Expression of PDK-1 and DMBT1 in the thyroid carcinoma and its clinicopathological significance

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Abstract. This study was designed to explore the expression of phosphoinositide-dependent protein kinase 1 (PDK-1), deleted in malignant brain tumors (DMBT1) in the thyroid carcinoma. A total of 87 fresh samples of thyroid carcinoma from surgical resection in The Second People's Hospital of Lianyungang from June 2016 to March 2018 were collected for the ELISA to detect the protein expression of PDK-1 and DMBT1. Then the pathological significance of the expression of PDK-1 and DMBT1 in the thyroid carcinoma and the correlation between them were analyzed, using the ROC curve to study the diagnostic value of each index. The expression of PDK-1 in the thyroid carcinoma tissue was significantly higher than that in the normal thyroid tissue with a statistical difference between them (P<0.05); the expression of DMBT1 in the thyroid carcinoma was statistically significantly lower than that in the normal thyroid tissue (P<0.05); the PDK-1 and DMBT1 expressions were in negative correlation in the thyroid carcinoma (r=-0.889, P<0.001). The AUG, specificity and the sensitivity of the PDK-1 in diagnosing the thyroid carcinoma were 0.862, 86.21% and 78.16%, respectively; the AUG, specificity and the sensitivity of the DMBT1 in diagnosing the thyroid carcinoma were 0.708, 66.67% and 67.82%, respectively; while the AUG, the specificity and the sensitivity of the combination of PDK-1 and DMBT1 in diagnosing the thyroid carcinoma were 0.888, 89.66% and 81.61%. In conclusion, the occurrence and progression of the thyroid carcinoma were related to the high expression of the PDK-1 and the low expression of the DMBT1 in the thyroid carcinoma tissues, the two of which were in connection with factors involving lymph node metastasis, pathological type, neoplasm staging, and clinical staging. Thus, the combined detection of PDK-1 and DMBT1 could be used as an effective index to determine the occurrence of thyroid carcinoma.

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Key words: thyroid carcinoma, phosphoinositide-dependent protein kinase 1, deleted in malignant brain tumors, case parameters

Introduction

Thyroid carcinoma, the most common endocrine carcinoma (1), is seeing an increasingly high incidence worldwide in recent years (2), with a 10th-ranking incidence among tumors in China (3). Recently more scholars have a rising interest in the pathogenesis of thyroid carcinoma. Phosphoinositide-dependent protein kinase 1 (PDK-1), a monomeric polypeptide enzyme consisting of more than five hundred amino acids including the N-terminal kinase domain and the C-terminal PH domain, which is normally expressed in a variety of peripheral tissues including the heart, stomach, spleen, kidney, brain and other tissues, has a ligand that plays an important role in the regulation of the immune system, tumor metastasis, embryonic development and angiogenesis (4). Studies showed that the expression level of deleted in malignant brain tumors (DMBT1) was greatly decreased in breast carcinoma (5), human oral squamous cell carcinoma (6) compared with that in the normal tissues, which suggested the potential ability of DMBT1 gene as a tumor suppressor gene to get involved in the regulation of the occurrence and development of the carcinogenesis of tumor cells. In recent years, few studies of the expression levels of DMBT and PDK-1 gene in the thyroid tissue have been reported. In the following parts, this study investigated the expression levels of PDK-1 and DMBT1 genes in the thyroid tissue and the correlation between the two, and further explored the relationship between the expression levels of PDK-1 and DMBT1 and the molecular biological mechanisms of the occurrence, development, metastasis, proliferation and malignant transformation of the thyroid carcinoma.

Patients and methods

General information. Eighty-seven patients (34 males and 53 females) with thyroid carcinoma diagnosed in The Second People's Hospital of Lianyungang (Lianyungang, China) from June 2016 to March 2018 were selected as the research subjects. Inclusion criteria: i) adults with no history of mental illness who were capable of normal communication, self-care, and clear consciousness and ii) patients (or their immediate

Table I. Basic information of patients.

Factors	n=87
Age (year)	
<35	31 (35.63)
≥35	56 (64.37)
Sex	
Male	52 (59.77)
Female	35 (40.23)
Obesity	
Yes	47 (54.02)
No	40 (45.98)
Clinical staging	
Stage I-II	31 (35.63)
Stage III-IV	56 (64.37)
Pathological type	
Undifferentiated	51 (58.62)
Differentiated	36 (41.38)
Size of tumor	
Microcarcinoma	52 (59.77)
Non-small cell carcinoma	35 (40.23)

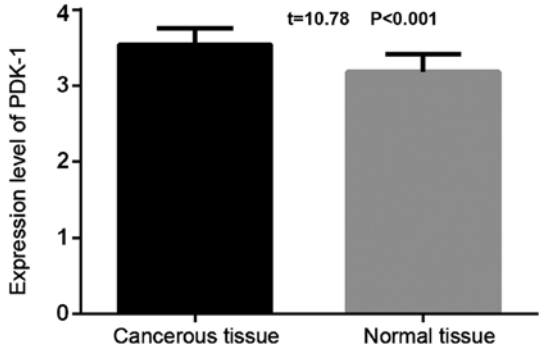

Figure 1. The expressions of PDK-1 in the thyroid carcinoma tissues and their adjacent normal tissues. The expression level of PDKP-1 in the thyroid carcinoma tissues is greatly higher than that in their adjacent normal tissues, with a statistical difference (t=10.78, P<0.001). PDK-1, phosphoinositide-dependent protein kinase.

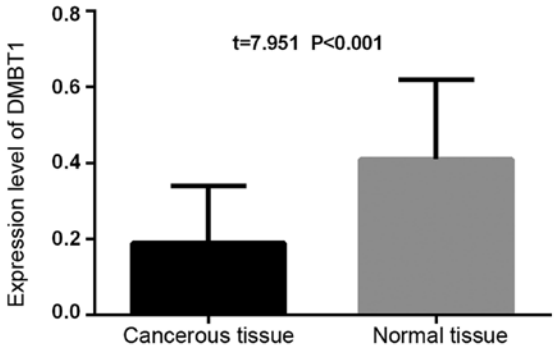

Figure 2. The expressions of DMBT1 in the thyroid carcinoma tissues and their adjacent normal tissues. The expression level of DMBT1 in the thyroid carcinoma tissues is statistically greatly lower than that in their adjacent normal tissues (t=7.95, P<0.001). DMBT1, deleted in malignant brain tumors.

families) that signed the informed consent. Exclusion criteria: i) patients with permanent intracardiac conduction disorder, cardiogenic shock and a history of severe mental illness and ii) patients with acute inflammation, hematological disease, and severe heart and liver dysfunction. Patients in this study received no chemotherapy, radiotherapy or immunotherapy ever. Immediately after the surgery, the resected thyroid carcinoma tissues and normal tissues over 2 cm away from the carcinoma with no observed cancer cell infiltration were stored in the refrigerator at -80˚C (Table I).

The study was approved by the Ethics Committee of The Second People's Hospital of Lianyungang. Patients who participated in this research had complete clinical data. The signed informed consents were obtained from the patients or the guardians.

Main reagents and instruments. DMBT1 ELISA test kit for human (article no. IC-DMBT1-Hu; Shanghai Yu Bo Biotechnology Co., Ltd., Shanghai, China), PDK-1 ELISA test kit for human (article no. EH15196; Wuhan Fine Biotech Co., Ltd., Wuhan, China).

Experimental methods. This experiment was carried out in a sterile environment, with all the instruments autoclaved and dried before the use. The normal thyroid tissue and the thyroid carcinoma tissue were taken out from the -80˚C refrigerator and thawed. Then, 0.1 g of normal thyroid tissue and 0.1 g of thyroid carcinoma were weighted. With a small amount of liquid nitrogen, the tissues were separately crushed into powder in the mortar quickly. Next, the powder was transferred into the 2 ml-sized Ep tube, afterward got mixed together with 1.2 ml of PBS (pH 7.3) at the speed of 1,500 x g and got centrifugalized at 4˚C for 20 min to get the supernatant liquid. Then the homogenate of normal thyroid tissue and thyroid carcinoma tissue was detected in strict accordance with the instructions of the DMBT1 ELISA kit for human and the PDK-1 ELISA kit for human.

Statistical analysis. The SPSS 20.0 software (IBM Corp., Armonk, NY, USA) was used to perform the statistical analysis. The basic count data of patients were expressed as the percentage [n (%)]; the expression levels of DMBT1 and PDK-1 were expressed as the mean ± standard deviation (SD). Pearson's correlation was used for the correlation between the expression of PDK-1 and DMBT1. The t-test was used for statistical analysis and P<0.05 was considered to indicate a statistically significant difference.

Results

Expression levels of DMBT1 and PDK-1 in thyroid carcinoma tissues and normal tissues adjacent to them. The expression level of PDK-1 in the thyroid carcinoma tissue (3.54±0.21) was statistically higher than that of the adjacent normal thyroid tissues (3.18±0.23; t=10.78, P<0.001). The expression level of PDK-1 in the thyroid carcinoma tissue (0.19±0.15) was lower than that of the adjacent normal thyroid tissues (0.41±0.21), and the difference was statistically significant (t=7.951, P<0.001; Figs. 1 and 2).

Table II. Relationship between the expression level of PDK-1 and clinicopathological features of patients with thyroid carcinoma.

Factors	PDK-1	t	P-value
Age (year)			
<35	3.41±1.52	1.166	0.245
≥35	3.67±1.42		
Gender			
Male	3.41±1.79	0.988	0.325
Female	3.67±1.68		
Clinical staging			
Stages I-II	3.21±1.47	2.758	0.007
Stages III-IV	3.87±1.68		
Lymph node metastasis			
Yes	3.94±1.56	3.549	<0.001
No	3.14±1.41		
Pathological type			
Undifferentiated	4.56±1.71	8.536	<0.001
Differentiated	2.52±1.43		
Size of tumors			
Microcarcinoma	2.30±1.32	11.43	<0.001
Non-small carcinoma	4.88±1.64		

PDK-1, phosphoinositide-dependent protein kinase.

Relationship between the expression levels of DMBT1 and PDK-1 and the clinicopathological features of patients with thyroid carcinoma

Relationship between the expression level of PDK-1 and the clinicopathological features of patients with thyroid carcinoma. The expression level of PDK-1 in the thyroid carcinoma tissues was significantly lower than that in the adjacent normal thyroid tissues, and the difference was statistically significant (P<0.001). The expression of PDK-1 in thyroid carcinoma was proved to be greatly correlated with factors like pathological type, clinical stage, tumor size and lymph node metastasis (P<0.001), in no significant correlation with factors such as sex and age (P>0.05). In the thyroid carcinoma tissues, the expression of PDK-1 in the lymph node metastasis (3.94±1.56) was statistically greatly higher than that in the places without lymph node metastasis (3.14±1.41; P<0.001). The PDK-1 expression in the undifferentiated tissues (4.56±1.71) was much higher than that in the differentiated thyroid carcinoma tissues (2.52±1.43), with a statistical difference (P<0.001). The expression level of PDK-1 in the thyroid carcinoma tissues at stage I to stage II (3.21±1.47) was statistically significantly lower than that in the thyroid carcinoma tissues at stage III to stage IV (3.87±1.68; P<0.05). The expression level of PDK-1 in the microcarcinoma tissues (2.30±1.32) was greatly lower than that in the non-small carcinoma thyroid tissues (4.88±1.64), and the difference was statistically significant (P<0.001; Table II).

Relationship between the expression level of DMBT1 and the clinicopathological features of patients with thyroid carcinoma. The expression level of DMBT1 in the thyroid carcinoma tissues was significantly lower than that that in the adjacent normal thyroid tissues, and the difference was statistically significant (P<0.001). The expression of DMBT1 in thyroid carcinoma was proved to be greatly correlated with factors like pathological type, clinical stage, tumor size and lymph node metastasis (P<0.001), in no significant correlation with factors such as sex and age (P>0.05). In the thyroid carcinoma tissues, the expression of DMBT1 in the lymph node metastasis (0.17±0.14) was statistically lower than that in the places without lymph node metastasis (0.21±0.11; P<0.001). The DMBT1 expression in the differentiated tissues (0.23±0.14) was much higher than that in the undifferentiated thyroid carcinoma tissues (0.15±0.08), with a statistical difference (P<0.001). The expression level of DMBT1 in the thyroid carcinoma tissues at stage I to stage II (0.22±0.14) was statistically significantly higher than that in the thyroid carcinoma tissues at stage III to stage IV (0.16±0.09; P<0.05). The expression level of DMBT1 in the microcarcinoma tissues (0.27±0.13) was greatly higher than that in the non-small carcinoma thyroid tissues (0.11±0.09), and the difference was statistically significant (P<0.001; Table III).

Correlation between the expression of DMBT1 and the expression of PDK-1 in the thyroid carcinoma. Correlation analysis showed that the expressions of DMBT1 and PDK-1 were negatively correlated in the thyroid carcinoma (r=-0.889, P<0.001) (Fig. 3).

Clinical diagnostic value of DMBT1 and PDK-1. According to the ROC curve, the AUG, the specificity, and the sensitivity of the protein PDK-1 in diagnosing thyroid carcinoma were 0.862, 86.21% and 78.16%, respectively, with the best cut-off point for diagnosing thyroid carcinoma of 199; the AUG,

Table III. Relationship between the expression level of DMBT1 and the clinicopathological features of patients with thyroid carcinoma.

Factors	DMBT1	t	P-value
Age (year)			
<35	0.20±0.12	1.244	0.215
≥35	0.18±0.09		
Gender			
Male	0.20±0.12	1.146	0.253
Female	0.18±0.11		
Clinical staging			
Stages I-II	0.22±0.14	3.363	0.001
Stages III-IV	0.16±0.09		
Lymph node metastasis			
No	0.21±0.11	2.096	0.037
Yes	0.17±0.14		
Pathological type			
Differentiated	0.23±0.14	4.628	<0.001
Undifferentiated	0.15±0.08		
Size of tumors			
Microcarcinoma	0.27±0.13	9.439	<0.001
Non-small carcinoma	0.11±0.09		

DMBT1, deleted in malignant brain tumors.

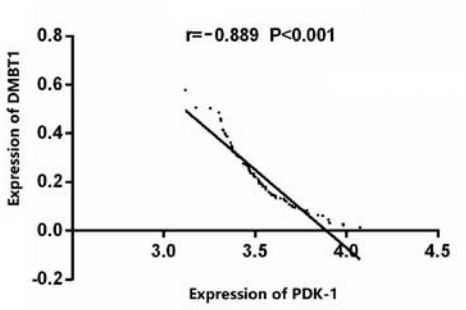

Figure 3. The correlation between the expression of PDK-1 and the expression of DMBT1 in the thyroid carcinoma. According to Pearson's correlation analysis, the expression of PDK-1 and the expression of DMBT1 are negatively related (r=-0.889, P<0.001). PDK-1, phosphoinositide-dependent protein kinase; DMBT1, deleted in malignant brain tumors.

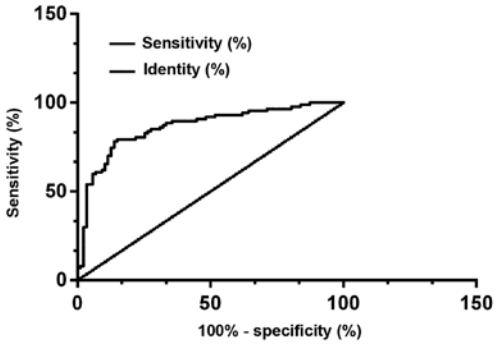

Figure 4. The diagnostic value of the expression of PDK-1 for the thyroid carcinoma. ROC was used to evaluate the diagnostic value of protein PDK-1 in thyroid cancer. PDK-1, phosphoinositide-dependent protein kinase.

the specificity, and the sensitivity of the protein DMBT1 in diagnosing thyroid carcinoma were 0.708, 66.67% and 67.82%, respectively, with the best cut-off point for diagnosing thyroid carcinoma of 199; and the AUG, the specificity, and the sensitivity of the combination of protein PDK-1 and protein DMBT1 in diagnosing thyroid carcinoma were 0.888, 89.66% and 81.61%, respectively, with the best cut-off point for diagnosing thyroid carcinoma of 199 (Figs. 4, 5 and 6).

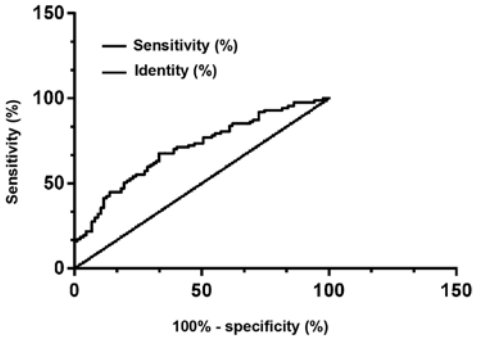

Figure 5. The diagnostic value of the expression of DMBT1 for the thyroid carcinoma. The diagnostic value of protein DMBT1 in thyroid cancer was evaluated using the ROC curve. DMBT1, deleted in malignant brain tumors.

Discussion

Citing from the American Carcinoma Society, 37,340 new cases (about 0% women) of thyroid carcinoma were diagnosed in the

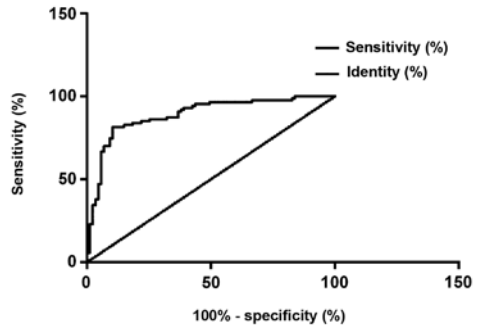

Figure 6. The diagnostic value of the combined detection the expressions of PDK-1 and DMBT1 for the thyroid carcinoma. The diagnostic value of PDK-1 combined with DMBT1 inthyroid cancer was evaluated by ROC curve. PDK-1, phosphoinositide-dependent protein kinase; DMBT1, deleted in malignant brain tumors.

United States in 2018, making the thyroid carcinoma the sixth destructive carcinoma among women (7). Thyroid carcinoma, a common malignant tumor in the head and neck (8), is prone to spread and metastasis in its early stage (9). PDK1, as the main regulator of the upstream AGG family that plays an important role in the regulation of pathological processes such as cell growth, differentiation, and apoptosis (10,11), is found in recent years to be highly expressed in non-small cell carcinoma, breast carcinoma, and pancreatic carcinoma tissues (12-14). The close relation between the deterioration and the occurrence of tumors is publicly known, and the PDK1, as an important kinase in cells, has a significant regulatory effect on the cell reproduction (15,16). Located on the long arm of the human's number l0 chromosome (17), the DMBT1 gene has its sequence that is mainly composed of repeated highly homologous exons and introns (18). Some studies discovered that the expression level of DMBT1 gene in tumors like esophageal carcinoma (19), colon carcinoma (20), bladder carcinoma (21), prostate carcinoma (5), and non-small cell carcinoma (22) was significantly decreased compared with its expression in normal tissues, suggesting that DMBT1 might be able to inhibit the development of oncogenes. According to the study of Mollenhauer's team (23), DMBT1 might play an important role in the development of one unclear part of the human body. It's likely that DMBT1 may inhibit the occurrence of tumors by promoting cell differentiation since the formation of tumors can lead to cell disorders. This study is the first one to detect the expression of PDK-1 and DMBT1 proteins in the thyroid carcinoma tissues and in their adjacent normal tissues more than 2 cm away with no carcinoma cells infiltrating using the ELISA method and analyze the correlation between the two and the pathological significance of the thyroid carcinoma. The results of this study revealed that the expression level of PDK-1 in the thyroid carcinoma tissues was statistically significantly higher than that in the normal tissues adjacent to the carcinoma ($t=10.78$, $P<0.001$), while the expression level of DMBT1 in the thyroid carcinoma tissues was statistically significantly lower than that in the normal tissues adjacent to carcinoma ($t=7.491$, $P<0.05$). Previous studies showed that the positive expression of DMBT1 in breast carcinoma was significantly lower than that in the normal tissues (24), which helpfully supports the results of this study. By now no relevant study of the expression level of PDK-1 in the thyroid carcinoma tissues has been reported. This study also analyzed the relationship between the expression levels of DMBT1 and PDK-1 and the clinicopathological features of patients with thyroid carcinoma. The results showed that the expression of PDK-1 in thyroid carcinoma was proved to be greatly correlated with factors like pathological type, clinical stage, tumor size and lymph node metastasis ($P<0.001$), in no significant correlation with factors such as sex and age ($P>0.05$); in the thyroid carcinoma tissues, the expression of PDK-1 in the lymph node metastasis was statistically greatly higher than that in the places without lymph node metastasis ($P<0.001$); the PDK-1 expression in the undifferentiated tissues was much higher than that in the differentiated thyroid carcinoma tissues, with a statistical difference ($P<0.001$); the expression level of PDK-1 in the thyroid carcinoma tissues at stage III to stage IV was statistically significantly higher than that in the thyroid carcinoma tissues at stage I to stage II ($P<0.05$); the expression level of PDK-1 in the non-small carcinoma thyroid tissues was greatly higher than that in the microcarcinoma tissues, and the difference was statistically significant ($P<0.001$). The expression of DMBT1 in the thyroid tissues was in a contrary situation: in the thyroid carcinoma tissues, the expression of DMBT1 in the lymph node metastasis was statistically greatly lower than that in the places without lymph node metastasis; the DMBT1 expression in the undifferentiated tissues was much lower than that in the differentiated thyroid carcinoma tissues, with a statistical difference ($P<0.001$); the expression level of DMBT1 in the thyroid carcinoma tissues at stage III to stage IV was statistically significantly lower than that in the thyroid carcinoma tissues at stage I to stageII ($P<0.05$); the expression level of DMBT1 in the non-small carcinoma thyroid tissues was greatly lower than that in the microcarcinoma tissues, and the difference was statistically significant ($P<0.001$). Finally, referring to the results of the correlation and partial correlation between the expression of DMBT1 and the expression PDK-1 in the thyroid carcinoma that DMBT1 and PDK-1 were negatively correlated in the thyroid carcinoma ($r=-0.889$, $P<0.001$), this study made a speculation that the pathological features of thyroid carcinoma were closely related to the expression of DMBT1 and PDK-1, with a highly expressed PDK-1 in it to promote the development of thyroid carcinoma, and with a lowly expressed DMBT1 in it to possibly inhibit the thyroid carcinoma. Despite the few reports about the relationship between the expression of DMBT1 and PDK-1 and the clinicopathological features of thyroid carcinoma in patients, some previous reports on the thyroid carcinoma are still helpful to this study. Following the detection of the expression of DMBT1 and PDK-1, the ROC curve was drawn to investigate the diagnostic value of DMBT1 alone, PDK-1 alone and the combination of the two for thyroid carcinoma, leading to the results that the sensitivity and specificity of the combined detection of DMBT1 and PDK-1 for thyroid carcinoma detection were significantly higher than the single detection of DMBT1 or PDK-1. No study of the diagnostic value of DMBT1 and PDK-1 for the thyroid carcinoma has been reported so far, so this study which specifically explored the correlation between the expression of DMBT1 or PDK-1 and the occurrence and development of the thyroid carcinoma, is of certain significance for the diagnosis and clinical treatment of thyroid carcinoma. Finally, with the research results and

some supportive views by other studies on hand, this study draw the conclusion that monitoring the expression of DMBT1 or PDK-1 in the protein had certain clinical diagnostic and therapeutic significance for the occurrence and development of the thyroid carcinoma, and that the combined detection of the expression changes of DMBT1 and PDK-1 could diagnose the thyroid carcinoma conveniently, quickly, and accurately, worthy of clinical promotion.

Considering the limited resources and the small number of research subjects, contingency was possible in this study. In the future, more time and energy will be invested in the improvement of this research to achieve better study results.

In summary, PDK-1 was highly expressed in the thyroid carcinoma, while the DMBT1 was lowly expressed. The combined detection of DMBT1 and PDK-1 could improve the accuracy of diagnosing the thyroid carcinoma to reduce the rate of misdiagnosis.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

ZS analyzed and interpreted the general data of patients and drafted this paper. ZS and LX were responsible for ELISA. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The Second People's Hospital of Lianyungang (Lianyungang, China). Patients who participated in this research had complete clinical data. The signed informed consents were obtained from the patients or the guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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