 50% of AD tumors showed activation of DSG3. Taking together, DSG3 was expressed in most examined lung cancer samples; however, carcinoid tumors had the highest expression. On the contrary, small-cell carcinoma had only 32.3% of cases with positive DSG3.

Moreover, survival analysis showed that positive desmoglein 3 was considerably correlated with a promising prognosis in NSCLC and carcinoid tumors [6]. Interestingly, researchers also confirmed that DSG3 could be a specific marker for SCC lung cancer in other independent studies. The authors stated that immunohistochemistry results gave sensitivity and specificity of DSG3 for lung cancers at a level equal to almost 100% [7].

However, in further publication on the function of DSG3 and keratin 14 (KRT14) in lung cancer, it has been indicated that both mentioned molecules were associated with a worse prognosis in SCC patients. Moreover, researchers evaluated that apoptosis-related pathways, such as TRAIL (tumor necrosis factor (TNF)-related apoptosis-inducing ligand signaling pathway) and TNF receptor signaling pathway were associated with worsened prognosis in SCC patients [8]. This observation is most likely because DSG3 is a crucial regulator of many cell signals, including programmed cell death pathways [3].

Further study on DSG3 and Napsin A double stain showed high sensitivity and specificity of mentioned molecules for SCC differentiation from the other subtype of adenocarcinoma. According to the authors, DSG3 was indicated as positive in 92.8% of the SCC samples and negative in 100% of the non-SCC exanimated cases. Interestingly, expression of DSG3 was not detected in the remaining 25 samples involving large-cell carcinoma, small-cell carcinoma, and carcinoid tumor [9]. Thus, the above data is another example that DSG3 could serve as useful markers in the differentiation of NSCLC [10].

Additional interesting insight on intercellular adhesion proteins has been gained from examining plakophilin-1 (PKP1), keratin-15 (KRT15), and DSG3 in samples from 75 primary NSCLC in non-treated patients. Remarkably, the staining pattern of these proteins differed between SCC and ADs. Rendering the authors, membrane staining for all three proteins was distinctive of squamous cell carcinomas. More intriguing, the staining of examined proteins defined intercellular junction, which is prominent for stratified squamous epithelium and neoplasias with this type of differentiation. Moreover, according to researchers, this feature can be beneficial in diagnosing patients with squamous cell carcinoma of the lung. Furthermore, specific membrane and cytoplasmic staining for used protein could be helpful for the differential diagnosis of non-small-cell carcinomas [11].

It is worth mentioning a study conducted by Saaber et al., who indicated that DSG1-3 was downregulated in most of the lung cancer cell lines. However, after the demethylation process, the authors noticed the re-expression of DSG2 and DSG3 in several cancer cell lines. Moreover, researchers detected that in primary lung tumors, greater protein expression of DSG2 and DSG3 correlated to SCC diagnosis ($P=0.009$ and $P<0.001$, respectively). Furthermore, citing the authors, higher tumor grade correlated with lower expression of DSG3 ($P=0.012$). Taking the results together, this is another study that suggests DSG3 could be a potential differentiation marker for lung cancer [12].

CONCLUSIONS

The data presented in this brief review support the opinion that DSG3 can be useful for differentiating NSCLC subtypes. In most available articles, the researchers identify DSG3 as a perfect molecule to distinguish SCC from ADs. Since NSCLC is the histologically heterogenic type of cancer, differentiation between subtypes can be very informative in treatment selection. However, some of the data indicate that evaluation of DSG3 status and other molecules can give the most relevant results in the differentiation of NSCLC.

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Conflicts of interests

None declared.

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