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Non-Coding RNAs as Future Cancer Biomarkers

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microRNAs as Diagnostic Tools in Cancers

microRNAs as diagnostic biomarkers in hepatocellular carcinoma

It was reported in a study that microRNA-21, microRNA-122 and microRNA-223 were deregulated in primary HCC, showing a significant high expression level in serum of HCC patients compared with healthy individuals as well as in serum of patients with chronic hepatitis. Furthermore, they were able to reflect liver injury caused by inflammation as well as acting as potential markers for discriminating HCC patients from healthy controls [1].

Another microRNA called microRNA 10b, was proved to act as a diagnostic microRNA in HCC. A study revealed that the expression level of MicroRNA-10b in serum of HCC patients was significantly high than in serum of controls. Furthermore, combining microRNA 10b with 2 others microRNA: MicroRNA-106b, and MicroRNA-181a showed a more diagnostic accuracy than using MicroRNA 10b alone with an AUC of 0.94 (95% CI: 0.89–0.99) in distinguishing the HCC group from the healthy controls [2].

microRNAs as diagnostic tools in lung cancer

Plasma microRNA-21 was proved to act as a diagnostic biomarker for the detection of NSCLC as well as acting as a bio-

marker for the prediction of sensitivity of NSCLC patients to chemotherapy. A study reported that plasma microRNA21 was significantly higher in NSCLC patients than in their paired controls. Additionally, microRNA21 level was related to TNM stage but not related to age, sex, smoking status, histological classification, lymph node status, and metastasis. Furthermore, plasma microRNA21 showed a good diagnostic ability with 76.2% sensitivity and 70.0% specificity [3].

Serum microRNA 29c and microRNA 429 were proved to act as diagnostic biomarkers for early detection of NSCLC. It was revealed in a study that microRNA-29c expression was significantly increased in serum from NSCLC patients however serum microRNA-429 expression was significantly decreased. Additionally, serum levels of microRNA-29c and microRNA-429 showed a good diagnostic ability distinguishing NSCLC patient from healthy controls with a 65.7% sensitivity and a specificity of 74.1%. Finally, the serum level of MicroRNA-429 expression was associated with the overall survival of NSCLC patients [4].

microRNAs as diagnostic tools in gastric cancer

Measuring the level of microRNA-26a in plasma of gastric patients was proposed to act as a diagnostic biomarker for detection of gastric cancer. It was reported in a study that expression of microRNA-26a in plasma was significantly decreased in gastric patients compared to controls. Furthermore, the plasma level of microRNA-26a in gastric patients was proved to be a



good diagnostic biomarker, with an AUC of 0.882 and a sensitivity and specificity of 83.6% of 81.5% respectively [5].

Detecting the level of plasma microRNA-940 in gastric cancer patients was proposed to be a biomarker for detection of gastric cancer. It was reported in a study that the expression of microRNA-940 was downregulated in both the initial set and the validation set of plasma samples of patients with gastric cancer.

Furthermore, the sensitivity of plasma microRNA-940 as a diagnostic biomarker was obviously higher than the current biomarkers CEA and CA19-9 (81.25 % vs. 22.54 % and 15.71 %) [6].

Micrnas as Prognostic Tools in Cancers

microRNAs as prognostic tools in hepatocellular carcinoma

Measuring the level of serum microRNA-218 was correlated to the prognosis of HCC. It was reported in a study that serum microRNA-218 was markedly under expressed in HCC patients compared to controls. Additionally, its low level was obviously related to tumor size, vascular invasion and higher TNM stage (III–IV). Furthermore, log-rank test and cox regression analysis demonstrated that the decreased serum expression of microRNA-218 had a significant impact on overall survival of the patients with HCC [7].

microRNA-34a and microRNA-217 levels in HCC were related to the prognosis of HCC patients. It was showed in a study that both microRNA-34a and microRNA-217 were significantly down regulated in HCC tissues, this reduced expression was associated with vascular invasion and advanced TNM stage. Furthermore, Kaplan-Meier revealed that the reduced expression of microRNA-34a and microRNA-217 in HCC patients was associated with poor overall survival [8].

microRNAs as prognostic tools in lung cancer

microRNA-195 was proposed to act as a predictive biomarker for NSCLC patient's prognosis. A study reported that the plasma microRNA-195 was significantly downregulated in NSCLC patients compared to healthy controls. Additionally, microRNA-195 expression levels were significantly lower in stage III patients than those in stage I or II patients. Furthermore, the Kaplan-Meier method and log-rank test revealed that the overall survival of NSCLC patients with low plasma microRNA-195 levels was significantly shorter than those with high plasma microRNA-195 levels [9].

Another microRNA which is microRNA-375 was also proved to be correlated with prognosis of lung cancer patients. It was stated in a study that microRNA-375 expression was significantly down-regulated in NSCLC patients with brain metastasis compared with NSCLC without brain metastasis, this low expression level was linked to advanced disease stage and brain metastasis in NSCLC patient. Survival analysis showed that the low-expression group had significantly shorter overall survival than high-expression group in NSCLC patients with brain metastasis. Furthermore, multivariate Cox proportional hazards model analysis indicated that low microRNA-375 expression was independently linked to poor survival of patients with NSCLC [10].

MicroRNAs as prognostic tools in gastric cancer

The levels of microRNA-26a and microRNA-148a in gastric cancer patients were proposed to be linked to patient's prog-

nosis.

A study reported that the down-regulation of microRNA-26a and microRNA-148a was significantly associated with shorter OS of GC patients either in the test set or in the validation set. Furthermore, when two sets were combined, cox regression analysis demonstrated that both of microRNA-26a and microRNA-148a were independent prognostic factors for predicting OS of patients with gastric cancer [11].

Circulating microRNA-203 in gastric cancer patients was postulated to act as a predictor for metastases, early recurrence, and poor prognosis in human gastric cancer patients. It was reported in a study that the expression levels of serum microRNA-203 in gastric cancer patients were significantly lower than in normal controls as microRNA-203 was significantly suppressed in the serum of patients with stage IV compared with stage I gastric cancer. Furthermore, the level of circulating microRNA-203 was correlated with the prognosis of gastric cancer patients as Kaplan–Meier analysis showed that gastric cancer patients with low microRNA-203 expression had significantly poorer OS and DFS than those with high microRNA-203 expression [12].

Micrnas as Biomarkers in Breast Cancer

microRNAs as diagnostic biomarkers in breast cancer

microRNAs as diagnostic biomarkers in breast cancer serum

Serum microRNA-34c: Measuring serum microRNA-34c level was proved to act as a diagnostic biomarker for the detection of BC. It was reported in a study that the expression of microRNA-34c was down-regulated in the serum of patients with BC compared with those of healthy controls. Furthermore, its down-regulation was significantly correlated with stage, tumor grade and lymph node status. Finally, serum microRNA-34c showed a high diagnostic value with an AUC of 0.854 combining with a sensitivity of 72.0% and a specificity of 88.8% [13].

Serum microRNA-21/microRNA-155/microRNA-365: A study showed that the combined measurement of serum microRNA-21, microRNA-155 and microRNA-365 in BC patients acted as a good diagnostic biomarker. It was reported in the study that serum levels of microRNA-21 and microRNA-155 was significantly higher, while serum microRNA-365 level was significantly lower in BC patients compared with healthy controls. Additionally, the serum levels of microRNA-21 and microRNA-155 significantly decreased following surgical resection. Furthermore, microRNA-155 level was highly detected at stages I and II compared to stage III. Interestingly, the serum microRNA-145 level was remarkably higher in PR-positive patients than PR-negative. Finally, combining microRNA-21, microRNA-155 and microRNA-365 yielded much higher AUC value as well as an enhanced sensitivity and specificity in acting as diagnostic biomarkers in BC patients compared to each microRNA alone [14].

microRNAs as diagnostic biomarkers in peripheral blood of breast cancer patients

microRNA-155, microRNA-21, and microRNA-10b: Measuring the level of microRNA-155, microRNA-21, and microRNA-10b in blood of BC patients was proved to act as a diagnostic biomarker of BC. It was proved in a study that, the levels of circulating microRNA-155, microRNA-21, and microRNA-10b were significantly up-regulated in BC patients compared with healthy participants. Furthermore, microRNA-155, microRNA-21 and microRNA-10b were proved to have high

diagnostic value, as microRNA-155 showed 66.0% sensitivity and 68.9% specificity, microRNA-21 showed 77.4% sensitivity and 67.9% specificity and microRNA-10b showed 68.9% sensitivity and 75.3% specificity [15].

Micrnas as Prognostic Tools in Breast Cancer

microRNAs as prognostic tools in breast cancer serum

Serum microRNA-155: Serum microRNA-155 was postulated to act as prognostic as well as diagnostic biomarker in BC patients. A study reported that microRNA-155 expression was up-regulated 2.62-fold in BC serum subjects compared to control subjects, relative serum microRNA-155 expression level significantly differed with patients with different cancer stages as well as, its expression was directly increased with the advancement of cancer stage. Additionally, subjects with BC with high serum microRNA-155 expression had a relatively poor prognosis as the mean survival of the low microRNA-155 expression group was 39.77 months however, the mean survival of the high microRNA-155 expression group was 26.81 months. Finally, serum microRNA-155 concentration of 1.24 U/mL was determined to be the optimal critical point for BC diagnosis [16].

microRNA-329: The level of microRNA-329 in both tissues and serum of BC patients was proved to act as both a diagnostic as well as a prognostic biomarker for BC. It was postulated in a study that microRNA-329 expression was downregulated in cancerous samples compared with healthy controls. Additionally, microRNA-329 expression in serum specimens positively correlated with its expression in tissue samples, the decreased expression of microRNA-329 correlated with lymph node metastasis and TNM stage. Interestingly, microRNA-329 was proved to have a high diagnostic accuracy with an AUC of 0.932, a sensitivity and specificity of 87.1% and 89.6%, respectively. Furthermore, the level of microRNA-329 was correlated with prognosis of BC patients, as patients with lower microRNA-329 expression had shorter survival times than those with high levels [17].

microRNAs as prognostic tools in breast cancer tissues

microRNA-148a: Tissue microRNA-148 a level in BC was proved to be an indicator for poor prognosis in TNBC patients. A study showed that microRNA-148 was lowly expressed in TNBC tissues compared to non TNBC tissues. Furthermore, the low expression of microRNA-148 in TNBC patients was correlated with poorer prognosis and worse overall survival [18].

microRNA-17: microRNA-17 was proved to have a role as a prognostic biomarker in BC. It was reported in a study that microRNA-17 expression level was significantly increased in cancer tissues compared with adjacent normal tissues, in addition, the expression of microRNA-17 was higher in tumors with pathological stages. Furthermore, high level of expression of microRNA-17 was correlated with poor prognosis and short survival in BC patients as BC patients with a low expression of microRNA-17 had a significantly longer survival time compared with those with a high expression of microRNA-17 [19].

Micrnas as Biomarkers for Survival in Breast Cancer

microRNAs as biomarkers for survival in breast cancer tissues

microRNA-181-a: Measuring the level of microRNA-181-a in TNBC patients was proposed to be a predictor of poor survival and a prognostic biomarker of chemo resistance. It was revealed

in a study that microRNA-181a expression was significantly increased in TNBC tissue samples compared with the neighbouring non-tumor tissues. Additionally, high level of microRNA-181a expression was associated with higher tumor grade, positive lymph node metastasis and response to neoadjuvant chemotherapy. Interestingly, Kaplan-Meier analysis showed that high expression of microRNA-181a was significantly correlated with poor OS in patients without receiving non-adjuvant chemotherapy. Furthermore, patients with high level of microRNA 181-a receiving non-adjuvant chemotherapy showed worse OS with a median survival of 35 months. Finally, multivariate analyses revealed that MicroRNA-181a was an independent prognostic factor of OS in TNBC [20].

microRNA-146a and microRNA-638 in BRCA1-deficient triple negative breast cancer tumors

High level of microRNA-146a and microRNA-638 in BRCA1-deficient triple negative BC was proposed to be a biomarker for survival of BC patients. It was reported that microRNA-146a and microRNA-638 were overexpressed in 36% and 59% of TNBC tumors respectively. Furthermore, overexpression was preeminent in BRCA1-deficient tumors and significantly associated to a better overall survival [21].

Micrnas as Biomarkers of Recurrence in Breast Cancer

microRNAs as biomarkers of recurrence in breast cancer tissues

microRNA-133a, microRNA-191, and microRNA-204: Comparing the level of microRNA-133a, microRNA-191, and microRNA-204 between primary and recurrent BC tissues was proposed to be used as a biomarker for prediction of recurrence. A study reported that microRNA-133a and microRNA-191 showed significantly different expression level between primary and recurrent tumor in the validation cohort. The results showed that microRNA-133a was down-regulated and microRNA-191 was upregulated in recurrent tumor. Furthermore, microRNA-191 and microRNA-204 were significantly correlated with Disease-Free Survival (DFS). Finally, higher expression of microRNA-191 and lower expression of microRNA-204 revealed worse prognosis [22].

microRNA-4734 and microRNA-150-5p signature: It was reported in a study that microRNA-4734 and microRNA-150-5p expression level was significantly different between the recurrent and nonrecurrent BC patients. Additionally, microRNA-4734 and microRNA-150-5p were proved to act as a microRNA signature for prediction of recurrence in HER2 patients. Interestingly, the level of microRNA-4734 and microRNA-150-5p was independently and significantly associated with DFS. Finally, this signature predicted the five-year DFS better than other clinicopathological factors and added prognostic value to the TNM staging system [23].

Lncrnas as Diagnostic Biomarkers in Cancers

lncRNAs as diagnostic biomarkers in hepatocellular carcinoma

It was stated in a study that the two lncRNAs: PVT1 and uc002mbe. 2 can be used as a lncRNA signature for diagnosis of HCC. The study mentioned that the expression level of the 2 lncRNAs was associated with the clinical parameters including tumor size and serum bilirubin. Additionally, the sensitivity and specificity values of the two lncRNAs signature for distinguishing HCC patients from the healthy group were 60.56% and

90.62% respectively. Furthermore, the diagnostic ability of the combination of the serum 2-lncRNA signature with AFP was much greater than that of AFP alone [24].

Another lncRNA called SPRY4-IT1 was proved to be a diagnostic biomarker in HCC. It was stated in a study that the level of SPRY4-IT1 was upregulated in HCC and was associated with tumour differentiation, tumor size and Tumor-Node-Metastasis (TNM) stage. Furthermore, lncRNA SPRY4-IT1 was indeed a good diagnostic biomarker in differentiating HCC patients from controls with a sensitivity of 87.3% [25].

lncRNAs as diagnostic biomarkers in lung cancer

SPRY4-IT1, ANRIL, and NEAT1 are three circulating lncRNAs that were proved to act as biomarker for early diagnosis of NSCLC. It was reported in a study that circulating SPRY4-IT1, ANRIL, and NEAT1 were significantly increased in plasma samples of NSCLC patients during training set and validation set compared to controls. Additionally, using plasma ANRIL as a biomarker provided the highest diagnostic performance with an AUC of 0.798. Furthermore, combined measurement of SPRY4-IT1, ANRIL, and NEAT1 indicated a higher power AUC [26].

Another study stated that, XIST & HIF1A level in tumour tissue and serum of NSCLC patients can be used as a predictive biomarker for NSCLC screening. The study proved that, levels of XIST and HIF1A-AS1 were significantly increased in tumor tissues and serum from NSCLC patients as compared to those of control group. Moreover, serum levels of XIST and HIF1A-AS1 were significantly decreased after surgical treatment as compared to their pre-operative. Additionally, serum levels of XIST and HIF1A-AS1 showed strong separation between the NSCLC patients and control group, with an AUC of 0.834 for XIST and 0.876 for HIF1A-AS1. Finally, combining XIST and HIF1A-AS1 yielded an AUC of 0.931, which was significantly improved as compared to XIST or HIF1A-AS1 alone [27].

lncRNAs as diagnostic biomarkers in gastric cancer

Plasma lncRNA-GACAT2 was proved to be a valuable marker for the screening of gastric cancer. It was proved in a study that plasma GACAT2 levels in patients with gastric dysplasia and patients with preoperative GC were significantly higher than those in the healthy controls. Additionally, the level of plasma GACAT2 in the postoperative gastric cancer patients was significantly lower than that in the preoperative group showing that GACAT2 expression significantly decreased following surgery. Furthermore, the preoperative plasma GACAT2 succeeded to act as a tumor biomarker for GC screening, with an AUC 0.622 and a sensitivity and specificity: 87.2 and 28.2%, respectively [28].

In Another study, it was proved that the combined measurement of four lncRNAs: AK001058, INHBA-AS1, MICRORNA4435-2HG, and CEBPA-AS1 can act as a diagnostic marker in gastric cancer. The study showed that AK001058, INHBA-AS1, MICRORNA4435-2HG and CEBPA-AS1 were significantly increased in gastric cancer tissues compared to control. Additionally, plasma level of the four lncRNAs was significantly higher in gastric cancer patients compared with the controls. Finally, combination of plasma lncRNAs AK001058, INHBA-AS1, MICRORNA4435-2HG and CEBPA-AS1 to be used in diagnosis of GC exceeded the ability of each lncRNA alone in diagnosis of GC, with an AUC 0.921[29].

lncRNAs as Prognostic Biomarkers in Cancers

lncRNAs as prognostic biomarkers in hepatocellular carcinoma

noma

LINC01225 was proved to act as a biomarker for early diagnosis of HCC. It was reported in a study that LINC01225 expression level in serum from patients with HCC was elevated in patient's serum compared to serum from healthy controls. Additionally, expression of LINC01225 in serum of HCC patients was negatively associated with cancer-specific survival. Furthermore, LINC01225 was proved to be an effective predictor for HCC diagnosis with a sensitivity of 0.761 and a specificity of 0.443 [30].

As for another lncRNA named linc00974, it was presented as a biomarker for diagnosis and prognosis of HCC. A study results showed that linc00974 was upregulated in HCC tissues compared to normal tissues with a sensitivity 51.1 and specificity 95.6. Moreover, linc00974 was stably expressed in plasma of HCC patients. Furthermore, combining linc00974 with CYFRA21-1, a well-known biomarker for tumor, especially in lung cancer, indicated a significant prediction of tumor growth and metastasis of HCC [31,32].

lncRNAs as prognostic biomarkers in lung cancer

BRAF activated non-coding RNA (BANCR) was proved to act as a biomarker related to poor prognosis of NSCLC. It was proved in a study that BANCR expression was significantly downregulated in cancerous tissues compared with normal tissues, this significant low expression was more predominant in the later stages of tumor development and in tumors that had undergone extensive metastasis. Additionally, BANCR expression levels in NSCLC were significantly correlated with tumor size, advanced pathological stage, and lymph node metastasis. Moreover, Multivariate analysis has confirmed that a low BANCR expression level was an independent predictor of poor survival for NSCLC. Furthermore, the overall survival time of patients with lower BANCR expression levels was significantly shorter than that for patients with higher BANCR expression levels [32].

Another study postulated that, lncRNA LOC344887 can act as a biomarker for indication of poor prognosis in NSCLC patients. The study has proved that the expression level of Loc344887 was increased in NSCLC tissues compared with those in normal lung tissues. Additionally, high Loc344887 expression level was significantly associated with lymph node metastasis, advanced stage, and poorer differentiation. Furthermore, patients with high expression of Loc344887 had a significantly shorter overall survival time compared with those with low Loc344887 expression in NSCLC. Furthermore, Cox regression analysis has showed that high expression of Loc344887 in NSCLC was an independent predictor of poor prognosis [33].

lncRNAs as prognostic biomarkers in gastric cancer

Detecting the level of lncRNA SNHG6 in gastric cancer patients was proved to be related to their prognosis. It was reported that compared with matched adjacent normal tissues, SNHG6 level was significantly increased in GC tissues. Additionally, increased level of SNHG6 was significantly correlated with tumor invasion depth, lymph node metastasis distant metastasis and TNM stage, however, there was no significant correlation with sex, age, and histological grade. Furthermore, high level of lncRNA SNHG6 in GC patients was related to a poor prognosis as Kaplan Meier analysis results showed that patients with high level of SNHG6 had a significantly shorter overall survival than those with low level of SNHG6 [34].

Another lncRNA named PVT1, was proved to be linked to the prognosis of GC patients. It was postulated in a study that PVT1 expression was remarkably increased in GC tissues and cell lines compared with that in the normal control. Additionally, PVT1 up-regulation was significantly correlated to invasion depth, advanced TNM stage and regional lymph nodes metastasis in gastric cancer.

Furthermore, PVT1 levels were robust in differentiating gastric cancer tissues from controls with an AUC 0.728. Finally, Kaplan Meier analysis showed that increased PVT1 expression contributed to poor overall survival and DFS of GC patients [35].

Lncrnas as Biomarkers in Breast Cancer

lncRNAs as diagnostic biomarkers in breast cancer

lncRNAs as diagnostic biomarkers in breast cancer serum

Serum level of lncRNA MALAT1: Measuring the level of lncRNA MALAT1 in serum of BC patients was proved to act as a diagnostic as well as a prognostic biomarker in BC patients, in addition to its ability in prediction of poor survival in BC patients receiving cyclophosphamide-based treatment. A study reported that MALAT1 expression was significantly increased in serum samples from BC patients compared with healthy individuals. The serum MALAT1 level was significantly associated with lymph node status, ER status and TNM stage. Additionally, MALAT1 was proved to have a high diagnostic ability with an AUC: 0.784, a sensitivity and specificity: 72.73% and 63.64% respectively. As for patient's prognosis, the study data showed that patients with high circulating MALAT1 expression was associated with shorter OS compared with low MALAT1 patients. Furthermore, the five-year survival rate was significantly lower in BC patients who expressed high circulating MALAT1 expression compared to patients expressing low levels of MALAT1. Finally, measuring serum MALAT1 level was able to predict poor survival in BC patients receiving cyclophosphamide-based treatment [36].

Lncrnas as Diagnostic Biomarkers in Breast Cancer Tissue

lncRNAs RP11-434D9.1, LINC00052, IGKV, and BC016831

lncRNAs RP11-434D9.1, LINC00052, IGKV, and BC016831 were proposed to be four diagnostic lncRNAs able to differentiate between TNBC patients from NTNBC patients. It was reported in a study that Receiver Operating Characteristic (ROC) curve analysis proved that these four long non-coding RNAs are powerful tools for predicting TNBC patients from NTNBC patients with an AUC value of 0.792 for lncRNARP11-434D9.1, 0.823 for the LINC00052, 0.854 for IGKV and 0.802 for BC016831 [37].

lncRNAs as diagnostic biomarkers in breast cancer plasma

lncRNAs ANRIL, HIF1A-AS2, and UCA1: lncRNAs ANRIL, HIF1A-AS2 and UCA1 were proposed to act as a three lncRNAs signature to differentiate between TNBC patients and NTNBC patients. A study stated that: ANRIL, HIF1A-AS2, and UCA1 were markedly upregulated in plasma of patients with TNBC compared with patients with NTNBC. Furthermore, AUC of ANRIL, HIF1A-AS2, and UCA1 was 0.785, 0.739 and 0.817 respectively in acting as a diagnostic biomarker to differentiate between TNBC and NTNBC.

Finally, combining the three lncRNAs together to act as a three lncRNA signature showed excellent diagnostic performance with an AUC of 0.934, sensitivity of 76.0% and specificity of 97.1% [38].

Lncrnas As Prognostic Biomarkers In Breast Cancer

lncRNAs as prognostic biomarkers in breast cancer tissue

lncRNAEPB41L4A-AS2: Measuring lncRNAEPB41L4A-AS2 in BC tissues was proved to be an indicator for both prognosis and survival of BC patients. It was reported in a study that, EPB41L4A-AS2 levels were downregulated in BC tissues compared with corresponding normal tissues. Interestingly, EPB41L4A-AS2 was more highly expressed in the luminal A subtype than the other four subtypes. Additionally, there was a positive correlation between the low level of EPB41L4A-AS2 and clinicopathological features of breast cancer patients. Furthermore, level of EPB41L4A-AS2 was correlated to BC prognosis as BC patients with low EPB41L4A-AS2 expression had poor OS than patients expressing high EPB41L4A-AS2 [39].

lncRNA HOTAIR: HOTAIR expression in BC tissues was proved to act as an independent prognostic biomarker for BC. It was revealed in a study that, HOTAIR expression differed between patients with a metastatic endpoint and patients without a metastatic endpoint. Interestingly, there was an association between level of HOTAIR and prognosis of BC patients as patients who were defined as having high HOTAIR expression in their primary tumors had significantly worse Metastasis Free Survival (MFS) than patients with low HOTAIR expression [40].

lncRNA GAS6-AS1: The measurement of GAS6-AS1 level in BC tissues and cells was proved to act as a biomarker for prognosis of BC patients. A study reported that GAS6-AS1 was significantly downregulated in tumor tissue compared to healthy controls. Additionally, there was a positive correlation between level of GAS6-AS1 and clinicopathological characteristics of BC patients as the expression of GAS6-AS1 in BC was significantly correlated with lymph node metastasis and histologic grade. Furthermore, there was an association between Level of GAS6-AS1 and BC patient's survival. The OS was significantly lower in patients with down regulated GAS6-AS1 than patients with up regulated GAS6-AS1 [41].

lncRNA MEG3: Low expression level of MEG3 in BC tissues was proved to be a biomarker of a poor prognosis. A study reported that, lncRNA MEG3 was down-regulated in BC tissues compared to the adjacent non-tumor tissues. In addition, the decreased expression of lncRNA MEG3 was significantly associated with the lymph node metastasis, TNM stage and molecular subtypes.

Furthermore, patients with decreased expression of lncRNA MEG3 had poor OS. Finally, multivariate cox proportional hazard model analysis demonstrated that high lncRNA MEG3 expression was an independent poor prognostic factor for BC patients [42].

lncRNA LINC00978: The level of lncRNA LINC00978 in BC tissues was proposed to act as a potential biomarker to predict prognosis. A study reported that LINC00978 showed significantly higher expression in cancer tissues compared to normal tissues. Additionally, LINC00978 expression was negatively associated with HR status in BC patients. Furthermore, Kaplan–Meier survival analysis showed that patients with high LINC00978 expression have poorer DFS than those with low LINC00978 expression. Finally, multivariate analysis has identified LINC00978 as an independent prognostic factor in BC [43].

lncRNAs as prognostic biomarker in breast cancer cell lines

lncRNA00544: Measuring the level of lncRNA00544 in BC

tissues was proved to act as a biomarker for prognosis of BC patients, especially in Luminal B subtype. A study revealed that the expression of lncRNA00544 was increased in all BC cell lines compared with a normal breast cell line (MCF10A) and more significantly, in luminal BC cell lines (MCF-7, ZR751, T47D) than in other BC cell lines. Interestingly, high expression of lncRNA00544 was associated with positive Ki67 expression. Additionally, high level of lncRNA00544 was correlated with poor prognosis in BC patients as patients with high lncRNA00544 expression showed significantly shorter DFS than those with low lncRNA00544 expression. Also, lncRNA00544 expression was correlated with prognosis of HR+ subtype of BC patient than in HR- patients. High expression of lncRNA00544 was significantly associated with prognosis of the HER2-/HR + BC group but not with that of the HER2+/HR + BC group. All these data revealed that, lncRNA00544 was an independent prognostic indicator for BC patients specially in patients with HR + HER2- expression [44].

lncRNAs as biomarkers of recurrence in breast cancer

The nine lncRNA recurrence breast cancer signature: LINC00705, LINC00310, LINC00704, LINC00574, FAM74A3, UMODL1-AS1, ARRDC1-AS1, HAR1A and LINC00323 were proved to be a nine lncRNAs signature that acts as a predictor of recurrence in BC patients. Each lncRNA individually was upregulated with alteration frequency of 2 to 5%. Furthermore, the nine lncRNAs together were upregulated with an alteration frequency of 28% in BC samples. Upregulation of this nine lncRNA signature was found distinctly different from the no upregulation group [45].

lncRNAs as Biomarkers of Survival in Breast Cancer

lncRNAs as biomarkers of survival in breast cancer tissues

The four lncRNAs signature: It was proved in a study that LINC00657, LINC00346, LINC00654 and HCG11 acts as a four lncRNA signature that can predict OS in BC patients. It was stated in the study that these four lncRNAs signature expression level was associated with HER-2 expression in BC patients. Also, their level of expression was associated with OS in both HER-2 neu positive and HER-2 neu negative patients. Furthermore, in HER-2 positive patients, the five-year survival rate was about 90% for cases with upregulation of this signature compared to approximately 65%. In contrast, in HER-2 negative patients the five-year survival rate was approximately 85% for cases with upregulation of this signature compared to approximately 65% for cases without upregulation implying poorer prognosis for HER-2 positive patients with upregulation of this signature than for HER-2 negative patients [45].

lncRNA CCAT1: Measuring level of lncRNA CCAT1 in BC tissues was proved to act as a biomarker of survival of BC patients. It was proved in a study that the level of lncRNA CCAT1 was significantly higher in BC tissues compared with adjacent normal tissues. High level of lncRNA CCAT1 was significantly correlated with differentiation grade, TNM stage, and lymph node metastases of BC patients. Interestingly, the five-year OS of high lncRNA CCAT1 expression group was significantly shorter than that of low lncRNA CCAT1 expression group. Furthermore, the five-year progression-free survival of high lncRNA CCAT1 expression group was also significantly shorter than that of low lncRNA CCAT1 expression group [46].

lncRNA Z38: Measuring the level of lncRNA Z38 in BC tissues was postulated to act as a prognostic biomarker for BC patient's

survival. A study reported that lncRNA Z38 was highly expressed in BC tissues compared to corresponding normal breast tissues. Additionally, lncRNA Z38 was a good candidate to discriminate tumor specimens from corresponding normal specimens with a sensitivity: 78% and specificity: 70%. Interestingly, the high level of lncRNA Z38 was remarkably correlated with TNM stage and lymph node metastasis, however, not correlated with patient's age, family history, tumor grade. Furthermore, the level of lncRNA Z38 was correlated with OS of BC patients as the five years OS rates of the high expression group versus the low expression group were 20.8% and 68.4% respectively [47].

lncRNA linc-ITGB1: Measuring the level of lncRNA linc-ITGB1 in BC patient's tissue was proved to act as a biomarker for prediction of survival of BC patients. It was reported in a study that the level of linc-ITGB1 in BC tissues was significantly up-regulated than that in normal breast tissues. The overexpressed linc-ITGB1 was positively correlated with clinicopathological features of BC patients. Furthermore, there was a positive correlation between high level of linc-ITGB1 in BC patients and poor survival. Furthermore, Log-rank test results demonstrated that patients with higher level of linc-ITGB1 had dramatically shorter OS and DFS than the patients with lower levels of lncRNA linc-ITGB1 [48].

The six lncRNAs survival signature: A study identified a novel lncRNA signature comprising six lncRNAs (HAGLR, STK4-AS1, DLEU7-AS1, LINC00957, LINC01614 and ITPR1-AS1) that can robustly predict the survival of BC patients with ER-positive status. The study reported that: this six-lncRNA signature was validated in the training dataset, testing dataset as well as the entire TCGA dataset, demonstrating significant prognostic performance in the three patient datasets. Furthermore, the identified six-lncRNA signature demonstrated good performance in predicting three- and five-year survival and may can act an independent prognostic marker in survival prediction for ER-positive BC patients [49].

lncRNA BC040587: Measuring the level of lncRNA BC040587 in BC tissues was proposed to act as a biomarker for prediction of survival. It was reported in a study that BC040587 expression level was much lower in BC tissues than in normal tissues. Additionally, there was a significant association between level of lncRNA BC040587 and BC patient's survival as the overall survival was significantly lower in patients with lower BC040587 expression than those with high expression, however, the DFS showed no significance. Finally, Log-rank test of prognostic parameters for OS showed that patients with low BC040587 were significantly associated with a poorer OS [50].

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