Study on conversion of microstates in breast cell ensemble at the gene level based on the eigen-microstate method

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Breast cancer is a malignant disease that seriously threatens women's health. Studying the mechanism of cancer occurrence and development is an urgent problem to be solved. In this paper, the eigen-microstate method was used to study conversion of normal breast cells into breast cancer cells and the reason. The main conclusions are as follows: the microstates of normal breast cell and breast cancer cell are different. There is a state conversion when a normal breast cell transforms into a breast cancer cell. The main reason for this state conversion is the combined effect of tumor suppressor genes and oncogenes. By analyzing the function of key genes, it was found that these genes do play an important role in the development of breast cancer. The findings contribute to understanding the mechanism by which breast cancer occurs and progresses, and key genes can serve as potential biomarkers or target genes for breast cancer treatment.

Keywords: eigen-microstate, conversion, breast cancer, key genes

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1. Introduction

Breast cancer is a non-contagious and malignant disease that ranks among the leading causes of death in women. According to the latest statistics on global cancer in 2018 released by the World Health Organization's International Research Agency, there were about 2.1 million new cases of breast cancer and 6×10^5 deaths. Last year's cancer statistics showed that breast cancer accounted for 30 percent of all new female cancer cases in the United States.[1] Breast cancer places a double health and financial burden on patients. The best way to fight this disease is to know how it occurs and how a normal breast cell becomes a cancer cell. It is well known that cells are the basic functional units of all living things, their functions are controlled by gene expression. Selective expression or mutation of certain genes in cells may lead to dysfunction, while activation of certain oncogenes will cause the cells to proliferate abnormally and become cancerous. Many studies have shown that it is gene mutations that lead to the occurrence of most breast cancer cases,[2] and analyzing gene expression profiles is an effective means of understanding the complexity of breast cancer.[3] For example, the mutations in breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) increase the likelihood that women will develop breast cancer.[4] Ribonucleotide reductase M2 (RRM2) has close relationship with advanced tumor grade and stage, and the cell division of high-grade tumors is promoted by increasing RRM2 expression.[5] Stanniocalcin 2 (STC2) could inhibit epithelial–mesenchymal transformation (EMT) process in a manner of regulating the expressions of protein kinase C (PKC) and Claudin-1, thereby inhibiting breast cancer cells to migrate and invade.[6] Therefore, it has a fundamental significance to study the occurrence and development of breast cancer at the genetic level.

A cell is a complex nonequilibrium thermodynamics system. One reason is that cells need energy to maintain cellular activity, for example, cells maintain appropriate levels of solute by pumping potassium into cells and actively pumping sodium out of cells. Another reason is that the number of molecules and molecular structure in cells change over time, for example, the structure of molecular motors always changes when transporting substances between cells. "Clearly, living systems have to be out of equilibrium", says Mackintosh. Nonequilibrium thermodynamics is a very useful method to chase the secrets of life.[7]

A cell can be thought of as a system containing a large number of genes that is highly non-uniform and far from equilibrium. Gene expression is time-dependent and influenced by environmental factors such as temperature, light, chemicals, signals from other cells, and more. At a given time, the microstate of a cell can be expressed in terms of the amount of gene expression. The microstate varies according to the amount of gene expressions. If we establish a high-dimensional coordinate system in which each axis shows a kind of gene, a point in the gene space coordinate system represents a microstate of the cell, and all phase points in this coordinate system form a cell ensemble under certain thermodynamic conditions, which can be described by the probability

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density of microstates. The process is characterized by non-equilibrium, in which normal cells destroy their original state and constantly establish new states, even develop into a cancerous state. So we can apply statistical physics to study the state transition of cells.

For the cell ensemble above, there is a huge challenge ahead of us. A cell is a system far from equilibrium, and the probability density of their microstates is unknown. Recently, Chen[8] proposed the eigen-microstate (EM) method that can overcome this challenge. According to this method, the microstates and the ensembles of a system can be obtained from their experimental data or simulation data. In the original ensemble, different microstates have the same weights and are dependent. Using the data of original microstates, we can construct the matrix of microstates and then compute the correlation matrix of the microstates. The eigen-microstates (EMs), which are the eigenvectors of the correlation matrix, are independent and form a new ensemble. When condensation does not occur in a complex system and the number of microstates tends to infinity, the weight of every EM approaches zero. When condensation does occur, the characteristic microstate weights become finite limits, and the EM become a new phase of the system. Eigenvalues can act as order parameters in this complex system. The EM method has been applied successfully to study renormalization group theory,[9] collective behaviors in living systems,[10] climate system,[11] and so on.

In this paper, we apply the EM method to study the conversion of microstate in breast cell ensemble. The article is organized as follows. In Section 2, breast cell ensemble and its eigen ensemble were introduced. The EM, their weights and the reason of state transition were analyzed and discussed in Section 3. Finally, conclusions were concluded in Section 4.

2. Breast cell ensemble and its eigen ensemble

2.1. Microstates and ensembles

The Cancer Genome Atlas (TCGA), a well-known cancer genomics program that provides more than 2.5 petabytes of data on 33 cancer types for anyone to use, has greatly facilitated cancer-related research. RNA sequencing (RNA-seq) is a common method that utilizes next-generation sequencing technology to study the entire transcriptome. The extracted RNA is reverse transcribed into DNA and sequenced on next-generation sequencing platform, the number of reads of each transcript are proportional to their expression level. RNA-seq data is a collection of all the gene expression level in samples, including tumor samples. RNA-seq data in each sample can be described by a matrix having N rows and 2 columns, N represents the number of genes, the first column's value is the gene name and the second column's value is the expression of corresponding gene. We first downloaded RNA-seq data from breast cells adjacent to cancer (normal breast cells) and breast cancer cells. The sample size is denoted by M. We use $T_i(t)$ represents the expression of gene $i = 1,2,\ldots,N$ in the sample $t = 1,2,\ldots,M$. For a given t, the matrix $T(t)$ with N rows and 1 column denotes the microstate of a cell from sample t. The average gene expression of sample t is

$$\langle T_t \rangle = \frac{1}{N}\sum_{i=1}^{N} T_i(t). \tag{1}$$

The root-mean-square value of the sample t is

$$\Delta_t = \sqrt{\frac{1}{N}\sum_{i=1}^{N} \delta T_i(t)^2}, \tag{2}$$

where $\delta T_i(t)$ represents

$$\delta T_i(t) = T_i(t) - \langle T_t \rangle. \tag{3}$$

For a given sample t, there are fluctuations of gene $i = 1,2,\ldots,N$

$$\delta S_i(t) = \frac{T_i(t) - \langle T_t \rangle}{\Delta_t}. \tag{4}$$

The microstate t is

$$\delta \boldsymbol{S}(t) = \begin{bmatrix} \delta S_1(t) \\ \delta S_2(t) \\ \cdots \\ \delta S_N(t) \end{bmatrix}. \tag{5}$$

For M samples, there are M microstates and these microstates form a statistical ensemble. this ensemble can be described by an $\boldsymbol{N} \times \boldsymbol{M}$ matrix with elements

$$A_{it} = \delta S_i(t). \tag{6}$$

2.2. EM and weights

The correlation between microstate t and microstate t' is obtained by their vector product

$$C_{tt'} = \delta S(t)^{\mathrm{T}} \cdot \delta S(t') = \sum_{i=1}^{N} \delta S_i(t)\, \delta S_i(t'), \tag{7}$$

where $C_{tt'}$ is its elements, then we get an $M \times M$ correlation matrix of microstates

$$\boldsymbol{C} = \boldsymbol{A}^{\mathrm{T}} \cdot \boldsymbol{A}. \tag{8}$$

The correlation between gene i and gene j is

$$K_{ij} = \delta S(t) \cdot \delta S(t)^{\mathrm{T}} = \sum_{t=1}^{M} \delta S_i(t)\, \delta S_j(t), \tag{9}$$

K_{ij} represents its elements and $N \times N$ correlation matrix of genes is gotten

$$\boldsymbol{K} = \boldsymbol{A} \cdot \boldsymbol{A}^{\mathrm{T}}. \tag{10}$$

An $M \times M$ unitary matrix is composed by the eigenvectors V_t of C

$$\boldsymbol{V} = [V_1\, V_2\, \cdots\, V_M]. \tag{11}$$

With eigenvectors U_i of K, we can compose an $N \times N$ unitary matrix

$$U = [U_1 \ U_2 \ \cdots \ U_N]. \tag{12}$$

The ensemble matrix $\boldsymbol{A}$ can be factorized by using the singular value decomposition (SVD) as[12]

$$\boldsymbol{A} = \boldsymbol{U} \cdot \boldsymbol{\Sigma} \cdot \boldsymbol{V}^{\mathrm{T}}, \tag{13}$$

where $\boldsymbol{\Sigma}$ is an $N \times M$ diagonal matrix with elements

$$\Sigma_{ij} = \begin{cases} \sigma_i, & i = j \le r, \\ 0, & \text{otherwise}, \end{cases} \tag{14}$$

where the rank $r \le \min(N, M)$.

Combining the Eqs. (13) and (14), the ensemble matrix $\boldsymbol{A}$ can be decomposed as

$$\boldsymbol{A} = \sum_{I=1}^{r} \sigma_I \boldsymbol{U}_I \otimes \boldsymbol{V}_I, \tag{15}$$

where, $\boldsymbol{U}_I \otimes \boldsymbol{V}_I \equiv A_I^{\mathrm{e}}$ is called an eigen-ensemble matrix and it is orthogonal. The decomposition here is similar to the decomposition of the wave function in quantum mechanics into the characteristic wave function.

Based on the relations above, we interpret ω_I^{E} as the probability of eigen-ensemble matrix A_I^{e} in the statistical ensemble $\boldsymbol{A}$ and ω_I^{E} satisfies

$$\omega_I^{\mathrm{E}} = \frac{\sigma_I^2}{\sum_{I=1}^{r} \sigma_I^2}. \tag{16}$$

For an overview of the weight distribution of EM, we define the cumulant of m EMs

$$c(m) = \sum_{I=1}^{m} \omega_I^{\mathrm{E}}. \tag{17}$$

For the normal breast cell ensemble (NBCE) and the breast cancer cell ensemble (BCCE), we can calculate the weights of all EMs ω_I^{E}. If all the weights ω_I^{E} tend to zero in the limits of $N \to \infty$ and $M \to \infty$, there is no localization in the ensemble. if one of weights becomes dominant and finite in the limits of $N \to \infty$ and $M \to \infty$, there is a localization in the ensemble, the ensemble microstate condenses to the corresponding EM A_I^{e}. the phase of cell system can be expressed by U_I and the time fluctuation mode can be expressed by V_I. In Section 3, the EMs and their weights will be discussed.

3. Results and discussion

3.1. The EMs and their weights

In this paper, the sample sizes of normal breast cells and breast cancer cells are the same and M is equal to 109. For each sample, there is 10022 kinds of genes and so N is 10022. The NBCE and the BCCE were constructed. The EMs and their corresponding weights of the two ensembles were calculated by using the EM method as described above, and the weights of the first ten EMs are represented in Fig. 1.

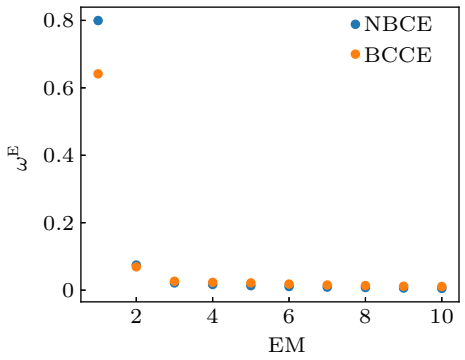


Fig. 1. The weights of the first ten EMs of NBCE and BCCE, in which blue dots represent the EMs of NBCE and orange dots represent the EMs of BCCE.

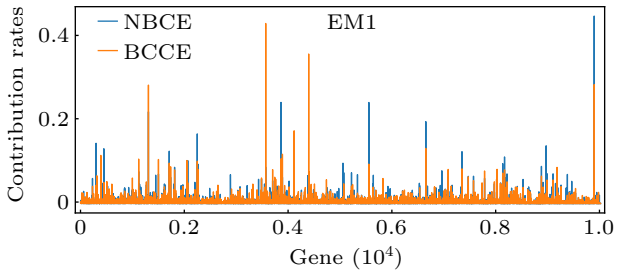


Fig. 2. The first EM of NBCE and BCCE, in which blue line represents the first EM of NBCE and orange line represents the first EM of BCCE.

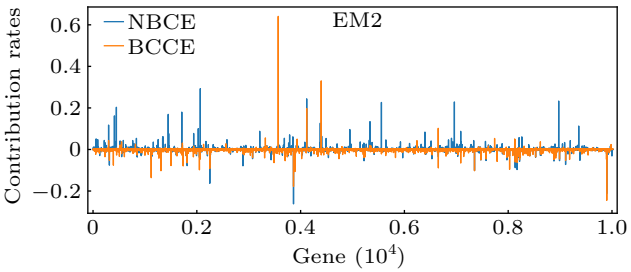


Fig. 3. The second EM of NBCE and BCCE, in which blue line represents the second EM of NBCE and orange line represents the second EM of BCCE.

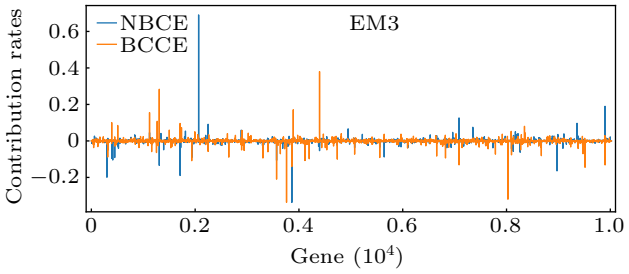


Fig. 4. The third EM of NBCE and BCCE, in which blue line represents the third EM of NBCE and orange line represents the third EM of BCCE.

As can be seen from Fig. 1, the first EM weight of NBCE is about 80%, and the first EM weight of BCCE is about 65%. They are much larger than those of other EMs in the same ensemble. Compared with the weight of the first EM, the

weights of the second EMs of the two ensembles are significantly reduced, but they are more important than other EMs. The weights of the EMs of the two ensembles decrease as the number of the microstates increases. The corresponding cumulative weights of the first three EMs of the two ensembles are large enough so that the original microstate can be expressed by superposition of the first three EMs, respectively.

Figures 2–4 show the first three EMs of NBCE and BCCE. The horizontal axis in each figure shows the gene number and each gene has a given number. The vertical axis is the contribution rate of each gene to the EM. From these figures, it can be concluded that the contribution rates of every gene are different among the first three EMs of the two ensembles, which means that the EMs of NBCE differ from the corresponding microstates of BCCE. The results suggest that there is a state transition when a normal cell becomes a cancer cell.

It can be seen from Fig. 5 that the correlation coefficients among the EMs of the two ensembles is neither 0 nor 1, which shows that they are related and different. The correlation coefficient between the first EM of the two ensembles is biggest and is 0.76, which is consistent with the results in Fig. 1. The close relationship and the difference between the first three EMs again demonstrate that there is a state transition when a normal cell becomes a cancer cell, but the reason needs to be further elucidated.

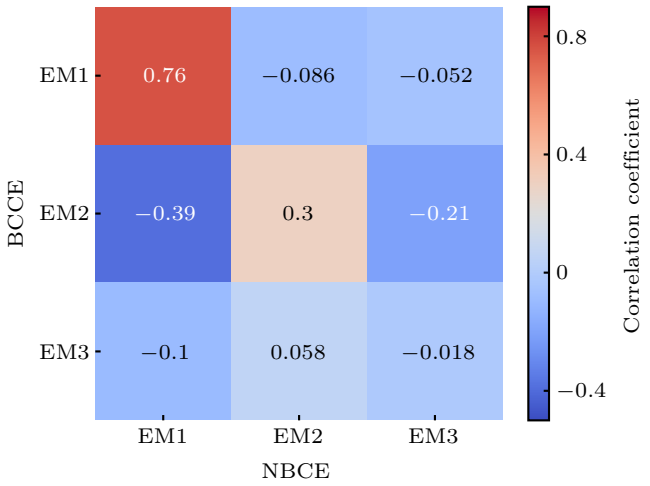


Fig. 5. The correlation coefficients among the first three EMs of NBCE and BCCE.

3.2. The reason for state conversion

The conversion of normal cells into cancer cells has been studied in many different cancers and cell types, and the results indicated that gene expression differences or gene mutations are closely relevant to this conversion.[14–16] We have concluded that the contribution rate difference of every gene leads to the difference of the EMs. We will further investigate which genes are the main drivers of state conversion.

First, we defined the important genes whose contribution rate values are greater than or equal to the threshold. The important genes form the new EM. We then calculated the Pearson correlation coefficient between the new EM and the original EM, and the results are shown in Fig. 6. If the correlation coefficient is larger than 0.95, we thought the new EM can replace the original EM.

EdgeR was designed for the analysis of replicated count-based expression data and is an implementation of methodology developed by Robinson and Smyth in 2007. EdgeR has been widely used on sources of count data, including barcoding experiments and peptide counts so far.[17] we applied the software edgeR to analyze the expression differences of 10022 genes, and the results are shown in Fig. 6. The results indicate that the number of differentially expressed genes is 2012, including 1004 upregulated genes and 1008 downregulated genes.

We defined the key genes are the common genes of the important genes and the differentially expressed genes. We investigated further the function of the key genes and classified them as oncogenes (OG) or tumor suppressor genes (TSG). In Tables 1 and 2, we summarized the numbers, the total contribution rate to the EMs, and a detailed list of these key genes.

Table 1. Analysis of the number and contribution rate of key genes to EM.

EM		TSG		OG	
		Numbers	Rates (%)	Numbers	Rates (%)
EM1	NBCE	24	10.31	31	12.29
	BCCE	19	5.63	37	18.75
EM2	NBCE	21	21.79	21	18.78
	BCCE	6	4.48	20	26.17
EM3	NBCE	6	27.68	9	17.92
	BCCE	15	12.11	28	30.43
The superposition state of EM1, EM2, and EM3	NBCE	30	10.46	35	11.60
	BCCE	25	4.24	26	14.64

From Table 1, we can get the results as follows: the contribution rates of TSG to the first three EMs of normal breast cells are greater than those of breast cancer cells. However, the contribution rates of OG to the first three EMs of normal breast cells are smaller than those of breast cancer cells. For the superposition state of the first three EMs, the contribution rates of TSG and OG have the same characteristics as those of the first three EMs. These details above lead us to believe that the different contribution rates of TSG and OG turn a normal breast cell into a breast cancer cell.

In our study, we recognized 113 key genes listed in the Table 2, including 46 TSG and 67 OG. Many researches have shown that these key genes play important role in the occurrence and development of the breast cancer. For instance, down-regulation of GATA3 expression promotes the development of invasive breast cancer. KLF6 is considered as a potent growth inhibitor of breast cancer cells. Knockout of TRPS1 reduces nucleokinesis, apoptosis and tumor growth of breast cancer cell. Overexpression of ZFP36L2 is an effective driver

Table 2. The summary of key genes.

			NBCE			
		TSG			OG	
EM1	ACSL1[18]	ACTA2[19]	ANXA1[20]	AHNAK[21]	DCN[22]	COL1A1[23]
	CCN1[25]	CD36[26]	CX3CL1[27]	DST[28]	SFRP1[29]	SPARCL1[30]
	EGR1[33]	GSN[34]	KIT[35]	FHL1[36]	TAGLN[37]	FOSB[38]
	KRT17[44]	LDHB[45]	LRP1[46]	FN1	EMP1[47]	DUSP1[48]
	LUM[50]	MCAM[51]	MYL9[52]	SORBS1[53]	KLF6[54]	GPAM[55]
	MYLK[62]	NFIB[63]	PDK4[64]	CRYAB[65]	CXCL12[66]	SCGB2A2[67]
	PIK3R1[72]	SCD[73]	SLC39A6[74]	DHCR24	CTSD[75]	EFEMP1[76]
	VIM[78]	ZFP36[79]	ZFP36L2[80]	DPT[81]	MAGED2[82]	ARF1[83]
				AEBP1[84]	EHD2[85]	COL17A1[86]
				UTRN[88]	CHRDL1[89]	CAV1[90]
				SPTBN1[93]		
EM2	SCD	GSN	CD36	AHNAK	FHL1	DCN
	VIM	LRP1	ACSL1	SORBS1	GPAM	SFRP1
	MCAM	PDK4	ACTA2	DPT	CRYAB	DST
	PRKAR2B[98]	KRT17	RBP4[99]	CHRDL1	EMP1	ITIH5[100]
	ZFP36	ANXA1	CAT[101]	FN1	FOSB	EHD2
	LAMA4[102]	KIT	SLC39A6	G0S2[103]	SCGB2A2	TACC1[104]
	MYLK	CX3CL1	KRT18[105]	ITGA7[106]	SPTBN1	CAV1
EM3	SCD	GSN	ACSL1	DCN	COL1A1	FHL1
	VIM	CD36	LUM	GPAM	DPT	SFRP1
				FN1	CRYAB	EMP1
			BCCE			
		TSG			OG	
EM1	SLC39A6	VIM	SCD	COL1A1	FN1[24]	AHNAK
	LUM	KRT18	SFRP2[31]	POSTN[32]	SCGB2A2	CTSD
	GATA3[39]	CA12[40]	CRABP2[41]	ERBB2[42]	DHCR24[43]	AEBP1
	TBC1D9[49]	LRP1	GSN	MAGED2	DCN	ARF1
	SULF1[56]	GJA1[57]	GPRC5A[58]	TRPS1[59]	AGR2[60]	VCAN[61]
	SLC9A3R1	CERS2	MMP11[68]	ESR1[69]	COL5A1[70]	CCND1[71]
	FOXA1			CPB1[77]	STAT1	MMP14
				HDGF	HSPB1	SH3BGRL
				ERBB3	EZR	SDC1[87]
				FKBP4[91]	MAL2	PRDX1[92]
				GFRA1	IFI6	ENAH[94]
				PRSS23[95]	PRLR[96]	SPARCL1
				SPTBN1		
EM2	SLC39A6	LUM	SCD	COL1A1	FN1	POSTN
	SFRP2	MMP11	CA12	AEBP1	CTSD	DCN
				COL5A1	AGR2[97]	VCAN
				ESR1	ERBB2	ARF1
				HDGF	STAT1	TRPS1
				COL11A1	SCGB2A2	MMP14
				FKBP4	MAL2	
EM3	SLC39A6	TBC1D9	GJA1	FN1	SCGB2A2	COL1A1
	CA12	GATA3	BMPR1B[107]	CPB1	ESR1	CTSD
	FOXA1	KRT17	MLPH	AGR2	AHNAK	MAGED2
	SCGB2A1	TSPAN13	SFRP2	S100A8	ERBB2	S100A7[108]
	SLC9A3R1	EGFR[109]	VIM	STAT1	CCND1	CASP14[110]
				GFRA1	SPP1	SDC1
				DHCR24	ERBB3	HDGF
				PRSS23	SLC7A5	NUCB2
				STMN1	MAL2	TRPS1
				POSTN		

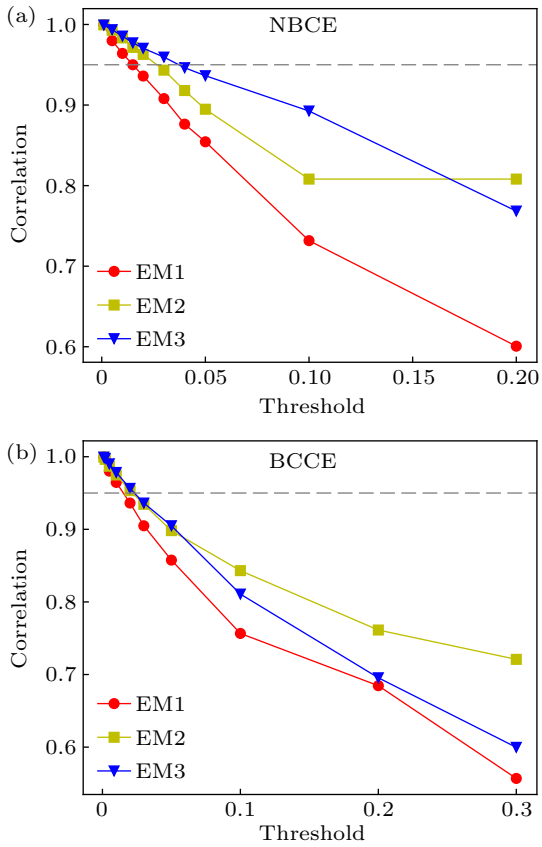


Fig. 6. The Pearson correlation coefficients between the new EMs and the original EMs: (a) the NBCE, (b) the BCCE.

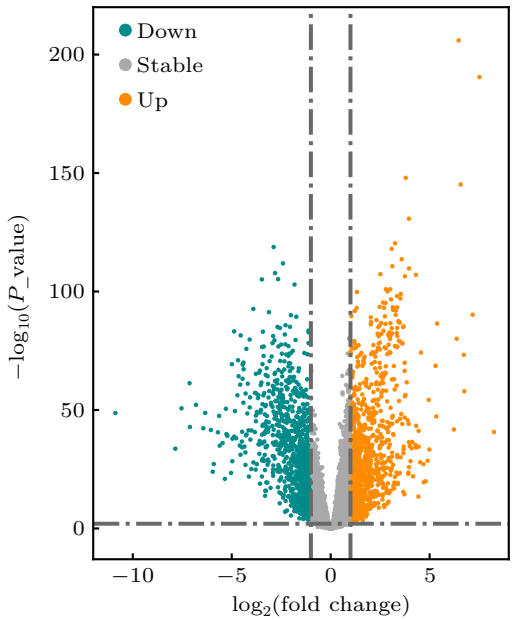


Fig. 7. The expression difference analysis of 10022 genes. The blue dots, gray dots, and orange dots symbolize down-regulated, stably expressed, and up-regulated genes with absolute logFC > 2 and corrected $P < 0.01$ as thresholds, respectively.

of breast cancer. ACSL1 can inhibit cell proliferation, migration, and growth. The expression of CA12 is closely related to the histological grade and degree of tumor. Down-regulation of PRDX1 expression can slow the growth rate of MCF-7 and ZR-75-1, which are breast cancer cell lines. Overexpression of CTSD can promote the migration, invasion, and metastasis of breast cancer cells by increasing the expression of the adhesion molecule ICAM-1. A decrease in BMPR1B expression is associated with a poor prognosis in breast cancer patients and increases the proliferation of breast cancer cells *in vitro*. LRP1 promotes aggressiveness of breast cancer cells. These results proved that the key genes are involved in the development of the breast cancer and they may become potential biomarkers for breast cancer treatment.

4. Conclusion and perspectives

Breast cancer is a very common malignant disease and is the leading cause of cancer death in women. Studying the evolutional mechanism of breast cancer is very important to improve its treatment and prognosis. Breast cell is a system that is far from equilibrium, and the EM method is a very effective way to study state conversion in non-equilibrium systems. First, data on normal breast cells and breast cancer cells are downloaded from TCGA. Second, the original microstates of normal breast cells and breast cancer cells are obtained by processing the data. Third, the EMs of normal breast cells and breast cancer cells are obtained by using the EM method. Finally, the results were analyzed and the results showed that the EMs of normal breast cells and breast cancer cells were different. We further investigated the causes of differences in EMs. The main results are as follows: the weights of the EMs of NBCE and BCCE are not equal to zero and are finite values. The weights of the first three EMs of normal breast cells and breast cancer cells are greater than the weights of other EMs. We can think that the microstate of the breast cells ensemble is superposed by the first three EMs respectively. The first three EMs of normal breast cells differ from those of breast cancer cells, indicating that there is a state conversion when normal cells evolve into cancer cells. By analyzing the contribution rates of key genes, it was found that different contribution rates of TSG and OG led to this conversion.

In physics, we are able to distinguish microstates of breast cells and identify the core drivers of the conversion — the different contribution rates of TSG and OG. In biology, we find that key genes do play an important role in the development of breast cancer when analyzing the function of these genes.

In conclusion, the research sheds light on the mechanisms by which breast cancer occurs and progresses, with key genes that may be potential biomarkers for clinical diagnosis and target genes for breast cancer treatment. This work is of great significance for the breast cancer.

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References

[1] Siegel R L, Miller K D and Jemal A 2020 *CA Cancer J. Clin.* **70** 31912902
[2] Wang Z, Zhang J, Zhang Y, Deng Q and Liang H 2018 *Int. J. Mol. Med.* **42** 30221688
[3] Shiovitz S and Korde L A 2015 *Ann. Oncol.* **26** 25605744
[4] Eeles R A 1999 *Eur. J. Cancer* **35** 10711238
[5] Ma X J, Salunga R, Tuggle J T, Gaudet J, Enright E, McQuary P, Payette T, Pistone M, Stecker K, Zhang B M, Zhou Y X, Varnholt H, Smith B, Gadd M, Chatfield E, Kessler J, Baer T M, Erlander M G and Sgroi D C 2003 *Proc. Natl. Acad. Sci. USA* **100** 12714683
[6] Hou J, Wang Z, Xu H, Yang L, Yu X, Yang Z, Deng Y, Meng J, Feng Y, Guo X and Yang G 2015 *PLoS One* **10** 25830567
[7] Ornes S 2017 *Proc. Natl. Acad. Sci. USA* **114** 28096502
[8] Hu G, Liu T, Liu M, Chen W and Chen X 2019 *Sci. China Phys. Mech. Astron.* **62** 990511
[9] Liu T, Hu G, Dong J, Fan J, Liu M and Chen X 2022 *Chin. Phys. Lett.* **39** 080503
[10] Li X, Xue T, Sun Y, Fan J, Li Hui, Liu M, Han Z, Di Z and Chen X 2021 *Chin. Phys. B* **30** 128703
[11] Sun Y, Hu G, Zhang Y, Lu B, Lu Z, Fan J, Li X, Deng Q and Chen X 2021 *Commun. Theor. Phys.* **73** 065603
[12] Strang G 2009 *Introduction to linear algebra* (Wellesley: Cambridge Press) p. 284
[13] Li X T and Chen X S 2016 *Commun. Theor. Phys.* **66** 355
[14] Cristian M, Paola D L, Kevin G, Elba V and Adriana D S 2010 *Cell Cycle* **9** 3119
[15] Yin X, Wang P, Yang T, Li G, Teng X, Huang W and Yu H 2020 *Aging* **13** 2519
[16] Bao S and He G 2022 *Med. Sci. Monit.* **28** e935515
[17] Mark D R, Davis J M and Gordon K S 2010 *Bioinformatics* **26** 139
[18] Chen W C, Wang C Y, Hung Y H, Weng T Y, Yen M C and Lai M D 2016 *PLoS One.* **11** 27171439
[19] Li Z, Xu W, Ren X, Xu J and Chen J 2019 *Mol. Med. Rep.* **19** 30483784
[20] Vecchi L, Alves Pereira Zóia M, Goss Santos T, de Oliveira Beserra A, Colaço Ramos C M, França Matias Colombo B, Paiva Maia Y C, Piana de Andrade V, Teixeira Soares Mota S, Gonçalves de Araújo T, Van Petten de Vasconcelos Azevedo F, Soares F A, Oliani S M and Goulart L R 2018 *Biochim. Biophys. Acta Mol. Cell Res.* **1865** 29932988
[21] Chen B, Wang J, Dai D, Zhou Q, Guo X, Tian Z, Huang X, Yang L, Tang H and Xie X 2017 *J. Exp. Clin. Cancer Res.* **36** 28494797
[22] Zhao H, Wang H, Kong F, Xu W, Wang T, Xiao F, Wang L, Huang D, Seth P, Yang Y and Wang H 2019 *Hum. Gene. Ther.* **30** 30032645
[23] Liu J, Shen J X, Wu H T, Li X L, Wen X F, Du C W and Zhang G J 2018 *Discov Med.* **25** 29906404
[24] Yang X, Hu Q, Hu L X, Lin X R, Liu J Q, Lin X, Dinglin X X, Zeng J Y, Hu H, Luo M L and Yao H R 2017 *Discov. Med.* **24** 28972876
[25] Espinoza I, Liu H, Busby R and Lupu R 2011 *Mol. Cancer Ther.* **10** 21393426
[26] Feng W W, Wilkins O, Bang S, Ung M, Li J, An J, Del Genio C, Canfield K, DiRenzo J, Wells W, Gaur A, Robey R B, Guo J Y, Powles R L, Sotiriou C, Pusztai L, Febbraio M, Cheng C, Kinlaw W B and Kurokawa M. 2019 *Cell Rep.* **29** 31825825
[27] Liang Y, Yi L, Liu P, Jiang L, Wang H, Hu A, Sun C and Dong J 2018 *J. Cancer* **9** 30310518
[28] Jain P B, Guerreiro P S, Canato S and Janody F 2019 *Sci. Rep.* **9** 31882643
[29] Kong L Y, Xue M, Zhang Q C and Su C F 2017 *Oncotarget* **8** 28099945
[30] Cao F, Wang K, Zhu R, Hu Y W, Fang W Z and Ding H Z 2013 *Asian Pac. J. Cancer Prev.* **14** 23534723
[31] Veeck J, Noetzel E, Bektas N, Jost E, Hartmann A, Knüchel R and Dahl E 2008 *Mol. Cancer* **7** 18990230
[32] Malanchi I, Santamaria-Martínez A, Susanto E, Peng H, Lehr H A, Delaloye J F and Huelsken J 2011 *Nature* **481** 22158103
[33] Wong K M, Song J and Wong Y H 2021 *Sci. Rep.* **11** 33436746
[34] Chen Z Y, Wang P W, Shieh D B, Chiu K Y and Liou Y M 2015 *J. Biomed. Sci.* **20** 26482896
[35] Janostiak R, Vyas M, Cicek A F, Wajapeyee N and Harigopal M 2018 *Exp. Mol. Pathol.* **105** 29852185
[36] Ding L, Niu C, Zheng Y, Xiong Z, Liu Y, Lin J, Sun H, Huang K, Yang W, Li X and Ye Q 2011 *J. Cell Mol. Med.* **15** 19840196
[37] Sayar N, Karahan G, Konu O, Bozkurt B, Bozdogan O and Yulug I G 2015 *Clin. Epigenetics* **7** 26421063
[38] Park J A, Na H H, Jin H O and Kim K C 2019 *Mol. Cells* **42** 31735020
[39] Shahi P, Wang C Y, Lawson D A, Slorach E M, Lu A, Yu Y, Lai M D, Gonzalez Velozo H and Werb Z 2017 *Proc. Natl. Acad. Sci. USA* **114** 28258171
[40] Li Y, Lei B, Zou J, Wang W, Chen A, Zhang J, Fu Y and Li Z 2019 *Neoplasma* **66** 30784287
[41] Feng X, Zhang M, Wang B, Zhou C, Mu Y, Li J, Liu X, Wang Y, Song Z and Liu P 2019 *J. Exp. Clin. Cancer Res.* **38** 31419991
[42] Di Oto E, Brandes A A, Cucchi M C and Foschini M P 2017 *Virchows Arch.* **471** 28573512
[43] Qiu T, Cao J, Chen W, Wang J, Wang Y, Zhao L, Liu M, He L, Wu G, Li H and Gu H 2020 *Cancer Sci.* **111** 32713162
[44] Escobar-Hoyos L F, Shah R, Roa-Peña L, Vanner E A, Najafian N, Banach A, Nielsen E, Al-Khalil R, Akalin A, Talmage D and Shroyer K R 2015 *Cancer Res.* **75** 26109559
[45] McCleland M L, Adler A S, Shang Y, Hunsaker T, Truong T, Peterson D, Torres E, Li L, Haley B, Stephan J P, Belvin M, Hatzivassiliou G, Blackwood E M, Corson L, Evangelista M, Zha J and Firestein R 2012 *Cancer Res.* **72** 23139210
[46] Benes P, Jurajda M, Zaloudík J, Izakovicová-Hollá L and Vácha J 2003 *Breast Cancer Res.* **5** 12793904
[47] Sadr-Nabavi A, Ramser J, Volkmann J, Naehrig J, Wiesmann F, Betz B, Hellebrand H, Engert S, Seitz S, Kreutzfeld R, Sasaki T, Arnold N, Schmutzler R, Kiechle M, Niederacher D, Harbeck N, Dahl E and Meindl A 2009 *Int. J. Cancer* **124** 19115204
[48] Li Z, Xu W, Ren X, Xu J and Chen J 2019 *Mol. Med. Rep.* **19** 30483784
[49] Andres S A, Brock G N and Wittliff J L 2013 *BMC Cancer* **13** 23819905
[50] Karamanou K, Franchi M, Piperigkou Z, Perreau C, Maquart F X, Vynios D H and Brézillon S 2017 *Sci. Rep.* **7** 28332606
[51] Liang Y K, Zeng D, Xiao Y S, Wu Y, Ouyang Y X, Chen M, Li Y C, Lin H Y, Wei X L, Zhang Y Q, Kruyt F A and Zhang G J 2017 *Cancer Lett.* **386** 27838413
[52] Zhang C, Luo X, Liu L, Guo S, Zhao W, Mu A, Liu Z, Wang N, Zhou H and Zhang T 2013 *Acta Biochim. Biophys. Sin.* **45** 24084383
[53] Song L, Chang R, Dai C, Wu Y, Guo J, Qi M, Zhou W and Zhan L 2017 *Oncotarget* **8** 27791200
[54] Liu J, Du T, Yuan Y, He Y, Tan Z and Liu Z 2010 *Mol. Cell Biochem.* **335** 19707857
[55] Brockmöller S F, Bucher E, Müller B M, Budczies J, Hilvo M, Griffin J L, Orešič M, Kallioniemi O, Iljin K, Loibl S, Darb-Esfahani S, Sinn B V, Klauschen F, Prinzler J, Bangemann N, Ismaeel F, Fiehn O, Dietel M and Denkert C 2012 *J. Proteome. Res.* **11** 22070544
[56] Zhou Q, Jiang Y, Yin W, Wang Y and Lu J 2016 *Onco. Targets Ther.* **9** 27274271
[57] Busby M, Hallett M T and Plante I 2018 *Int. J. Mol. Sci.* **19** 29495625
[58] Yang L, Ma T and Zhang J 2016 *Oncol Rep.* **36** 27599526
[59] Witwicki R M, Ekram M B, Qiu X, *et al.* 2018 *Cell Rep.* **25** 30380416
[60] Xiu B, Chi Y, Liu L, Chi W, Zhang Q, Chen J, Guo R, Si J, Li L, Xue J, Shao Z M, Wu Z H, Huang S and Wu J 2019 *Mol. Cancer* **18** 31856843
[61] Zhang Y, Zou X, Qian W, Weng X, Zhang L, Zhang L, Wang S, Cao X, Ma L, Wei G, Wu Y and Hou Z 2019 *Cell Death Differ.* **26** 29955124
[62] Sundararajan V, Gengenbacher N, Stemmler M P, Kleemann J A, Brabletz T and Brabletz S 2015 *Oncotarget* **6** 26334100
[63] Moon H G, Hwang K T, Kim J A, Kim H S, Lee M J, Jung E M, Ko E, Han W and Noh D Y 2011 *Mol. Oncol.* **5** 21925980
[64] Guda M R, Asuthkar S, Labak C M, Tsung A J, Alexandrov I, Mackenzie M J, Prasad D V and Velpula K K 2018 *Am. J. Cancer Res.* **8** 30323966
[65] Ruan Q, Han S, Jiang W G, Boulton M E, Chen Z J, Law B K and Cai J 2011 *Mol. Cancer Res.* **9** 21984182
[66] Yu P F, Huang Y, Xu C L, Lin L Y, Han Y Y, Sun W H, Hu G H, Rabson A B, Wang Y and Shi Y F 2017 *Oncogene* **36** 27669436
[67] Picot N, Guerrette R, Beauregard A P, Jean S, Michaud P, Harquail J, Benzina S and Robichaud G A 2016 *Mol. Carcinog.* **55** 26207726

[68] Wang Y, Wei Y, Fan X, Zhang P, Wang P, Cheng S and Zhang J 2020 *Thorac. Cancer* **11** 32291953
[69] Dustin D, Gu G and Fuqua SAW 2019 *Cancer* **125** 31318440
[70] Zhao B, Song X and Guan H 2020 *Life Sci.* **244** 31863774
[71] Ai B, Kong X, Wang X, Zhang K, Yang X, Zhai J, Gao R, Qi Y, Wang J, Wang Z and Fang Y 2019 *Cell Death Dis.* **10** 31243265
[72] Turturro S B, Najor M S, Yung T, Portt L, Malarkey C S, Abukhdeir A M and Cobleigh M A 2019 *Breast Cancer Res. Treat.* **177** 31209687
[73] Angelucci C, D'Alessio A, Iacopino F, Proietti G, Di Leone A, Masetti R and Sica G 2018 *Oncotarget* **9** 29849946
[74] Kasper G, Weiser A A, Rump A, Sparbier K, Dahl E, Hartmann A, Wild P, Schwidetzky U, Castaños-Vélez E and Lehmann K 2005 *Int. J. Cancer* **117** 15986450
[75] Zhang C, Zhang M and Song S 2018 *Cancer Lett.* **438** 30227221
[76] Sadr-Nabavi A, Ramser J, Volkmann J, Naehrig J, Wiesmann F, Betz B, Hellebrand H, Engert S, Seitz S, Kreutzfeld R, Sasaki T, Arnold N, Schmutzler R, Kiechle M, Niederacher D, Harbeck N, Dahl E, Meindl A 2009 *Int. J. Cancer* **124** 19115204
[77] Bouchal P, Dvořáková M, Roumeliotis T, Bortlíček Z, Ihnatová I, Procházková I, Ho J T, Maryáš J, Imrichová H, Budinská E, Vyzula R, Garbis S D, Vojtěšek B and Nenutil R 2015 *Mol. Cell Proteomics.* **14** 25903579
[78] Wu S, Du Y, Beckford J and Alachkar H 2018 *J. Transl. Med.* **16** 29925392
[79] Pan Q H, Fan Y H, Wang Y Z, Li D M, Hu C E and Li R X 2020 *J. Biol. Regul. Homeost. Agents* **34** 32691576
[80] Koo J, Cabarcas-Petroski S, Petrie J L, Diette N, White R J and Schramm L 2015 *BMC Cancer* **15** 26573593
[81] Gamage C D B, Park S Y, Yang Y, Zhou R, Taş İ, Bae W K, Kim K K, Shim J H, Kim E, Yoon G and Kim H 2019 *Int. J. Mol. Sci.* **20** 31141929
[82] Jia B, Zhao X, Wang Y, Wang J, Wang Y and Yang Y 2019 *Oncol. Lett.* **18** 31516568
[83] Xie X, Tang S C, Cai Y, Pi W, Deng L, Wu G, Chavanieu A and Teng Y 2016 *Oncotarget* **7** 27517156
[84] Majdalawieh A F, Massri M and Ro H S 2020 *J. Oncol.* **2020** 32565808
[85] Yang X, Ren H, Yao L, Chen X and He A 2015 *Tumour. Biol.* **36** 25557791
[86] Yodsurang V, Tanikawa C, Miyamoto T, Lo P H Y, Hirata M and Matsuda K 2017 *Oncotarget* **8** 28915553
[87] Sayyad M R, Puchalapalli M, Vergara N G, Wangensteen S M, Moore M, Mu L, Edwards C, Anderson A, Kall S, Sullivan M, Dozmorov M, Singh J, Idowu M O and Koblinski J E 2019 *Breast Cancer Res. Treat.* **178** 31327090
[88] Li Y, Huang J, Zhao Y L, He J, Wang W, Davies K E, Nosé V and Xiao S 2007 *Oncogene* **26** 17384672
[89] Cyr-Depauw C, Northey J J, Tabariès S, Annis M G, Dong Z, Cory S, Hallett M, Rennhack J P, Andrechek E R and Siegel P M 2016 *Mol. Cell Biol.* **36** 26976638
[90] Shi Y, Tan S H, Ng S, Zhou J, Yang N D, Koo G B, McMahon K A, Parton R G, Hill M M, Del Pozo M A, Kim Y S and Shen H M 2015 *Autophagy.* **11** 25945613
[91] Mangé A, Coyaud E, Desmetz C, Laurent E, Béganton B, Coopman P, Raught B and Solassol J 2019 *Theranostics* **9** 31660083
[92] Bajor M, Zych A O, Graczyk-Jarzynka A, Muchowicz A, Firczuk M, Trzeciak L, Gaj P, Domagala A, Siernicka M, Zagozdzon A, Siedlecki P, Kniotek M, O'Leary P C, Golab J and Zagozdzon R 2018 *Br. J. Cancer* **119** 30287919
[93] Li D D, Deng L, Hu S Y, Zhang F L and Li D Q 2020 *Am. J. Cancer Res.* **10** 32368399
[94] Karagiannis G S, Pastoriza J M, Wang Y, Harney A S, Entenberg D, Pignatelli J, Sharma V P, Xue E A, Cheng E, D'Alfonso T M, Jones J G, Anampa J, Rohan T E, Sparano J A, Condeelis J S and Oktay M H 2017 *Sci. Transl. Med.* **9** 28679654
[95] Chan H S, Chang S J, Wang T Y, Ko H J, Lin Y C, Lin K T, Chang K M and Chuang Y J 2012 *PLoS One* **7** 22291950
[96] Johnston A N, Bu W, Hein S, Garcia S, Camacho L, Xue L, Qin L, Nagi C, Hilsenbeck S G, Kapali J, Podsypanina K, Nangia J and Li Y 2018 *Breast Cancer Res.* **20** 29778097
[97] Xiu B, Chi Y, Liu L, Chi W, Zhang Q, Chen J, Guo R, Si J, Li L, Xue J, Shao Z M, Wu Z H, Huang S and Wu J 2019 *Mol. Cancer* **18** 31856843
[98] Park J Y, Man Song K, Min Y S, Choi C J, Seok Kim Y and Lee S N 2015 *Sci. Rep.* **5** 26568414
[99] Papiernik D, Urbaniak A, Kłopotowska D, Nasulewicz-Goldeman A, Ekiert M, Nowak M, Jarosz J, Cuprych M, Strzykalska A, Ugorski M, Matkowski R and Wietrzyk J 2020 *Cancers* **12** 32156052
[100] Himmelfarb M, Klopocki E, Grube S, Staub E, Klaman I, Hinzmann B, Kristiansen G, Rosenthal A, Dürst M and Dahl E 2004 *Cancer Lett.* **204** 14744536
[101] Glorieux C, Sandoval J M, Dejeans N, Nonckreman S, Bahloula K, Poirel H A and Calderon P B 2018 *Oxid. Med. Cell Longev.* **2018** 29535798
[102] Yang Z X, Zhang B, Wei J, Jiang G Q, Wu Y L, Leng B J and Xing C G 2018 *Cancer Cell Int.* **18** 29434522
[103] Yim C Y, Sekula D J, Hever-Jardine M P, Liu X, Warzecha J M, Tam J, Freemantle S J, Dmitrovsky E and Spinella M J 2016 *Cancer Res.* **76** 26837760
[104] Xiang J, Qiu W, Wang X, Zhou F, Wang Z, Liu S and Yue L 2013 *Oncol. Rep.* **29** 23354013
[105] Ha S A, Lee Y S, Kim H K, Yoo J, Kim S, Gong G H, Lee Y K and Kim J W 2011 *Cancer Biomark.* **10** 22699783
[106] Bhandari A, Xia E, Zhou Y, Guan Y, Xiang J, Kong L, Wang Y, Yang F, Wang O and Zhang X 2018 *Cancer Manag. Res.* **10** 29760566
[107] Bokobza S M, Ye L, Kynaston H E, Mansel R E and Jiang W G 2009 *Cancer Genomics Proteomics* **6** 19451094
[108] Nasser M W, Wani N A, Ahirwar D K, Powell C A, Ravi J, Elbaz M, Zhao H, Padilla L, Zhang X, Shilo K, Ostrowski M, Shapiro C, Carson W E 3rd and Ganju R K 2015 *Cancer Res.* **75** 25572331
[109] Zhao Y, Ma J, Fan Y, Wang Z, Tian R, Ji W, Zhang F and Niu R 2018 *Mol. Oncol.* **12** 29215776
[110] Handa T, Katayama A, Yokobori T, Yamane A, Horiguchi J, Kawabata-Iwakawa R, Rokudai S, Bao P, Gombodorj N, Altan B, Kaira K, Asao T, Kuwano H, Nishiyama M and Oyama T 2017 *J. Surg. Oncol.* **116** 28570747