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Assessment of tumor activity in breast cancer patients: A study of serum lactate dehydrogenase, ferritin and alkaline phosphatase levels at a tertiary care hospital

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ABSTRACT

Carcinoma of breast is the second most common cause of cancer-related mortality. A hallmark of breast cancer is metabolic pathway reprogramming. It enables progression, metastasis and resistance to conventional therapies. Lactate Dehydrogenase (LDH) is upregulated in rapidly growing tumours to maintain glycolysis as an alternative source of energy. Serum ferritin level perturbations are associated with rapid progression by promoting neoplastic cell transformation. Elevated alkaline phosphatase levels indicate a heavy tumour burden and distant metastasis. Cross sectional study was done on 60 patients diagnosed with breast cancer admitted to Surgery Department at K R Hospital, Mysore between June and August 2022 and were subjected to TNM staging. 2 ml of venous blood sample was collected and analyzed for LDH, Ferritin and ALP by enzymatic method using fully automated analyzer. The results are expressed as Mean ± Standard deviation. $p<0.001$ is considered statistically significant. Statistical analysis was performed using One Way ANOVA and independent sample 't' test. The present study shows statistically significant increase in serum LDH, ferritin and ALP levels in patients with metastatic breast cancer with mean standard deviation of 505.53 ± 110.50 (U/L), 902.01 ± 257.57 (ng/ml) and 344.68 ± 91.86 (U/L) respectively. The values of LDH, ferritin and ALP is significantly increased statistically in patients with metastatic breast cancer. Owing to the need of detecting cancer onset and progression from the early stages in areas especially where sophisticated imaging and analysis are not easily available, the identification of blood-based biomarkers is appealing.

Keywords: LDH; Ferritin; ALP; Breast cancer; Metastasis

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INTRODUCTION

Breast carcinoma is the most prevalent cancer globally and ranks as the leading cancer among women in India, with an age-adjusted incidence rate of 25.8 per 100,000 women and a mortality rate of 12.7 per 100,000 women [1], with the poorest survival rates affecting women in all age groups [2]. One of the hallmarks of breast cancer is reprogramming of the metabolic pathways in response to the selective pressures imposed by the tumor microenvironment in order to sustain the malignant phenotype [3]. It enables progression, metastasis and resistance to conventional therapies [4]. Though mortality rates have reduced due to advancements in targeted therapy, a better understanding of cancer initiation mechanisms and identification of early metabolic derangements will further reduce mortality and morbidity rates. It is crucial to identify tumor and patient-related factors that can predict aggressive biological behavior and resistance to treatment. Commonly used biomarkers, such as Lactate Dehydrogenase (LDH), ferritin and Alkaline Phosphatase (ALP), may offer valuable insights into tumor biology and should be assessed for their diagnostic and prognostic significance [5].

According to Warburg hypothesis [6], tumor cells undergo glycolysis, despite the availability of oxygen. This interconvertible reaction is catalyzed by Lactate Dehydrogenase (LDH) [7]. The correlation between the c-MYC oncogene, expression of antiapoptotic proteins of bcl-2 family and LDH suggests that metabolic pathways could be deranged before the tumor becomes detectable [8]. Lactate is involved in gene expression regulation, partitioning of energy substrate and homeostasis of cellular redox reactions [4]. Increased cell numbers and elevated proliferative activity are linked to a heightened susceptibility to carcinogens [9]. Elevated lactate levels promote angiogenesis by enhancing the expression of Vascular Endothelial Growth Factor (VEGF) protein in endothelial cells [10].

Ferritin is responsible for iron storage. Homeostasis of iron metabolism is regulated by ferritin. Cancer cells demonstrate increased iron and ferritin levels, either through the upregulation of iron uptake and retention mechanisms or by reducing iron export [11]. Ferritin level perturbations are associated with rapid progression to malignancy by promoting neoplastic cell transformation *via* induction of oxidative stress pathway [12]. Inflammation and stress induced by tumor microenvironment causes dysregulation of iron homeostasis in cancer stem cells causing modifications in epigenetic, mitochondrial metabolism, transcriptional and translational controls, alternative splicing, protein stability and sub-cellular localization [13].

Alkaline Phosphatase (ALP) is a group of membrane proteins which are phosphatidylinositol-anchored with substrate specificity. Hydrolysis of phosphate esters in an alkaline environment is catalyzed by ALP. ALP is derived from liver, intestine, skeletal tissue, kidney, bone, placenta and a variety of tumors. Serum ALP levels are elevated in breast cancer patients indicating heavy tumor burden and distant metastasis [14]. Its bone-specific isoforms are produced by osteoblasts, which release significant amounts of these enzymes during periods of bone repair, such as in the case of bone metastasis [15].

Cancer can be cured effectively if detected at early stages. Distant metastasis is a major cause for mortality and early prognostic assessment is much essential. Any metabolic derangements can be easily detected in the blood samples. Blood, being easily accessible, minimally invasive and a routine part of hospital investigations, makes the identification of blood-based biomarkers particularly appealing. These biomarkers could serve as valuable diagnostic tools for disease monitoring, treatment evaluation, patient classification into distinct prognostic subgroups and hold great potential for accurately predicting individual clinical outcomes, especially in areas where sophisticated imaging and analysis are not easily available. Therefore, alteration in particular enzyme levels in serum could be a good index of cancer progression and malignancy in its early and best manageable stage.

MATERIALS AND METHODS

Cross-sectional study was done on 60 patients admitted to department of general surgery, Krishna Rajendra Hospital, Mysore medical college and research institute between July to August 2022, who were diagnosed with breast cancer and were subjected to TNM staging.

Ethical Clearance was taken from Institutional Ethical Committee with IEC number (EC REG: ECR/134/Inst/ KA/2013/RR-19 Dated on 24th May 2022) and written informed consent was taken from all study subjects.

Inclusion criteria: Study included patients aged between 18-70 years who were diagnosed with breast cancer. These patients were subjected to TNM staging. The subjects were chosen after they were confirmed to have breast cancer by radiological, histological or cytological investigations. These patients were staged clinically based on 8th TNM-AJCC classification (tumor, regional lymph node, metastasis-American joint committee for Cancer) into different TNM stages-stage I, II, III and IV (Figure 1) [16].

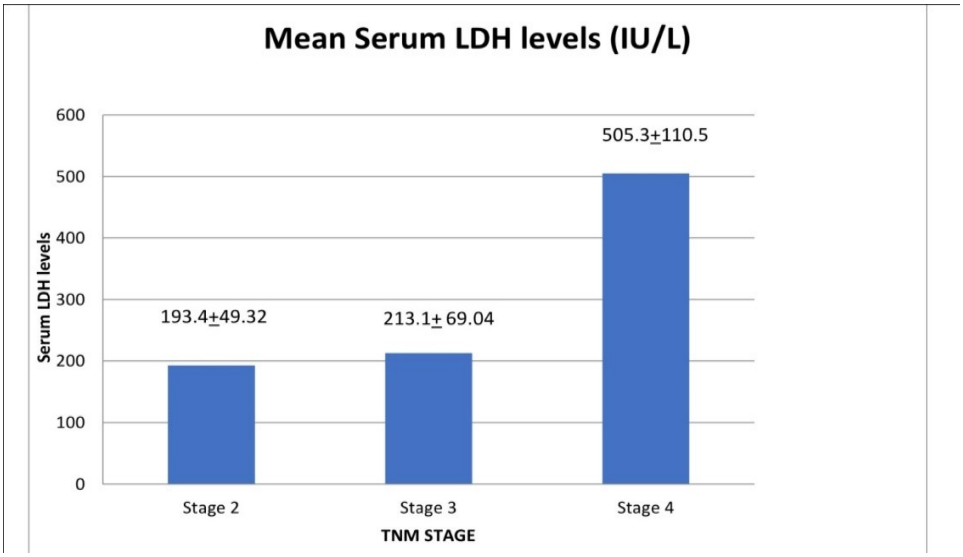

Fig. 1. Mean serum values of Lactate dehydrogenase (LDH) in U/L in different TNM stages of breast cancer.

Exclusion criteria: Patients suffering from-acute coronary syndrome, jaundice or liver disease, polycythemia, megaloblastic anemia, hemolytic anemia, diabetes mellitus, pancreatic disease, rheumatic fever, tuberculosis and bone disorders.

Study design: The study population was divided into stage I, II, III and IV based on TNM staging of breast cancer.

Data collection: Data regarding age, occupation, diet, family history, BMI, blood pressure and others information regarding staging was obtained.

Sample collection procedure: A 2 ml venous blood sample was collected from breast cancer patients in a plain vacutainer under aseptic conditions prior to the initiation of treatment. The serum was immediately analyzed for Lactate Dehydrogenase (LDH), ferritin and Alkaline Phosphatase (ALP) using enzymatic methods on a fully automated chemistry analyzer and immunoassay *via* the Cobas 6000 system.

Statistical analysis: Statistical analysis was performed using one-way ANOVA software and association between parameters was studied using independent sample 't' test.

RESULTS

The present study shows statistically significant increase in serum LDH, ferritin and ALP levels in patients with metastatic breast cancer (TNM stage 4) compared to patients without metastasis (stage 2 and 3). The mean values of ferritin, LDH and ALP increases as the tumor stage increases. The study showed a statistically significant positive association between these parameters and metastatic breast cancer showing aggressive tumor activity with p value<0.001 as shown in Table 1.

As shown in Table 1 and Figure 1 one-way ANOVA was conducted to compare the serum Lactate Dehydrogenase (LDH) levels across different TNM stages in breast cancer patients. The analysis revealed

a statistically significant increase in mean LDH values as the TNM stage progressed ($p<0.05$). Specifically, patients with TNM stage IV showed significantly higher LDH levels compared to those in earlier stages. The mean LDH values increased progressively with each stage, indicating a direct correlation between advancing TNM stage and rising LDH levels. The highest mean LDH levels were observed in patients with TNM stage IV, supporting the hypothesis that LDH levels increase with the severity of the disease.

Tab. 1. Serum LDH, ferritin and ALP levels across different TNM stages of breast cancer patients.

Parameter	TNM Stage 1	Stage 2	Stage 3	Stage 4	Total	P value
Number of subjects	1	39	10	10	60	
LDH (U/L)	151	193.38 ± 49.32	213.13 ± 69.04	505.53 ± 110.50	242.79 ± 91.21	<0.001
Ferritin (ng/ml)	114.20	49.54 ± 15.35	79.84 ± 27.98	902.01 ± 257.57	183.54 ± 414.7	<0.001
ALP (U/L)	107	96.05 ± 25.95	86.902 ± 2.13	344.68 ± 91.86	146.34 ± 18.89	<0.001

A one-way ANOVA was performed to compare serum ferritin levels across TNM stages II, III and IV in breast cancer patients (stage I was excluded from the analysis). The results demonstrated a statistically significant increase in mean ferritin levels as the TNM stage advanced ($p<0.05$) as depicted in Table 1 and Figure 2.

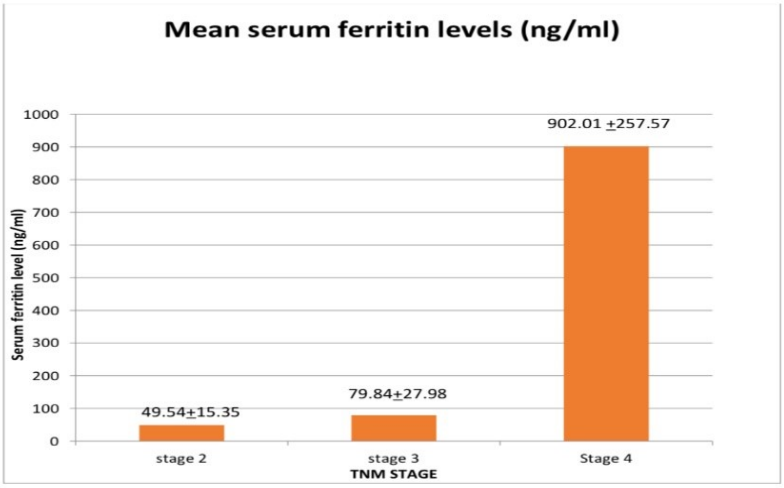

Fig. 2. Mean ferritin levels (ng/ml) in different TNM stages of breast cancer.

The mean ferritin levels were found to increase progressively with each advancing stage, with the highest levels observed in patients with TNM stage IV. This indicates that ferritin levels rise in conjunction with the progression of the disease.

A one-way ANOVA was conducted to analyze the serum Alkaline Phosphatase (ALP) levels across TNM stages II, III and IV in breast cancer patients (stage I was excluded from the analysis). The results revealed a statistically significant difference in ALP levels across the stages ($p<0.05$) as shown in Table 1 and Figure 3.

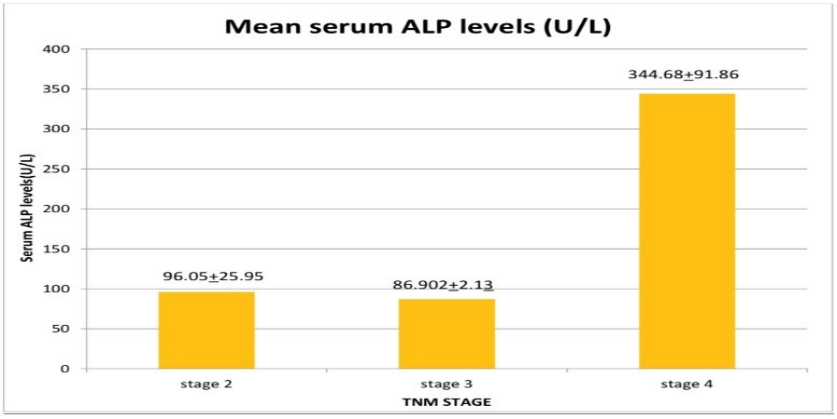

Fig. 3. Mean serum Alkaline Phosphatase (ALP) levels (U/L) in different TNM stages of breast cancer.

The mean ALP levels decreased from stage II to stage III, but there was a significant increase in ALP levels from stage III to stage IV. Patients in TNM stage IV exhibited the highest mean ALP levels, showing a distinct rise compared to earlier stages.

As depicted in Table 2 and Figure 4 an independent samples t-test was performed to compare serum Lactate Dehydrogenase (LDH) levels between patients with metastatic breast cancer and those without metastasis. The analysis showed a statistically significant difference in LDH levels between the two groups ($p<0.05$).

Tab. 2. Mean serum lactate dehydrogenase, ferritin and alkaline phosphatase levels in breast cancer patients with metastasis and without metastasis.

Metastasis	Mean serum LDH (U/L)	P value	Mean ferritin levels (ng/ml)	P value	Serum alkaline phosphatase levels (U/L)	P value
No (51)	196.42 ± 43.48	<0.001	56.75 ± 12.36	<0.001	94.47 ± 33.36	<0.001
Yes (9)	505.53 ± 90.50		902.01 ± 257.87		344.68 ± 101.86	

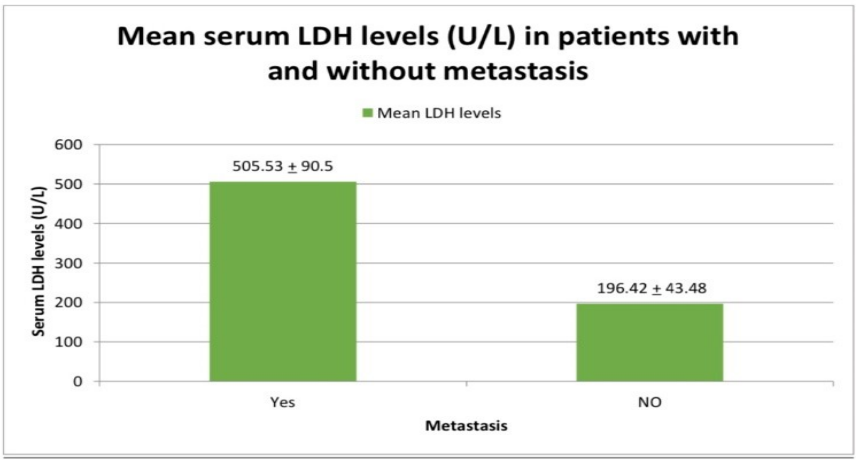

Fig. 4. Mean serum LDH levels (U/L) in patients with metastasis and without metastasis.

Patients with metastatic breast cancer had significantly higher mean LDH levels compared to non-metastatic patients, indicating a clear association between elevated LDH levels and the presence of metastasis.

An independent samples t-test was conducted to compare serum ferritin levels between patients with metastatic breast cancer and those without metastasis. The analysis revealed a statistically significant difference in ferritin levels between the two groups ($p<0.05$) as shown in Table 2 and Figure 5.

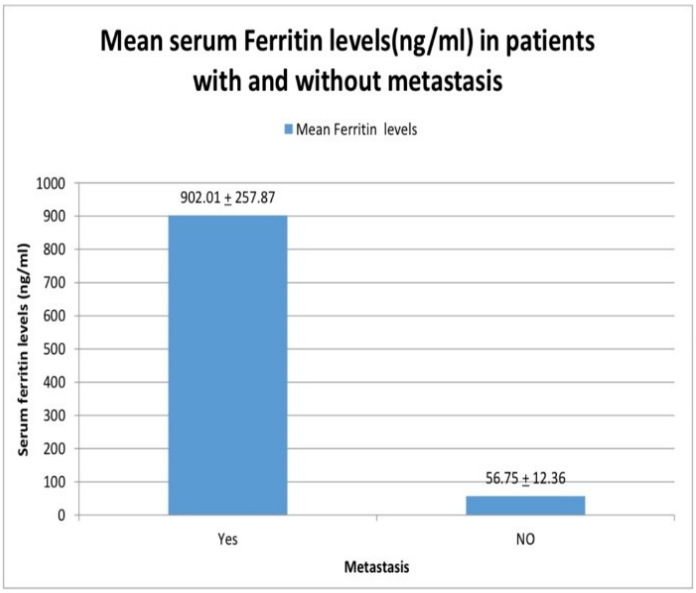

Fig. 5. Mean ferritin levels (ng/ml) in patients with metastasis and without metastasis.

Patients with metastatic breast cancer exhibited significantly higher mean ferritin levels compared to those without metastasis, indicating a notable correlation between elevated ferritin levels and the presence of metastasis.

An independent samples t-test was performed to compare serum Alkaline Phosphatase (ALP) levels between patients with metastatic breast cancer and those without metastasis. The analysis revealed a statistically significant difference in ALP levels between the two groups ($p<0.05$) as shown in Table 2 and Figure 6.

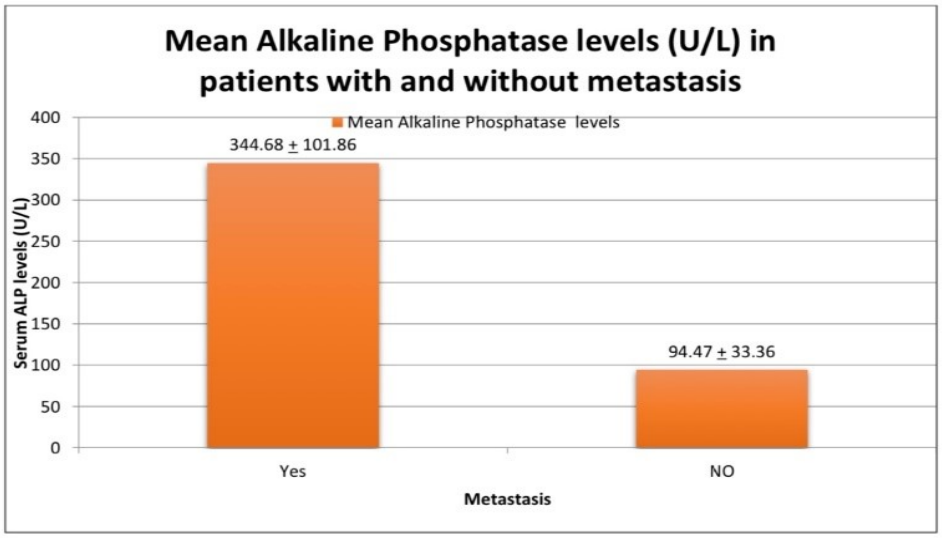

Fig. 6. Mean values of serum alkaline phosphatase (U/L) in breast cancer patients with and without metastasis.

Patients with metastatic breast cancer had significantly higher mean ALP levels compared to non-metastatic patients, indicating a strong association between elevated ALP levels and the presence of metastasis.

DISCUSSION

Breast cancer is a major public health issue. As the cancer stage increases, the mortality, morbidity and cost of treatment increases accordingly. Proper screening and early detection of breast cancer is the need of the hour in order to reduce financial burden, suffering and mental trauma. There is a need to identify simple biochemical investigations for the early detection of cancer, can be assayed at small laboratories in remote and rural areas and are inexpensive. Currently available markers lack sensitivity and specificity for detecting cancer early or to determine the tumor activity and burden. Also, no marker specific for breast cancer has been discovered yet. In view of this, the present study was undertaken to study the serum levels of LDH, ferritin and ALP in patients of breast cancer.

The present study shows a statistically significant increase in serum lactate dehydrogenase in patients with breast cancer. The mean serum values of LDH increased significantly and progressively as the tumor stage increased from TNM stage I to IV. The mean values were significantly higher (p value<0.001) in stage IV metastatic breast cancer compared to stage II, III and IV with a mean standard deviation of 505.53 ± 110 (U/L). Since lactate is involved in gene expression regulation, partitioning of energy substrate and homeostasis of cellular redox reactions, increased lactate levels can lead to metastasis [17]. Increased rate of glycolysis is expressed by changes in total activity of LDH along with the LDH isoforms [18]. Inflammatory action is tumor microenvironment is brought by LDH by activating (Interleukin) IL-12, IL-17 and Arginase I. Natural Killer and CD8+ T Lymphocytes are inhibited by LDH leading to evasion of immune response by cancer cells [3]. There is experimental proof that LDH measurement is an important auxiliary factor to monitor the course of disease in cancer [19] and that high pre-treatment LDH levels has poorer prognosis with worser survival outcomes as per studies done by Giacomo Pelizzari, et al. [3].

Serum ferritin levels were found to be increasing as the tumor stage increases. However, the values of ferritin were found to be significantly high in patients with stage IV compared to stage I, II and III with a mean standard deviation of 902.01 ± 257.57 (ng/ml) with p value <0.001. Higher serum ferritin levels are associated with rapid progression to malignancy by promoting neoplastic cell transformation *via* induction of oxidative stress pathway [11]. It is also associated with local release within the breast tumor microenvironment as a by-product [12]. Accelerated tumor growth leading to metastasis, recurrence, poor response to treatment and angiogenesis, could be due to dysregulation of extra and intracellular iron homeostasis [20]. Ferritin levels reflect accumulation of intracellular iron in tumor cells or inflammation involving macrophages associated with tumors and are thus associated with the stage of the disease as per studies done by Marina Plays, et al. [13].

Alkaline phosphatase is produced in large amounts during increased bone turnover as in bone metastasis. Studies done by Chengying Jiang et al. show that raised ALP levels are associated with short survival rates [15]. Serum ALP levels were found to be significantly higher statistically in patients with metastatic breast cancers. The mean values were found to be 344.68 ± 91.86 (U/L) in patients with stage IV compared to patients with stage I, II and III (p value<0.001). This study found that the mean serum ALP values did not increase progressively with disease stage, indicating that serum ALP levels are not associated within the breast tumor micro-environment. If any increase in ALP levels is found, it could be an indication to search extensively for metastasis.

CONCLUSION

Interpretation of LDH, ferritin and ALP helps in predicting the tumor activity of breast cancer at a tertiary care center with LDH being a marker of tumor activity while ferritin and alkaline phosphatase levels denoting tumor aggressiveness and metastatic potential. Their values directly correlate with the stage of tumor.

These parameters help in understanding the breast tumor microenvironment. However, further understanding of the tumor is required at a molecular level. This can pave way for newer targeted treatment modalities. Genetic level understanding is imperative to study the role of genes in tumor progression. These markers are economical, easy to estimate and can be easily assayed in smaller laboratories in rural and remote setting, which do not have sophisticated lab equipment and personnel. Alteration of serum enzymes could be an early marker of malignancy at its earliest and best manageable state.

LIMITATIONS

Since the study period was only for two months, the sample size was less. The serum values of LDH, ferritin and ALP couldn't be monitored or followed up after the initiation of treatment. A further study would help in identifying whether these serum markers could be used for treatment response and predict prognosis of the individual. LDH and ALP has got isoenzymes, whose values in breast cancer might help in increasing sensitivity and specificity.

The above pilot study enlightened us that there is a need to understand molecular basis responsible for changes in tumor microenvironment that in turn will help in development of targeted therapy to stop progression of the disease.

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