https://doi.org/10.46344/JBINO.2021.v010i01.28

CANCER: EFFECT OF CHEMOTHERAPEUTIC AGENTS ON DSC3 EXPRESSION

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ABSTRACT

DSC3 is a transmembrane cell adhesion protein. In carcinomas, DSC3 is either upregulated with its distribution as membrane and cytoplasmic protein or downregulated with undetectable DSC3 expression. The chemotherapeutic agent viz. gemcitabine, paclitaxel, cisplatin and doxorubicin known to induce the expression of cell adhesion molecules in cancer cells. We report the expression of DSC3 affected by these drugs in cancer cell lines originated from pancreatic cancer, lung cancer, melanoma and kidney fibroblast. At sub-therapeutic doses, all the DSC3 negative cell lines expressed DSC3 before death. In DSC3 positive cell lines, DSC3 conversion was less common. The conversion in DSC3 expression found variable with each drug and cell line evaluated. During drug treatment, we have observed localized expression of DSC3. For DSC3 negative cell lines membrane and cytoplasm are early to become DSC3 positive compared to nucleus; however, for DSC3 positive cell lines, nuclear negative DSC3 first observed in drug treated cells. The conversion of DSC3 in live cells is reversible in native condition. This study emphasize the status of DSC3 during chemotherapeutic drug treatment is crucial for resistance and can be an ideal target for combined therapies.

Keywords: Cancer, DSC3 expression, chemotherapeutic drug

Introduction:

Desmocollin 3 (DSC3) is an extracellular component of Desmosome. Calcium-dependent trans-membrane, glycoprotein that belongs to the cadherin super family (Chen et al., 2012). DSC3 is one of the desmosome adhesion molecule and is major adhesive force of epithelial cells (Garrod & Chidgey, 2008; Wheelock et al., 2001). In normal epithelium, DSC3 is known to be expressed as a membrane protein (Waschke 2008) and seen mainly in suprabasal layer of stratified epithelium, like tongue, tonsil, oesophagus, bladder, vagina etc (Uhlen et al., 2010). In rapidly dividing cells, it is present in cytoplasm also (Den et al., 2006). Its expression reported in various cancer (Chidgey and Dawson 2007). Desmocollins are integral membrane proteins, synthesized on ER-bound ribosomes (Magali et al., 2014). Loss of DSC3 expression contributes to the paucity of adhesion as seen in blistering skin disorders (Ayub et al., 2009).

During carcinogenesis DSC3 is either upregulated with its distribution as membrane and cytoplasmic protein or downregulated with undetectable DSC3 expression (M Chidgey and C Dawson 2007). On basis of DSC3 expression, epithelial cancer can be broadly categorized in two subsets, one where DSC3 is over expressed such as in squamous NSCLC (Valentina et al., 2009; Tsuta et al., 2011) colorectal cancer (Cui et al 2011) and skin cancer (Jiangli et al., 2012; Rezze et al., 2011); others where DSC3 is expression is absent such as breast (Oshiro et al., 2005) and prostate cancer (Pan et al., 2014).

DSC3 is a P53 regulated gene. P53 target the DSC3 promoter region, which stimulate histone acetylation at the binding site to increase the accessibility of the DSC3 gene (Cui T et al., 2011).

Loss of DSC3 expression is associated with low calcium levels, mutation/inhibition of SERCA pump (Magali S et al., 2014), mutation or hypermethylation of p53 (Oshiro et al., 2003) or its degradation (Jörg Weiske et al., 2001). Correction of alteration by appropriate agents results in expression of DSC3.

Chemotherapeutic drugs like Doxorubicin (T Cui et al 2011), Cisplatin (Xiaobing et al., 2011), Gemicitabine (Buranrat et al., 2010) and Paclitaxel (Giannakakou et al., 2001) are known to increase p53 expression and some of them are known to upregulate DSC3 expression in DSC3 negative cancers (Krunal et. al., 2019). However their effect on DSC3 expressing cancer cells is not described. There is no information on dose response as well as duration of treatment with these agents. We planned this study to evaluate the expression of DSC3 in various cancer and changes in expression of this adhesion molecule as result of chemotherapeutic drug treatment.

MATERIALS AND METHODS

Cell lines and cell culture

Pancreatic cells (SW1990, Panc-1, AsPc-1 and Mia-Pa-Ca2), Lung cancer cells (L132, A549), Colorectal cancer cells HCT15, HT-29), Mouse skin melanoma (B16F1 and B16F10) and Monkey kidney fibroblast cells (Cos7) were purchased from either American Type Culture Collection (ATCC Rockville, MD, USA) or National Centre for Cell Science, Pune (NCCS). SW1990, Panc-1, AsPc-1, Mia-Pa-Ca2, L132, HCT15, HT29, B16F1, B16F10 and Cos7 cells were cultured in

Dulbecco's Modified Eagles Medium (DMEM) supplemented with 10% FBS and maintained in a humidified atmosphere with 5 % CO_2 at 37°C. A549 cells were cultured in HAM's medium supplemented with 10% FBS and maintained in a humidified atmosphere with 5 % CO_2 at 37°C.

Drugs used for treatment of cells

Cisplatin (Platin injection 10 mg, from Cadila pharmaceuticals), Paclitaxel (Paclicad injection 30 mg, from Cadila pharmaceuticals), Doxorubicine (Cadria 50 mg, from cadila pharmaceuticals), Gemcitabine (Tabicad 200 mg, from Cadila Pharmaceuticals). Paclitaxel, Gemcitabine reconstituted in physiological saline were as Doxorubicine reconstituted in sterile WFI.

Drug treatment

All cells were cultured in T-75 flasks. Cells were harvested at 70 % confluence. $1X10^5$ cells were plated in each well of 12 well plates. Doxorubicine was added at final concentration of 5 µM, 10 µM and 20 µM, Cisplatin was added at final concentration of 5 µg, 10 µg and 20 µg, Paclitaxel was added at final concentration of 2.5 µg, 5 µg and 10 µg, Gemcitabine was added at final concentration of 1.25 µM, 2.5 µM and 5 µM. The drug concentration of these drugs selected on basis of previous experiences with these drugs (Krunal et. al., 2019). All drugs were diluted in culture media. Plates were incubated for 24 hours, before harvesting the cells for DSC3 expression. The cells were reseeded in fresh growth medium post drug treatment.

Immunohistochemistry (IHC)

Smears of the cancer cells were prepared onto the tissue culture slides and subjected to the air drying; the fixation was done with chilled methanol for 30 minutes. After fixation the slides were washed three times with PBS. For blocking slides were treated with blocking solution (5% BSA, 2% serum, 2% tritonX-100) for 1 hours. The cells further incubated for 1 hours at room temperature with Mouse Monoclonal anti-desmocollin 3 (Abcam-Ab55011) antibody. Detection was done with HRP conjugated antibody (Goat anti Mouse IgG-HRP, Genei). The slides were counter stained with 0.5% Methyl green for five minutes. All slides were read by two different Scientist. IHC was scored as Cytoplasm, Membrane and Nuclear positive or negative.

RESULTS

DSC3 Expression analysis in different cancer cell lines

DSC3 expression was seen (DSC3 +ve) in colorectal (HCT15, HT29), melanoma (B16F1, B16F10) as well as squamous NSCLC (L132) cell lines evaluated. It was present in one (SW1990) of four pancreatic cancer cell lines evaluated, It was absent (DSC3-ve) in three of four pancreatic, Adenocarcinoma of lung and control kidney cell line. (Table-1) The p53 status of each cell line reveals 4 of 5 of the DSC3 negative cell lines to harbor mutant p53 while 5 of six cell lines expressing wild type p53.

Table-1: Cell lines and p53 status

Sr. No.	Cell Line	Cancer Type	P53 Status	DSC3 Status
1	SW1990	Human Pancreatic	Wild type (Wu et al., 2019)	Positive
2	Panc- 1	Human Pancreatic	Mutant (Wu et al., 2019)	Negative
3	AsPc -1	Human Pancreatic	Mutant (Butz et al., 2003)	Negative
4	Mia-Pa-Ca2	Human Pancreatic	Mutant (Fiorini et al., 2015)	Negative
5	HCT 15	Human colorectal Adenocarcinoma	Mutant (Leroy et al., 2004)	Positive
6	HT-29	Human colorectal Adenocarcinoma	Mutant (Barberi-Heyob et al., 2004)	Positive
7	L-132	Human Non-small cell lung cancer (Squamous NSCLC)	Wild type (Takeyama et al., 2004)	Positive
8	A549	Human Non sma;; cell lung cancer (Adenocarcinoma)	Wild type (Margarita et al., 2020)	Negative
9	B16 F1	Mouse skin melanoma	Wild type (Melnikova et al., 2004)	Positive
10	B16 F10	Mouse skin melanoma	Wild type (Melnikova et al., 2004)	Positive
11	Cos 7	Monkey kidney fibroblast	Wild type (Mulloy et al., 1998)	Negative

Expression analysis of DSC3 in different cancer cell lines after chemotherapeutic drug treatment

Immunohistochemistry analysis of different cell lines post treatment with chemotherapeutic drugs at human therapeutic and sub-therapeutic dose, revealed DSC3 expression was changed post treatment (Table-2).

Table-2: Expression analysis of DSC3 in different cancer cell lines after drug treatment at therapeutic and sub-therapeutic dose.

		Cisplatin			Paclitaxel			Gemcitabine			Doxorubicin		
Cell Lines	**Media**	**5 µg/ml**	**10 µg/ml**	**20 µg/ml**	**2.5 µg/ml**	**5 µg/ml**	**20 µg/ml**	**1.2 µM**	**2.5 µM**	**5 µM**	**5 µM**	**10 µM**	**20 µM**
L-132													
SW1990													
HCT15													
B16 F1													
B16 F10													
HT- 29													
Cos 7													
Panc- 1													
AsPc -1													
Mia-Pa-Ca2													
A549													

* The cells were reseeded in fresh growth media without drug, cells were found attached and retained its native expression of DSC3.

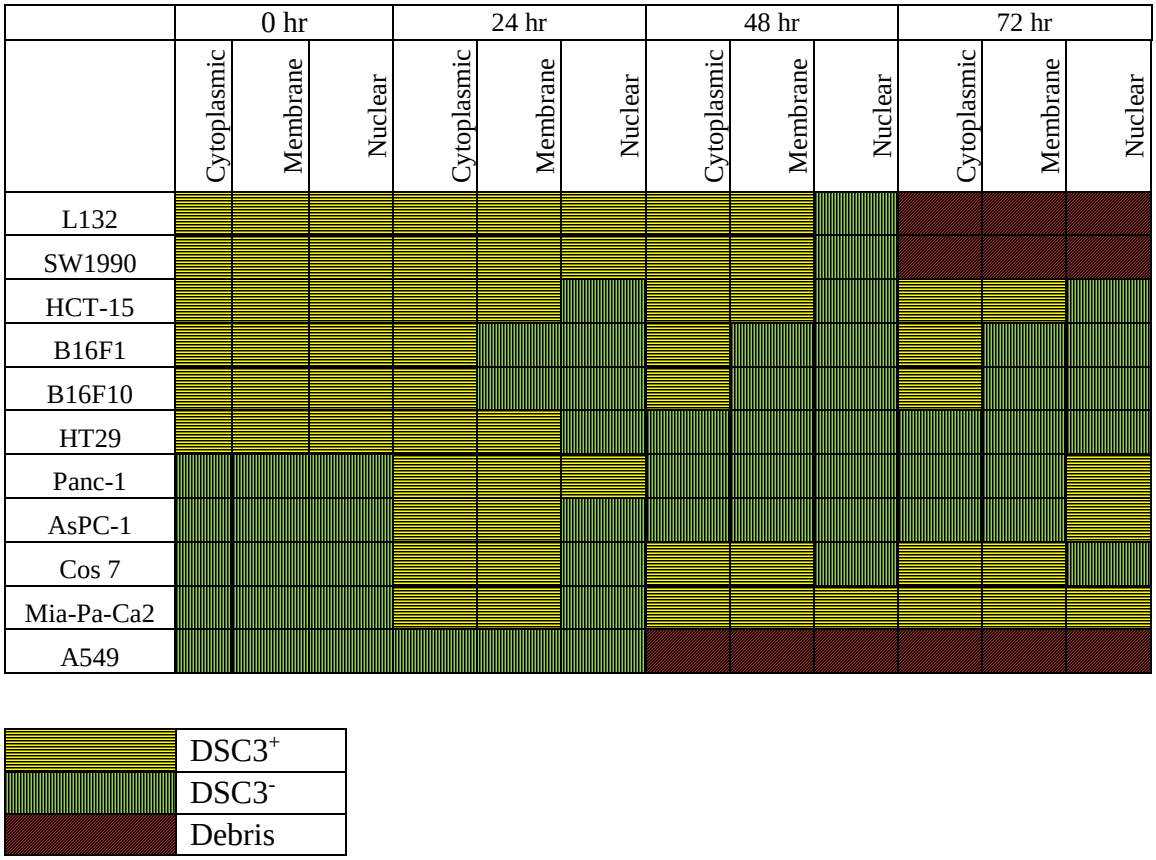
	Live, $DSC3^{+}$
	Live, $DSC3^{-}$
	Dead, $DSC3^{+}$
	Dead, $DSC3^{-}$

All the DSC3 negative cell lines had DSC3 conversion (DSC3 conversion; +ve to –ve or –ve to +ve) before death and at a sub-therapeutic level, however the DSC3 conversion was variable with each drug and cell line evaluated. Mia-Pa-Ca2 had DSC3 conversion with all the drugs at subtherapeutic concentration. Panc-1 and AsPc-1 were unique to undergo DSC3 conversion at a lowest dose and reconversion (DSC3-ve again) at a higher sub therapeutic dose (Table 2).

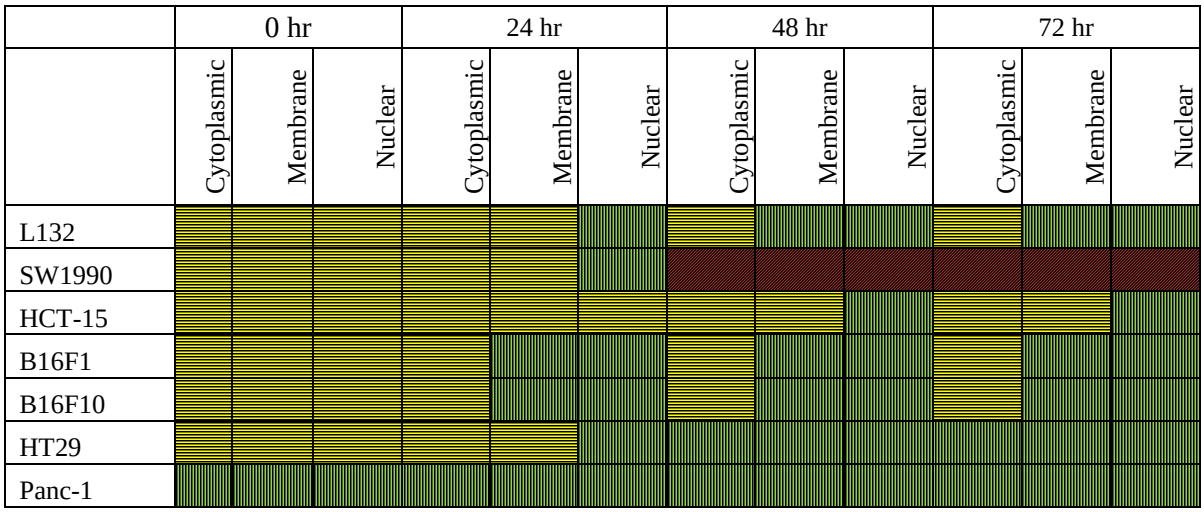
DSC3 conversion was less common in DSC3+ve cell lines. It was not seen in colorectal cancer cell lines (HCT 15, HT29) and was seen in melanoma cell lines (B16F1 and B16F10) with all four drugs evaluated (Table 2).

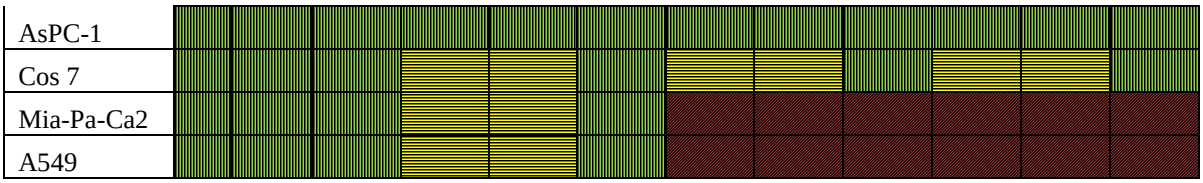
Table-3: Sequence of events analysis for DSC3 expression in different cancer cell lines.

A. Paclitaxel

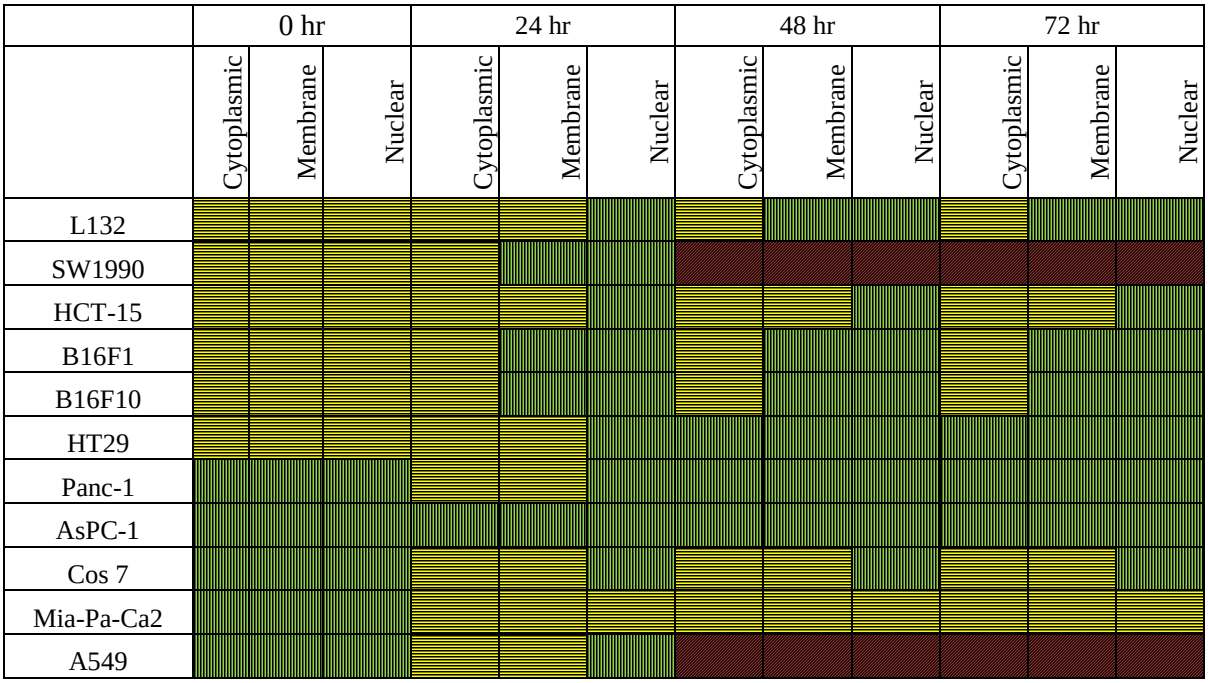


B. Cisplatin

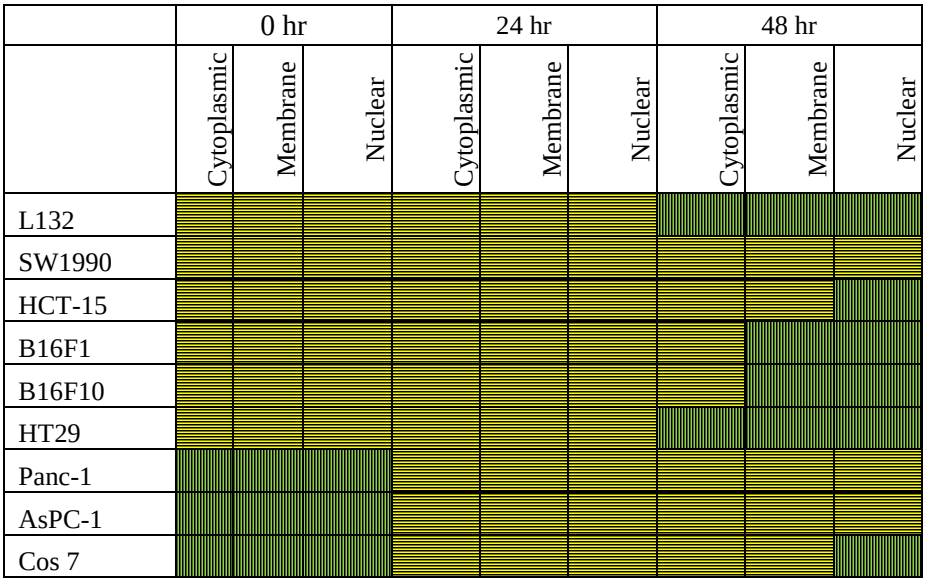


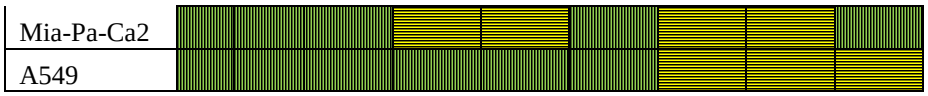


C. Doxorubicin



D. Gemcitabine





Evaluation of DSC3 conversion over time by various subcomponent reveals two distinct patterns. DSC3 conversion begins in cytoplasm and membranes in DSC3 negative cell lines while it seems to begin in nucleus in DSC3 positive cell lines. (Table3). Reconversion to original DSC3 status seen on transferring live cells to chemotherapeutic drug free culture medium. The DSC3 positive cells, which lose its DSC3 from surface and become DSC3 negative in drug treatment condition found dead and detached from the plate surface. The detached cells found dead post reseeding in fresh medium, may have initiated apoptosis process.

Discussion:

In this study, the expression of DSC3 have been analyzed in various cancer cell lines. The DSC3 expression in these cell lines is in line with previously described reports for expression of adhesion molecules in human cancer samples, for example, in NSCLC, DSC3 is expressed by squamous cell carcinoma and not by adenocarcinoma. (Valentina M et al., 2009; Tsuta K et al., 2011). Melanoma and colorectal cancers are known to express DSC3 (T Cui et al 2011; Jiangli C et al., 2012; Gisele Gargantini Rezze et al., 2011). DSC3 status in pancreatic cancer is not described so far. Relationship between DSC3 expression and p53 status in this study relates previous reports of DSC3 being p53 responsive gene (Cui T. et. Al., 2011).

Adhesion molecules are known to change their expression following exposure to Cispaltin, Paclitaxel, Gemcitabine and Doxorubicin (Yu et al., 2008; Raimonda et al., 2016, Duxbury et al., 2004, Cui et al., 2011). DSC3 being an adhesion molecule, conversion of DSC3 negative cell lines with chemotherapeutic agents seen in this study may be part of change in adhesion molecules. Chemotherapeutic agents are also known to increase wild type of p53 and DSC3 expression (Cui et al., 2012; Pan et al., 2014, Oshiro et al., 2005). DSC3 conversion at sub therapeutic dose and its reconversion on removal of chemotherapeutic agents is not described previously. This could be due chemotherapeutic agent induced stress on secretory pathway (endoplasmic reticulum + golgi apparatus) of cancer cells (Palam L et al., 2015). Disturbances of golgi apparatus and its fragmentation is known following chemotherapy. (Núñez-Olvera et al., 2020). Golgi apparatus known to control protein expression through E3 ligases. MDM2 is one of the E3 ligases known to suppress p53 (Sparks A et al., 2014; Gupta et al 2019). Loss of its activity may be responsible for DSC3 expression in DSC3 negative cells at a sub therapeutic level.

The conversion of DSC3 in positive cancer cell lines seen in this study, which begins at perinuclear area, has not been described before. Desmocollins are known to be retained at endoplasmic reticulum under stress induced by low calcium concentration (Magali S et al., 2014). The endoplasmic stress induced by chemotherapeutic agents is a plausible

explantion for observed changes. The other possibility for loss of DSC3 expression can be activation of the metalloproteinase and subsequent shedding of extracellular domain of DSC3 (Jörg Weiske et al., 2001).
Studying effect of chemotherapeutic agents on DSC3 expression by cancer cell lines suggests different biological processes and needs further studies. It also provides guidance on better use of DSC3 targeting therapy.

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