

## Desmocollin-3 and Cancer

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### Abstract

Desmocollin-3 [DSC3] is a transmembrane glycoprotein belonging to cadherin family of homophilic adhesion molecules, and is produced by the endoplasmic reticulum. DSC3 expression is seen in the suprabasal layer of stratified epithelium. DSC3 is a p53 responsive gene and can be detected by microarray. DSC3 protein expression is associated with expression of wild type p53 expression and can be detected by immune histochemistry. DSC3 protein is expressed on the surface of normal tissues. In proliferative tissues like, fetal and cancer, DSC3 protein is also seen in cytoplasm besides on cell surface. Expression of DSC3 is used as a diagnostic biomarker to differentiate squamous NSCLC from adenocarcinoma of lung. DSC3 expression is also seen in ovarian cancer, melanoma, colorectal cancer, cervical cancer, and meningioma cancer arising from oral cavity.

Expression of wild type p53 is associated with expression of DSC3. Chemotherapy, radiotherapy, targeted therapy [tyrosine kinase inhibitors], hypo methylating agents are known to induce expression of DSC3 in DSC3 negative cancers. As a homophilic adhesion molecule, it provides a unique opportunity for active immunotherapy by inducing DSC3 on surface of immune cells. CADI-05 is one such immunotherapy. It is found useful in management of squamous NSCLC and ovarian cancer when used with chemotherapy. It improves response rate and survival. As a mono therapy, it induces remission in melanoma and bladder cancer.

**Keywords:** Desmocollin- NSCLC; Cancer; CADI-05; Biomarker; Immunotherapy

**Abbreviations:** DSC3: Desmocollin-3; NSCLC: Non-small cell lung cancer

### Introduction

Desmocollin-3[DSC3] is one of the adhesion molecules of cadherin super family found in desmosome and is a major adhesive force of epithelial cells [1-6]. DSC3 is a transmembrane calcium-dependent glycoprotein produced by the endoplasmic reticulum, encoded by the DSC3 gene. DSC3 is expressed, mainly in basal and immediate suprabasal layers of the stratified squamous epithelia [7] like buccal mucosa, esophagus, cervix, fore skin tongue, trachea etc. [3,8]. As an adhesion molecule, DSC3 provides homophilic adhesion i.e. cells expressing DSC3 will adhere to each other at the site of expression but not with others; it also works as a receptor as well as ligand to participate in cell signaling [9].

### P53 and Desmocollin-3

DSC3 is one of the p53-responsive gene [1-11]. p53 is reported to be an upstream to DSC3. Expression of DSC3 gene is associated with expression of wild type of p53 and depends on the methylation status of the DSC3 DNA in the p53 binding site [10,11]. p53 expression in cancer is known to be altered by mutation or deletion of the p53 gene, with mutation of p53 being the most common event in human cancer [12]. Besides deletion and mutation of p53, p53 target genes are also silenced by epigenetic silencing like DNA methylation [1-11]. Mutant p53 inactivates p63 and is also associated with down regulation of DSC3 [10]. p63 is a master

regulator of epidermal gene transcription and plays an essential function in controlling epidermal development, cell proliferation, stratification and cell-matrix adhesion [13]. There are two main isoforms of p63, Tap63 and Delta Np63. Delta Np63 alpha isoform is the most abundantly expressed p63 isoform. Both p63 and delta Np63 are activator for desmocollin-3 gene [13]. Knockdown of p63 and delta Np63 results in marked reduction in expression of DSC3 without any effect on expression of another adhesion molecule E-cadherin [13].

### Desmocollin-3 and Cancer:

Desmosomal abnormalities are seen in cancer, as are alterations in DSC3 expression. In many epithelial cancers, DSC3 expression either over expressed or absent. DSC3 expression is not seen in many cancers e.g. adenocarcinoma of lung, breast, prostate cancer wherein there is mutation of P53 or hyper methylation. DSC3 was first cloned from human bladder cancer cell line [14]. Its presence can be detected by microarray (gene) or immunohistochemistry (protein)

**a. Lung Cancer:** DSC3 is not seen in normal lung tissue [15]. DSC-3 gene is over expressed 58 fold compared to adenocarcinoma [16]. Immunohistochemistry reveals in lung cancer expression of DSC3 is seen at basal layers of tumor. DSC3

expression is seen in around 30% of cases [17]. DSC3 expression is seen in squamous NSCLC and not in adenocarcinoma of lung. It is closely associated with p63 expression which is another marker used for differentiation of Squamous NSCLC from other varieties [18-20].

**b. Ovarian Cancer:** DSC3 is seen in around 85% of ovarian caners. Its expression seems to be dependent on FSH.

**c. Melanoma:** DSC3 is expressed in melanoma [21-24]. Its expression decreases with increased thickness and progression to metastatic melanoma [22].

**d. Colorectal Cancer:** DSC3 expression is seen in 60% colon cancer and also seen in 40% of colorectal lesion metastatic to the liver [10,25,26].

**e. Bladder Cancer:** DSC3 was first cloned from a bladder cancer cell line [14]. We have documented DSC3 expression in around 60% of bladder cancer irrespective of grade and stage of tumor.

**f. Meningioma:** DSC3 expression is described in around 60% of meningioma [21,27].

**g. Chondrosarcoma:** DSC3 gene expression is detected in 4 of the 5 chondrosarcoma cell lines [28].

**h. Pediatric Acute Lymphoblastic Leukemia:** DSC3 gene is described to be over expressed in all TEL-AML1 subtype of paediatric acute lymphoblastic leukemia [29].

**i. Skin Tumors:** Loss of DSC3 is seen with tumour development and progression [30] and is associated with increase in K-Ras induced skin tumors [31].

**j. Oral squamous cell carcinoma:** Oral mucosa normally expresses DSC3. However development of oral Squamous cell carcinoma is associated with reduction or absence of DSC3 expression. This reduction/absence of DSC3 expression was associated with higher histological grade (moderately or poorly differentiated) [32].

**k. Breastcancer:** DSC3 is expressed in a normal breast but is down-regulated in breast cancer cell lines and primary breast tumors at protein as well as gene level [3,33]. The loss of DSC3 protein expression is more likely to be aberrant methylation of rather than gene deletion or gross rearrangement of the gene [3].

**l. Prostatecancer:** DSC3 is expressed in normal prostate as well as benign prostate tumors but is absent in prostate cancer due to hyper methylation [34].

**Table 1:** Sensitivity of DSC3 for squamous NSCLC.

S. No	Reference	Squamous		Adenocarcinoma		Large cell carcinoma	
		DSC-3+ve	DSC-3	DSC-3 +ve	DSC-3	DSC-3 +ve	DSC-3
		/Total	+ve%	/Total	+ve%	/Total	+ve%
1	Warth et al. [7]	425/456	93.2%	5/530	1.0%	1/60	1.2%
2	Kim et al. [8]	156/171	91%	0/110	0%	-	-
3	Tsuta et al. [9]	109/150	72.70%	0/157	0%	-	-
4	Righi et al. [10]	13/16	86.70%	0/29	0%	12-Feb	16.70%
5	Monica et al. [11]	24/24	100%	1/40	2.50%	28/69	40.60%
	Total	727/817	88.70%	6/866	0.69%	31/141	11.70%

### Desmocollin-3 as a diagnostic biomarker:

**a. Squamous NSCLC:** DSC3 is used as a diagnostic biomarker to differentiate Squamous NSCLC from adenocarcinoma of lung [35-42]. DSC3 is more specific for squamous NSCLC compared to p63 as p63 is also expressed in Adenocarcinoma. DSC3 gene is up-regulated in squamous NSCLC and down regulated in adenocarcinoma [43]. Specificity of DSC3 is 100% while sensitivity is variable [18-20, 44,45] and varies with differentiation of tumor. Maximum sensitivity is seen in highly differentiated tumors and is lowest for poorly differentiated Squamous NSCLC. Sensitivity of DSC3 for squamous NSCLC is 93.2% in large cohort of 426 but drops to 59% in poorly differentiated squamous NSCLC (Table 1). DSC3 expression in NSCLC is also not related to stage or histologic grade [17] of a disease [46].

**b. Paediatric Acute Lymphoblastic Leukaemia:** DSC3 gene expression can be used to differentiate TEL-AML1 from other subtypes of paediatric acute lymphoblastic leukaemia [29].

### Desmocollin-3 as a prognostic biomarker

**a) NSCLC:** In spite of squamous NSCLC having poor prognosis, smaller clinical trials suggest that DSC3 expressing tumors are likely to have better survival compared to DSC3 negative tumors and may serve as a potential prognostic marker [1,17].

**b) Colorectal cancer:** Tumors with methylated DSC3 DNA were significantly correlated to a worse clinical outcome than unmethylated tumors. The methylation status of DSC3 DNA was not linked to any of clinical pathological parameters including

age, gender, size of tumor, tumor grading, and tumor stage in these patients [10].

**c) Prostatecancer:** Loss of DSC3 predicts poor prognosis.

### Effect of therapeutic intervention on DSC3 expression:

**a. DNA damaging agents:** Expression of wild type of p53 can also be increased or induced by DNA damaging agents like radiotherapy, doxorubicin, cisplatin, paclitaxel, gemcitabine etc. Expression of wild type p53 is sufficient to induce expression of DSC3 in breast, colorectal and lung cancers in absence of DSC3 DNA methylation [1,10,11]. Expression of wild type p53 converts DSC3 negative tumors in to DSC3 positive.

**b. Tyrosine Kinase inhibitors:** DSC3 expression has reciprocal relationship with ERK of MAPK family. Decreased ERK is seen following successful treatment with tyrosine kinase inhibitors. EGFR inhibitor like gefitinib converts DSC3 negative EGFR mutant adenocarcinoma of lung in to DSC3 positive.

**c. Hypomethylating/Demethylating agents:** DSC3 hypermethylation is seen in prostate and breast cancer leading to lack of DSC3 expression by these tumors [3, 6, 33]. Hypomethylating/Demethylating agents like azacytidine convert DSC3 negative tumors to DSC3 positive [3,47].

### Desmocollin-3 and immunotherapy:

DSC3 is a homophilic adhesion molecule, which works as a receptor as well as a ligand. This provides an opportunity to develop an active immunotherapy for DSC3 expressing tumors by inducing DSC3 on surface of tumor targeting activated immune cells. CADI-05 is one such active immunotherapy. It induces DSC3 expression on immune cells and also induces Th1 type of immune response through TLR2 agonist activity [48]. Cadi-05 increases tumor infiltrating immune cells [49] and found useful in management of cancers as a monotherapy for small size tumors [49,50]. As combination therapy with checkpoint modulators, radiotherapy as well as chemotherapy, Cadi-05 improves outcome of large size tumors [51].

Cadi-05 achieves and maintains remission in melanoma as well as in bladder cancer as a systemic monotherapy [52, 53]. In combination with chemotherapy, it improves response rate. Responses achieved are durable and results in improved survival. Identical results are seen when combined with radiotherapy. It is expected that combination with anti PD-L1 therapy will result in significant improvement in no. of durable responses.

### Conflict of Interest

Bakulesh Khama is an employee of Cadila Pharmaceuticals Limited.

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