Desmoplakin, DSP, is a potential tumour suppressive protein in human breast cancer

Hongyu Xiang, MD[1,2]; Xinyu Li, PhD[1]; Cai Wang, MD[1]; Tracey A. Martin, PhD[1]; Eleri Davies, MB BCh[3]; Kefah Mokbel, MB BS, FRCS[1]; Wen G. Jiang, MD, FRSB, FLSW[1];
[1]School of Medicine, Cardiff University, CARDIFF, UK; [2]Department of Thyroid and Breast Surgery, Peking University First Hospital, Beijing,CHINA; [3]Wales Breast Centre, University Hospital Llandough, Cardiff, UK

Abstract

Introduction Desmoplakin (DSP), a key desmosomal plaque protein, plays a critical role in cell adhesion. While its loss has been observed in high-grade breast tumours, its full prognostic significance remains unclear. This study investigates the clinical impact of DSP expression in breast cancer. **Methods** DSP transcript levels were quantitatively analyzed in a clinical breast cancer cohort (n= 151) with 10-year follow-up. Associations with clinicopathological factors and survival outcomes (Overall Survival, OS; Disease-Free Survival, DFS) were assessed using Kaplan-Meier, Cox regression, and Bayesian analyses. **Results** DSP expression showed strong prognostic value in breast cancer. Tumours from patients who developed breast cancer related events displayed significantly reduced DSP levels compared with disease-free patients (p=0.0063). The reduction was most evident in ER-positive and HER2-positive tumours. High DSP expression was associated with favourable overall survival (AUC=0.241; HR=0.063, 95% CI 0.008–0.477; p=0.007) and remained independently significant across molecular subtypes. DSP also predicted improved disease-free survival (p=0.006). **Conclusion** Desmoplakin is a favourable prognostic marker for overall and disease-free survival in breast cancer and shows predictive value for chemotherapy response, with its significance largely independent of molecular subtype.

Introduction

Desmoplakin (DSP) is a membrane subcoat plaque protein, primary co-located within the desmosomes, which are membrane structuresfound in tissues such as skin and muscles. Known DSP interactive proteins include desomosome cadherin desmogleins (DSG)and desmocollins (DSC).Although an early indication of a possible loss of the DSP protein, particularly in high grade tumours in human breast cancer was reported (Davies et al1999), the impact of DSP on the clinical course and prognosis in breast cancer has not been fully explored. Here, we investigated the expression of DSPtogether with the membrane integral demososome protein DSG1 (desmoglein-1), aiming to establish a possible prognostic significance in clinical breastcancer.

Methods and Materials

Breast cancer tissue samples from a Cardiff patient cohort with a 10-year clinical follow-up were analysed. Total RNA was extracted and DSP transcript levels were quantified using quantitative PCR (qPCR) with gene-specific primers. Expression levels were normalized with GAPDH and fully analysed against the clinical and pathological factors and the long term clinical outcome of the patients.. Whereappropriate, the prognostic significance was conducted using Kaplan-Meier model and Bayes analyses.

Results

The most significant finding was that the expressionlevels of DSP is linked to the clinical outcome of the patients. Breast tumours which developed breast cancer related events exhibited a significant reduction of DSP expression when compared with tumours from those who remained disease free (p=0.0063). The reduction of DSP was seen profoundly in ER positive tumours and HER2 positive tumours (p=0.061 and 0.1583, respectively). Survival analysis indicated that DSP expression is a favourable factor for overall survival (>OS) with an AUC at 0.241 (p<0.0001) and hazard ratio (HR) at0.063 (95% confidence internal 0.008-0.477, p=0.007 by Cox regression), a connection supported by an impressive Bayes factor (192.1). The connection with OS was observed across the molecular subtypes and when the molecular subtypes and hormone receptor status were considered, DSP remained asignificant OS indicator in multivariant analysis. Very similarly, DSP expression is also a favourable indicator for disease free survival (DSF) (p=0.006), againseen in most subtypes.

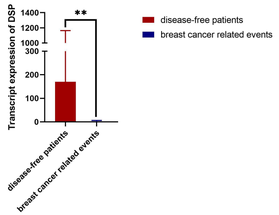


Figure 1. Differential expression of DSP transcript in disease-free patients and patients with breast cancer–related events. DSP expression was significantly reduced in patients with cancer-related recurrence, metastasis, or mortality (p =0.0063).

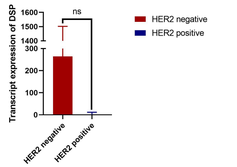


Figure 2. DSP transcript expression in HER2-negative and HER2-positive breast tumours. Although HER2-positive tumours showed a trend toward lower DSP expression, the difference was not statistically significant (p=0.061).

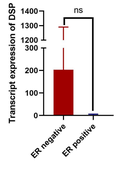


Figure 3. DSP transcript expression in ER-negative and ER-positive tumours. ER-positive tumours showed a trend toward lower DSP expression, but the difference was not statistically significant (p=0.1583).

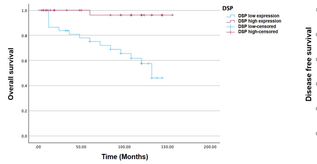
Discussion

In this study, we provide clear evidence that desmoplakin (DSP), a core component of the desmosomal adhesion complex, plays an important prognostic role in human breast cancer. Although earlier work suggested that loss of DSP may accompany high-grade breast tumours (Davies et al., 1999), its broader clinical relevance has remained poorly defined. By analysing DSP expression in a well-characterised breast cancer cohort with a ten-year follow-up, our findings demonstrate that reduced DSP expression is significantly associated with adverse clinical outcomes, including distant metastasis, local recurrence, and breast cancer–related mortality. These results support the concept that disruption of desmosomal integrity contributes to tumour aggressiveness and metastatic potential.

DSP expression emerged as a strong predictor of both overall survival (OS) and disease-free survival (DFS). The pronounced hazard ratio for OS and the robust Bayes factor further highlight its value as a favourable prognostic biomarker. Importantly, the prognostic impact of DSP persisted across molecular subtypes and remained significant after adjusting for hormone receptor status and other clinicopathological variables. This suggests that the biological functions of DSP in tumour progression may operate independently of classical subtype-driven pathways.

Conclusions

Desmoplakin exhibits characteristics as a favourable prognostic indicator for patient overall and disease free survival in breast cancer patients. The connection, which is less influenced by the molecular subtypes, also has value in predicting the chemotherapeutic response of the patients.

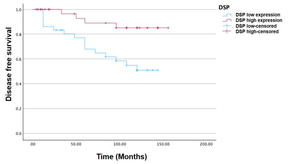


ANOVA

Status04liveDeathF	Sum of Squares	df	Mean Square	F	Sig.	Bayes Factor[a]
Between Groups	20.821	1	20.821	17.208	<.001	192.107
Within Groups	94.379	78	1.210			
Total	115.200	79				

a. Bayes factor: J2S method, testing model vs. null model.

Figure 4. Overall survival by DSP expression. Kaplan–Meier curves show significantly better overall survival in patients with high DSP expression compared with low expression (p < 0.001; Bayes factor = 192.107).



ANOVA

Allinc04f	Sum of Squares	df	Mean Square	F	Sig.	Bayes Factor[a]
Between Groups	21.863	1	21.863	11.108	.001	14.996
Within Groups	149.586	76	1.968			
Total	171.449	77				

a. Bayes factor: J2S method, testing model vs. null model.

Figure 5. Disease free survival by DSP expression. Kaplan–Meier curves show significantly better disease free l survival in patients with high DSP expression compared with low expression (p =0.006; Bayes factor = 14.996).

Variable	B	SE	Wald	Sig.	Exp(B)	95%CI
DSP	−3.020	1.120	7.271	0.007	0.049	0.005-0.438
ER	0.884	0.750	1.386	0.239	2.419	0.556-10.530
HER2	1.368	0.770	3.161	0.075	3.929	0.869-17.756
PR	0.232	0.747	0.096	0.756	1.261	0.292-5.457
HER1	−0.435	0.628	0.479	0.489	0.647	0.189-2.219
HER3	−0.037	0.627	0.003	0.953	0.964	0.282-3.293
HER4	−0.382	0.779	0.241	0.624	0.682	0.148-3.142
AR	−0.428	0.694	0.381	0.537	0.652	0.167-2.537

Table 1. Multivariate analysis of overall survival in breast cancer patients. Cox regression evaluating the independent effects of DSP and key clinicopathological markers on overall survival. DSP remained a significant protective factor (HR = 0.049, p = 0.007).

Variable	B	SE	Wald	Sig.	Exp(B)	95%CI
DSP	-4.62	1.552	8.857	0.003	0.01	0-0.207
ER	1.926	0.967	3.966	0.046	6.865	1.031-45.706
HER2	0.794	0.801	0.984	0.321	2.213	0.461-10.629
PR	-1.341	0.71	3.568	0.059	0.262	0.065-1.052
HER1	0.606	0.847	0.511	0.475	1.832	0.348-9.636
HER3	-0.231	0.707	0.107	0.743	0.793	0.198-3.173
HER4	-0.058	0.831	0.005	0.945	0.944	0.185-4.813
AR	-1.83	0.876	4.361	0.037	0.16	0.029-0.894

Table 2. Multivariate analysis of disease free survival in breast cancer patients. Cox regression evaluating the independent effects of DSP and key clinicopathological markers on disease free survival. DSP remained a significant protective factor (HR = 0.01, p = 0.003).

Contact

Hongyu Xiang
School of Medicine, Cardiff University; Peking University First Hospital
Email: xiangH3@cardiff.ac.uk
Phone: 44(0)7539147637

References

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