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ABOUT COVER

Peer-reviewer of *World Journal of Clinical Cases*, Dr. Mohamad Adam Bujang is a Research Officer at the Institute for Clinical Research, Ministry of Health, Malaysia. After receiving his Bachelor's degree in Statistics from MARA University of Technology in 2004, Dr. Adam undertook his postgraduate study at the same university, receiving his Master's degree (MBA) in 2008 and his PhD in Information Technology and Quantitative Sciences in 2017. Currently, he works as a biostatistician and researcher in the Clinical Research Centre, Sarawak General Hospital. His ongoing research interests involve such research methodologies as sampling techniques, sample size planning, and statistical analyses. Since 2016, he has served as an active member of the Malaysia Institute of Statistics and the Association of Clinical Registries Malaysia. (L-Editor: Filipodia)

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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Retrospective Study

Overexpression of CD155 is associated with PD-1 and PD-L1 expression on immune cells, rather than tumor cells in the breast cancer microenvironment

Rui-Bin Wang, Yu-Chen Li, Quan Zhou, Shu-Zhen Lv, Ke-Yu Yuan, Jiang-Ping Wu, Yan-Jie Zhao, Qing-Kun Song, Bin Zhu

ORCID number: Rui-Bin Wang 0000-0001-9592-1539; Yu-Chen Li 0000-0001-7091-3073; Quan Zhou 0000-0002-8856-5836; Shu-Zhen Lv 0000-0002-2341-966X; Ke-Yu Yuan 0000-0001-6769-4084; Jiang-Ping Wu 0000-0002-5105-8902; Yan-Jie Zhao 0000-0003-0831-6395; Qing-Kun Song 0000-0002-1159-257X; Bin Zhu 0000-0002-1024-3407.

Author contributions: Wang RB, Li YC and Zhou Q performed the majority of experiments and wrote the manuscript; Lv SZ, Yuan KY, Zhao YJ, and Song QK designed the study and corrected the manuscript; Wu JP and Wang RB contributed to data analysis; Song QK and Zhu B were responsible for designing and performing the study, manuscript reviewing and approval of the final version; Song QK and Zhu B contributed equally to this manuscript; all authors have read and approved the final manuscript.

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Rui-Bin Wang, Department of Emergency, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China

Yu-Chen Li, Department of Cancer Research, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China

Quan Zhou, Department of Pathology, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China

Shu-Zhen Lv, Ke-Yu Yuan, Department of Breast Surgery, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China

Jiang-Ping Wu, Yan-Jie Zhao, Department of Medical Oncology, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China

Qing-Kun Song, Department of Clinical Epidemiology and Evidence-based Medicine, Beijing Shijitan Hospital, Beijing 100038, China

Bin Zhu, Department of Surgical Oncology, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China

Corresponding author: Bin Zhu, MD, Professor, Department of Surgical Oncology, Beijing Shijitan Hospital, Capital Medical University, No. 10 Tieyi Road, Haidian District, Beijing 100038, China. binbinzhu99@sohu.com

Abstract

BACKGROUND

CD155 is an immune checkpoint protein in cancers and interacts with ligands to regulate the immune microenvironment. The expression of CD155 is correlated with the prognosis and pathological features of breast cancer.

AIM

To investigate the expression status of CD155 and the association with exhausted CD4⁺ helper and CD8⁺ cytotoxic tumor infiltrating lymphocytes (TILs) and PD-L1 in the breast cancer microenvironment.

Shijitan Hospital, Capital Medical University, No. 2017-KF01.

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statement: The study was reviewed and approved by the Ethics Committee of Beijing Shijitan Hospital, No. SJEC 2016-111.

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METHODS

One hundred and twenty-six breast cancer patients with invasive ductal breast cancer were consecutively recruited into this study. Immunohistochemistry was used to detect the expression CD155, PD-L1 and PD-1 on tumor-infiltrating immune cells and tumor cells in the microenvironment.

RESULTS

The proportion of patients with CD155 expression was higher in triple negative breast cancer (72.7%) than in Luminal A patients (22.2%, $P < 0.05$). Patients with positive CD155 expression had a higher percentage of CD4⁺/PD-1⁺ helper TILs (30%) than patients with negative CD155 expression (21%, $P < 0.05$). Patients with positive CD155 expression also had higher cell counts of exhausted CD4⁺ TILs [47 *vs* 20/high-power fields (HPF)] and unexhausted CD8⁺ TILs (30 *vs* 17/HPF) than patients with negative expression ($P < 0.05$). CD155 expression was correlated with increased PD-L1 expression in immune cells, 0.8% and 0.02% immune cells expressed PD-L1 in patients with positive and negative CD155 expression, respectively ($P < 0.05$).

CONCLUSION

CD155 was related to an inhibitory immune breast cancer microenvironment. CD155 was associated with a high proportion of exhausted CD4⁺ and unexhausted CD8⁺ TILs and high PD-L1 expression in immune cells.

Key Words: Breast cancer; CD155; PD-1; PD-L1; Tumor-infiltrating lymphocytes; Immune cells

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Core Tip: In this study, we showed that overexpression of CD155 in the breast cancer microenvironment had a significant association with a high level of programmed cell death ligand 1 expression, exhausted CD4⁺ helper T cells and unexhausted CD8⁺ cytotoxic T cells. CD155 expression was related to the inhibitory immune microenvironment and may be an immunotherapeutic target in breast cancer.

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INTRODUCTION

Breast cancer (BC) is the most common malignant tumor among Chinese women, and new cases of breast cancer accounted for 15% of all female cancer patients in 2015^[1]. The clinicopathological characteristics of Chinese women with BC are different to those of western women, with a lower expression rate of hormone receptors and higher expression rate of human epidermal growth factor receptor 2^[2].

CD155 is one ligand of the T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motifs (ITIM) domain (TIGIT) expressed in various cell types, including antigen-presenting cells and tumor cells^[3] and the interaction limits cell function through feedback inhibition^[4]. Normal tissues have no or low expression of CD155 but malignancies have upregulated expression^[5,6], which plays a key role in tumor cell invasion and migration.

PD-L1 is mainly expressed on the membrane surface of mature immune cells and various tumor cells^[7]. PD-1 is an immune checkpoint molecule and the interaction inhibits biological functions of effector T-cells. PD-1 expression on BC tumor infiltrating lymphocytes (TILs) was shown to be related with different clinicopathological characteristics^[8,9]. However, whether the exhausted phenotypes of

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effector TILs and PD-L1 are related to CD155 expression in BC has not been reported. Therefore, this study was performed to investigate the distribution of CD155 expression and its relationship with PD-L1 and phenotypes of exhausted CD4⁺ and CD8⁺ effector TILs to illustrate the effect of CD155 expression on the immune microenvironment of BC in Chinese patients.

MATERIALS AND METHODS

Ethical approval and informed consent

All procedures performed in this study involving human participants were approved by the ethical committee of Beijing Shijitan Hospital, Capital Medical University, in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments. This was a retrospective study and formal consent was waived.

Patients

A total of 126 patients with invasive ductal BC were consecutively recruited into this cohort study from January 1, 2012 to December 31, 2013. Patients were diagnosed with operable BC and received surgical treatment at the Department of Breast Surgery, Beijing Shijitan Hospital, Capital Medical University. All patients were diagnosed with primary invasive BC following pathology testing.

Tissue preparation

The surgical specimens from all patients were fixed using 4% neutral formaldehyde, embedded in paraffin (FFPE), and stained with hematoxylin and eosin. A series of 4- μ m thick sections from each specimen were used to determine the histopathological features. The Nottingham modification of the Bloom-Richardson system was used to classify histological grading of BC.

Immunohistochemistry

The expression of CD155, PD-L1 and PD-1 was detected by immunohistochemistry (IHC) on 4 μ m-thick FFPE sections. Monoclonal antibody against CD155 (rabbit anti-human, # 81254) was purchased from Cell Signaling Technology. Monoclonal antibody against PD-L1 (rabbit anti-human, # SP142) was from Roche. Monoclonal antibody against PD-1 (mouse antihuman, # UMAB199) CD4 (rabbit anti-human, # EP204) and CD8 (# SP16) were purchased from Beijing Zhong Shan Golden Bridge Biotechnology Co., Ltd. Sections were dehydrated in an oven at 60°C for 60 min, dewaxed for 20 min and washed in 100%, 100%, 95% and 75% alcohol for 2 min, respectively. The sections were then washed in phosphate buffered saline (PBS) 5 times for 2 min each time. EnVision TM FLEX Target Retrieval Solutions were used for antigen retrieval for 2 min 30 s. The sections were left at room temperature for 20 min, and washed in PBS 5 times for 2 min each time. The sections were incubated in 3% H₂O₂ at room temperature for 15 min; washed in PBS 5 times for 2 min each time and then sealed with 5% serum at 37°C for 15 min. The supernatant was discarded and the primary antibody was added at 4°C and left overnight. The samples were washed with PBS 5 times for 2 min each time, DAB was added and reacted for 5-10 min. PD-L1, PD-1 and CD155 were visualized with DAB, whereas CD4 and CD8 were visualized with AP-red. The slides were counterstained with hematoxylin.

IHC scoring

TILs located within the borders of the invasive tumor, excluding tumor zones with crush artifacts, necrosis, regressive hyalinization and biopsy sites were evaluated by two pathologists to estimate the average level. All mononuclear cells (including lymphocytes and plasma cells) were scored, and polymorphonuclear leukocytes were excluded. The average number of TILs was counted in 10 high-power fields (HPF, $\times$ 400) in randomly selected IHC sections.

Positive CD155 expression was recorded as brown membrane in tumor cells. Negative CD155 tumor cells were defined as having complete weak or incomplete strong staining on the cell membrane. Positive PD-L1 expression was recorded as brown cytoplasm and/or cytomembrane in immune and tumor cells. Positive PD-1 expression was recorded as brown cytoplasm in lymphocytes. CD4 and CD8 were expressed on the cytomembrane of lymphocytes and were red in color. Double staining of CD4/PD-1 and CD8/PD-1 showed red cytomembrane and brown cytoplasm in lymphocytes. PD-1, CD4 or CD8 positive cells in 100 TILs were counted

and the expression rate was calculated.

Statistical analysis

All analyses were conducted with SPSS software (version 17.0). The correlation of age and CD155 expression was analyzed by the Wilcoxon rank sum test. Histological grade and tumor node metastasis (TNM) stage were analyzed with CD155 expression by the Spearman correlation test. The relationship between CD155 expression and molecular subtype was estimated using the Chi-square test. Percentage and cell counts of phenotypic CD4⁺ and CD8⁺ effector TILs with CD155 expression were analyzed by the Wilcoxon rank sum test. The percentage of tumor and immune cells expressing PD-L1 with CD155 expression were analyzed by the Wilcoxon rank sum test. All analyses were two sided and the significance level was 0.05.

RESULTS

Patient age was not related to CD155 expression (Table 1). BC patients classified by histological grades and TNM stages had comparable expression of CD155 ($P > 0.05$, Table 1). Molecular subtypes were correlated with CD155 expression, as 22% of Luminal A BC patients were found to have positive CD155 expression, compared with 73% of triple-negative breast cancer (TNBC) patients ($P < 0.05$, Table 1).

CD155 expression was not associated with percentage of CD4⁺ helper TILs (Table 2). However, patients with positive CD155 expression had a higher level of CD4⁺/PD-1⁺ TILs and a lower level of CD4⁺/PD-1⁻ TILs ($P < 0.05$, Table 2). CD155 expression was not related to the percentage of phenotypic CD8⁺ TILs (Table 2).

The expression of CD155 was related to higher cell counts of CD4⁺ helper TILs (87 *vs* 54/HPF, Table 3). The increase in cell counts of exhausted, but not unexhausted CD4⁺ helper TILs was related to CD155 expression (47 *vs* 20/HPF, Table 3). CD155 expression was associated with higher cell counts of CD8⁺ TILs and unexhausted CD8⁺ TILs were increased by 76% in patients with positive CD155 expression ($P < 0.05$, Table 3).

CD155 expression was correlated with a higher proportion of immune cells expressing PD-L1 (Figure 1). The rate of immune cells with PD-L1 expression was 0.02% and 0.8% in patients with negative and positive CD155 expression, respectively ($P < 0.05$, Figure 1A and B). PD-L1 expression rates were 0.6% and 0.8% in tumor cells with negative and positive CD155 expression, and no significant relationship was observed.

DISCUSSION

CD155, originally identified as a poliovirus receptor, has similar characteristics of conserved amino acids and domain with the immunoglobulin superfamily^[10]. Due to the similar domain to nectin, CD155 is designated as the fifth member of the nectin-like molecular family, and is referred to as nectin-5^[11]. Up-regulated expression of CD155 can promote cell migration and enhances growth factor-induced cell proliferation^[12].

CD155 expression is increased in malignant tumor tissues. In this study, CD155 expression was correlated with molecular subtypes of BC, and the positive rate in TNBC was higher than that in Luminal A patients. Studies^[6] have shown that CD155 is less expressed in normal tissues, but is significantly increased in various malignant tumor tissues, and its overexpression was associated with tumor progression and poor prognosis. In addition, plasma soluble CD155 was significantly higher in cancer patients than that in healthy people, and the level in patients with advanced stage cancer was even higher than that in patients with early stage disease^[13]. These studies suggest that CD155 may serve as a biomarker for tumor progression and prognosis.

CD155 expression is reported to be regulated by the activation of signaling pathways such as Raf-MEK-ERK-AP1^[14], Sonic hedgehog^[15], and Toll-like receptor 4 (TLR4)^[16]. Overexpression of CD155 inhibited tumor cell apoptosis through the AKT/bcl-2 signaling pathway in colon cancer^[17]. In addition, DNA damage is one of the important mechanisms in the induction of CD155 expression. Reactive oxygen species or reactive nitrogen species can induce the expression of CD155 in multiple myeloma cells^[18]. Therefore, CD155 expression in tumor tissues is increased under the influence of multiple factors.

T cell activation is initiated after T cell receptor (TCR) recognition of antigens, and

Table 1 Relationship between CD155 expression and pathological characteristics

	CD155 expression		P value
	Negative (n = 78)	Positive (n = 48)	
Age ¹ , mean ± SD (yr)	58.2 ± 13.87	57.8 ± 13.26	0.914
Histological grade ² , n (%)			0.112
I	11 (15.3)	2 (4.3)	
II	47 (65.3)	32 (69.6)	
III	14 (19.4)	12 (26.1)	
TNM stage ³ , n (%)			0.662
I	20 (27.0)	10 (21.3)	
II	39 (52.7)	28 (59.6)	
III	12 (16.2)	6 (12.8)	
IV	3 (4.1)	3 (6.4)	
Molecular subtype ³ , n (%)			0.002
Luminal A	49 (77.8)	14 (22.2)	
Luminal B	16 (51.6)	15 (48.4)	
HER2 over-expression	5 (50.0)	5 (50.0)	
Triple negative	3 (27.3)	8 (72.7)	

¹Wilcoxon rank sum test.²Spearman correlation test.³Chi-square test. TNM: Tumor node metastasis.**Table 2 Association between CD155 expression and percentage of tumor infiltrating lymphocytes phenotypes¹**

TILs phenotypes	CD155 expression		P value
	Negative (n = 78)	Positive (n = 48)	
CD4 ⁺ TILs, mean ± SD	60% ± 22%	61% ± 22%	0.788
CD4 ⁺ /PD-1 ⁺ TILs, mean ± SD	21% ± 20%	30% ± 19%	0.004
CD4 ⁺ /PD-1 ⁻ TILs, mean ± SD	39% ± 20%	31% ± 19%	0.032
CD8 ⁺ TILs, mean ± SD	23% ± 13%	24% ± 11%	0.342
CD8 ⁺ /PD-1 ⁺ TILs, mean ± SD	4% ± 5%	5% ± 5%	0.280
CD8 ⁺ /PD-1 ⁻ TILs, mean ± SD	19% ± 10%	20% ± 9%	0.437

¹Wilcoxon rank sum test. TILs: Tumor infiltrating lymphocytes.

the co-signaling molecules affect T cell activation, subsets differentiation and survival^[19]. Co-stimulatory and co-inhibitory receptors determine the functional outcome of TCR signaling^[20]. TIGIT, like PD-1 and CTLA-4, is a co-inhibitory receptor that can be expressed by CD4⁺T cells, CD8⁺T cells, natural killer (NK) cells and other immune cells^[21]. CD155 can regulate the function of immune cells. In this study, patients with CD155 overexpression had a higher level of CD4⁺/PD-1⁺ TILs and higher cell counts of CD4⁺, CD8⁺ TILs. Lymphocytes, T-cells, B-cells, macrophages or NK cells, which moved from the vasculature and localized in tumor stroma are called TILs^[22]. The immune system, especially TILs in the epithelium, plays a major role in controlling the growth of virtually all solid tumors^[23]. TILs in the microenvironment reportedly affect cancer development, prognosis, and treatment efficacy. The existence of TILs has been determined to be a positive prognostic factor in a number of solid cancers including, but not limited to, colon cancer^[24] and BC^[25]. Although CD8⁺ or CD4⁺ T lymphocytes have been shown to recognize cancer antigens and inhibit the

Table 3 Association between CD155 expression and cell counts of tumor infiltrating lymphocytes phenotypes¹

TILs phenotypes	CD155 expression		P value
	Negative (n = 78)	Positive (n = 48)	
CD4 ⁺ TILs, mean ± SD	54 ± 46	87 ± 93	0.041
CD4 ⁺ /PD-1 ⁺ TILs, mean ± SD	20 ± 24	47 ± 57	0.002
CD4 ⁺ /PD-1 ⁻ TILs, mean ± SD	34 ± 30	41 ± 45	0.658
CD8 ⁺ TILs, mean ± SD	21 ± 20	37 ± 44	0.040
CD8 ⁺ /PD-1 ⁺ TILs, mean ± SD	4 ± 5	7 ± 13	0.069
CD8 ⁺ /PD-1 ⁻ TILs, mean ± SD	17 ± 17	30 ± 35	0.040

¹Wilcoxon rank sum test. TILs: Tumor infiltrating lymphocytes.

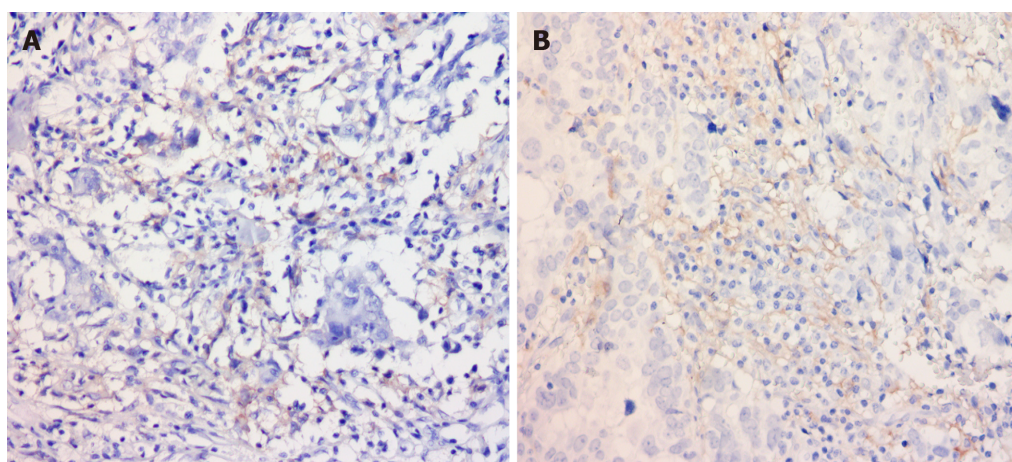


Figure 1 The relationship between PD-L1 expression in immune cells and CD155 expression in tumor cells. A: Low expression of PD-L1 among patients with negative CD155; B: High expression of PD-L1 among patients with positive CD155.

development of cancer, some cancer cells can thwart immune recognition and response^[26]. CD155 can interact with its receptors on immune cells to regulate immune function. TIGIT, CD96 and CD226 are common receptors for CD155. When CD155 binds with the co-stimulatory molecule CD226 on the surface of T cells or NK cells, these immune cells are activated to secrete cytokines and kill tumor cells; however, when CD155 interacts with co-inhibitory molecule TIGIT or CD96, the function of immune cells is inhibited^[27]. The interaction between CD155 and CD226 down-regulated the expression of CD226 in T cells and NK cells^[28]. In contrast to CD226, TIGIT is significantly upregulated on TILs, and its expression parallels that of other co-inhibitory receptors, most notably PD-1^[29]. It is now clear that co-signaling molecules have a crucial role in regulating T cell activation, subset differentiation, effector function and survival.

In this study, the proportion of immune cells with PD-L1 expression was correlated with CD155 expression in tumor cells. Studies have confirmed that during the activation process of T cells, interferon- γ (IFN- γ) molecules are secreted to up-regulate the expression of PD-L1 on DC cells, and its binding with PD-1 on T cells will generate inhibitory signals and inhibit the proliferation of T cells^[30]. Moreover, in tumor tissues, IFN- γ secretion induced by activation of the TLR4 signaling pathway induced CD155 expression^[16]. The common IFN- γ pathway shared by PD-L1 expression in immune cells and CD155 expression in tumor cells might explain this high co-expression.

In this study, although CD155 was observed to be correlated with the molecular phenotype of BC, and there was a significant correlation with TILs and PD-L1, the mechanism is still unclear. The unclear expression of TIGIT, CD96 and CD226 on TILs was the main limitation in this study. The relevant signaling pathways are not discussed in this paper.

CONCLUSION

CD155 was related to an inhibitory immune microenvironment in breast cancer patients. High CD155 expression was associated with a high level of exhausted CD4⁺ helper TILs and PD-L1 expression in immune cells. Further studies are warranted.

ARTICLE HIGHLIGHTS

Research background

CD155 is an immune checkpoint protein in cancers and interacts with ligands to regulate the immune microenvironment. The expression of CD155 is correlated with the prognosis and pathological features of breast cancer.

Research motivation

To define whether the expression of CD155 is correlated with the phenotype of tumor infiltrating lymphocytes (TILs) in the breast cancer microenvironment.

Research objectives

To investigate the expression status of CD155 and the association with exhausted CD4⁺ helper and CD8⁺ cytotoxic TILs and PD-L1 in the breast cancer microenvironment.

Research methods

This was a retrospective study of 126 breast cancer patients. Immunohistochemistry was used to detect the expression CD155, PD-L1 and PD-1 on TILs. Univariate and multivariable tests were performed for statistical analysis of the data.

Research results

The proportion of patients with CD155 expression was higher in triple negative breast cancer than in Luminal A patients. Patients with positive CD155 expression had a higher percentage of CD4⁺/PD-1⁺ helper TILs. Patients with positive CD155 expression also had higher cell counts of exhausted CD4⁺ TILs and unexhausted CD8⁺ TILs. CD155 expression was correlated with increased PD-L1 expression in immune cells.

Research conclusions

CD155 was related to an inhibitory immune microenvironment in breast cancer patients. High CD155 expression was associated with a high level of exhausted CD4⁺ helper TILs and PD-L1 expression in immune cells.

Research perspectives

CD155 overexpression resulted in a worse overall survival and may be a potential immunotherapy target in breast cancer.

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