ARTÍCULO ORIGINAL

Gac Méd Caracas 2022;130(Supl 1):S87-S94
DOI: 10.47307/GMC.2022.130.s1.17

Stem cell-like Subtypes in Triple-Negative Breast Cancer

Subtipos similares a células madre en el cáncer de mama triple negative

Betty Betty[1a*], Delyuzar Delyuzar[2a]

SUMMARY

Triple-negative breast cancers (TNBC) are breast cancers with no expression of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER-2). This study was done to identify stem cell-like subtypes in TNBC. This cross-sectional study was performed on breast cancer patients in Haji Adam Malik Hospital Medan from 2013 to 2016 by immunohistochemistry stained. Data about demographics were extracted from patients' records and histopathologic features. By using CD44, CD24, Twist, Claudin7, and Vimentin, a total of 67 breast tumor samples with TNBC were classified as 19 cases of stem cell-like and 48 cases of non-stem cell-like subtypes. Postmenopause women with a tumor size of more than 5 cm, higher stage, and grade histology were likely to have non-stem cell-like subtypes. Women with mucinous carcinoma and metaplastic carcinoma of no special type tended to have non-stem cell-like subtypes. Both stem cell-like and non-stem cell-like subtypes commonly had low Vimentin. By using immunohistochemistry staining, TNBC can be differentiated into stem cell-like and non-stem cell-like subtypes. Stemness in stem cell-like subtypes is resistant to therapy. Therefore, the identification of stem cells in TNBC needs special attention to assist in optimal handling.

Keywords: *CD24, CD44, Claudin7, TNBC, Twist, Vimentin.*

RESUMEN

Los cánceres de mama triple negativos (TNBC) son cánceres de mama sin expresión de receptores de estrógeno (ER), receptores de progesterona (PR) y receptor 2 del factor de crecimiento epidérmico humano (HER-2). Este estudio se realizó para identificar subtipos similares a células madre en TNBC. Este estudio transversal se realizó en pacientes con cáncer de mama en el Hospital Haji Adam Malik de Medan de 2013 a 2016 mediante tinción inmunohistoquímica. Los datos sobre la demografía se extrajeron de los registros de los pacientes y las características histopatológicas. Mediante el uso de CD44, CD24, Twist, Claudin7 y Vimentin, un total de 67 muestras de tumores de mama con TNBC se clasificaron como 19 casos de subtipos similares a células madre y 48 casos de subtipos no similares a células madre. Es probable que las mujeres posmenopáusicas con un tamaño tumoral de más de 5 cm, estadio y grado histológico más altos tengan subtipos no similares a las células madre. Las mujeres con carcinoma mucinoso y carcinoma metaplásico

DOI: https://doi.org/10.47307/GMC.2022.130.s1.17

ORCID ID: 0000-0001-5267-470X[1]
ORCID ID: 0000-0001-8083-0896[2]

[a]Department of Anatomical Pathology, Faculty of Medicine, Universitas Sumatera Utara, Indonesia

*Corresponding Author: Betty Betty
E-mail: andbethgo@yahoo.com

Recibido: 1 de mayo 2022
Aceptado: 5 de mayo 2022

de ningún tipo especial tendían a tener subtipos no similares a células madre. Tanto los subtipos similares a las células madre como los no similares a las células madre tenían comúnmente vimentina baja. Mediante el uso de tinción inmunohistoquímica, TNBC se puede diferenciar en subtipos similares a células madre y no similares a células madre. Stemness en subtipos similares a células madre es resistente a la terapia. Por lo tanto, la identificación de células madre en TNBC necesita una atención especial para ayudar a un manejo óptimo.

Palabras clave: *CD24, CD44, Claudin7, TNBC, Twist, Vimentina.*

INTRODUCTION

In developing and developed countries, breast cancer is the most common carcinoma in women and the leading cause of death worldwide (1-4). About 30 in 100 000 women per year in Asia will develop breast carcinoma (5). Breast carcinoma has heterogeneous histopathological features and molecular expressions. By gene expression profiling, TNBC is classified into 2 major parts, namely basal-like and claudin-low (6). TNBC does not express estrogen receptors (ER), progesterone receptors (PR), and HER-2 (7). Compared to their types of cancer, TNBC tends to be more aggressive and until now there has been a disagreement about the treatment because TNBC is not responsive to hormonal and targeted anti-HER2 therapy (8). This subtype has a variety of clinical manifestations, histopathological features, and molecular expressions, some of which are high grade, with high proliferation rates, grow aggressively and have a poor prognosis (9).

The basal-like subtype is expressed with ER^-, $HER2^-$, Ck5/6, and/or $EGFR^+$ (6); meanwhile, claudin-low is expressed with lacking luminal epithelial differentiation markers (claudin-3, claudin-4, claudin-7, occludins, E-cadherin) and increases in epithelial-mesenchymal transition markers (EMT), immune response gene and cancer stem cell (CSC) characteristics ($CD44^+$/$CD24^{-/low}$) (10,11). This supports that claudin-low is a cell deriving from immature progenitor cells or stem cells (12-14). Although Claudin's low and the basal-like subtype look alike, these two subtypes are completely different (15). In breast epithelial cells, EMT is correlated with the invasion of breast cancer cells and mesenchymal character, which is marked by the high expression of vimentin (16,17).

Breast cancer stem cells/BCSCs play an important role in the growth and development of breast cancer, resistance to therapy, and metastasis (12,18,19). Various stem cell markers are used to identify and isolate CSC from various solid tumors, such as CD44 and CD24. CD24 is a little more expressed in progenitor cells compared to differentiated cells (10,20). Therefore, for therapy to be effective, CSC must be recognized and must be differentiated from normal breast stem cells. This study aims to identify stem cell-like subtypes found in TNBC using immunohistochemistry staining and to determine stem cell-like subtypes based on clinicopathological characteristics in TNBC.

METHODS

This descriptive cross-sectional study was carried out in Haji Adam Malik Hospital/ Department of Anatomical Pathology, Faculty of Medicine USU Medan, and Department of Oncology/Surgical Haji Adam Malik Hospital Medan from March to October 2017. The research was done after getting permission from the Ethical Committee of the Medical Faculty USU Medan. The studied population was patients histopathologically diagnosed with breast cancer (mastectomy/ biopsy).

Clinical data such as age, tumor size, and clinical stage were obtained from medical records and a histopathological review of slides was done based on Bloom and Richardson's methods modified by Elston Ellis (subtypes and grading histology). This study used immunohistochemical staining for ER (clone 6F11, Dako, dilution 1: 100), PR (clone PgR 636, polyclonal Ab, Dako, dilution 1: 200), and HER-2 (clone A0435, polyclonal Ab, Dako, dilution 1: 200). Evaluations of ER and PR were based on ASCO/CAP guidelines. Tumors were considered positive for ER and PR if at least 1 % of nuclear tumor cells stained positive (21). HER-2 was considered positive in the case of strong and homogenous staining of cell membranes/ chicken wire pattern (score 3+). If weak or negative the score was 0 or 1+, and the score was 2 if membrane

cells were incompletely homogenously stained (borderline/moderate). Tumors were defined as TNBC if ER (-), PR (-), and HER2 (-).

TNBC tumors were further stained with CD44 (DF1485, Novocastra Laboratories Ltd., Newcastle upon Tyne, UK, dilution 1:100), CD24 (C-20, Santa Cruz Biotechnology, Palo Alto, CA, USA, dilution 1:100), TWIST-1 (H-81, Santa Cruz Biotechnology, Santa Cruz CA, dilution 1:100), Claudin-7 (NBPI-35677, Rabbit polyclonal antibody, Novus Biological, dilution 1:100), and Vimentin (VIM 3B4, Mouse monoclonal, Dako, 1:400). Interpretations of immunohistochemical stains of CD44 and CD24 were based on Ricardo et al. (2011). CD44, CD24, Twist-1, and Claudin-7 were stained in membrane cells, but Vimentin in the cytoplasm. CD44, CD24 and Twist-1 were scored as 0 if no staining or only <10 % positive tumor cells; 1 if 10-25 % positive tumor cells; 2 if 25-50 % positive tumor cells; and 3 if >50 % positive tumor cells (22). Claudin-7 staining was scored as 0 if there was no membranous staining; 1+ (1-10 % positive tumor cells); 2+ (10-30 % positive tumor cells); and 3+ (>30 % positive tumor cells) (23). Meanwhile, based on the percentage of positive cells, Vimentin has scored as 0 if no staining; 1 if <30 % positive tumor cells; 2 if 30-60 % positive tumor cells; and 3 if >60 % positive tumor cells. All intensity of staining was scored as 0 if unstained, 1 if weakly stained, 2 if intermediate, and 3 if strong. Interpretations of CD44, CD24, Twist-1, Claudin-7, and Vimentin staining were determined based on the multiplication of the percentage of positive cells and the intensity of staining. CD44 and CD24 were scored as 0 negative if (-), 1-3 (+1), 4-6 (+2), and 7-9 (+3). While Twist-1, Claudin-7, and Vimentin were considered weak if the total score was <6 and strong if the total score was >6 (24).

TNBC was classified as Claudin low (stem cell-like) when $CD44^{+}$. But if $CD44^{-}$, then TNBC was classified as non-stem cell-like subtypes. Then, stem cell-like and nonstem cell-like subtypes of TNBC were assessed based on Vimentin expression. The results of this study were processed using statistical software and displayed according to frequency distribution in tables.

RESULTS

To determine ontogeny and differentiation of TNBC subtypes in stem cell stages, we used CD44 immunohistochemical stains. In this study, researchers themselves tried to schematically illustrate ontogeny and differentiation of breast epithelial from stem cells to luminal cells with various TNBC molecular markers (Figures 1 and 2).

From 67 TNBCs in this study, through CD44, CD24, Twist-1, and Claudin-7 immunohistochemical stain, TNBC was classified as 19 cases of stem cell-like and 48 non-stem cell-like subtypes (Table 1 and Figure 3). Postmenopause women with tumor size more than 5 cm, higher stage, and grade histology were likely to have non-stem cell-like subtypes of TNBC (86.7 %, 71.6 %, 71.7 %, and 76 %, respectively). Women with mucinous carcinoma and metaplastic carcinoma of no special type tended to have non-stem cell-like subtypes of TNBC (100 % and 100 % respectively). Both stem cell-like and non-stem cell-like subtypes of TNBC commonly had low vimentin (Table 2).

Figure 1. Ontogeny of stem-cells like, basal, baso-luminal, and luminal subtypes.

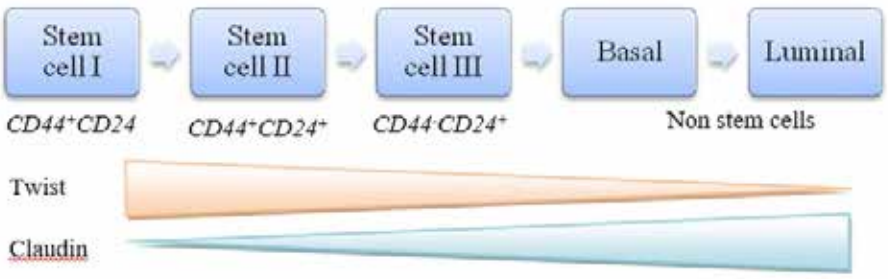

Figure 2. Schema of ontogeny differentiation of mammary epithelial from stem cells to luminal cells (non-stem cells) is correlated to various TNBC molecular marker panels.

DISCUSSION

This study aims to identify stem cells in breast cancer through immunohistochemical stains. CSCs or cancer-initiating cells (CICs) represent a minority in cell populations derived from the transformation of self-renewing stem cells, which initiate and maintain the growth of cancer cells. There are various 'stemnesses' used in identifying BCSCs (25,26), CD44 and CD24 being two of them. In this study, we tried to schematically illustrate the ontogeny of stem cells using CD44 and CD24 (27). BCSCs expresses high CD44 and negative/low CD24 ($CD44^{+}CD24^{-/low}$). $CD44^{+}CD24^{-/low}$ phenotype is often related to poor prognosis (12,13,28). CD44 is strongly expressed in immature stem cells and will get weaker on differentiation, whereas CD24 is strongly expressed in more mature cells (12,13).

Twist displays 'stemness' and plays a role in EMT (epithelial to mesenchymal) transformation. The twist is an E-cadherin repressor protein that stimulates EMT. EMT is characterized by a lack of keratin epithelial and E-cadherin expression but expressed Vimentin. During EMT, epithelial cells lose cell-to-cell contacts, undergo cytoskeletal remodeling resulting in loss of polarity, and acquiring a mesenchymal morphology (29). On the other hand, Claudin, an adhesion molecule found in untransformed epithelial cells, is strongly positive in mature differentiated epithelial cells. In this study, CD44, CD24, Claudin-7, and Twist-1 have been used as molecular markers of TNBC stem cell-like subtypes. Results from 67 TNBC showed marked heterogeneous and overlapping profiles.

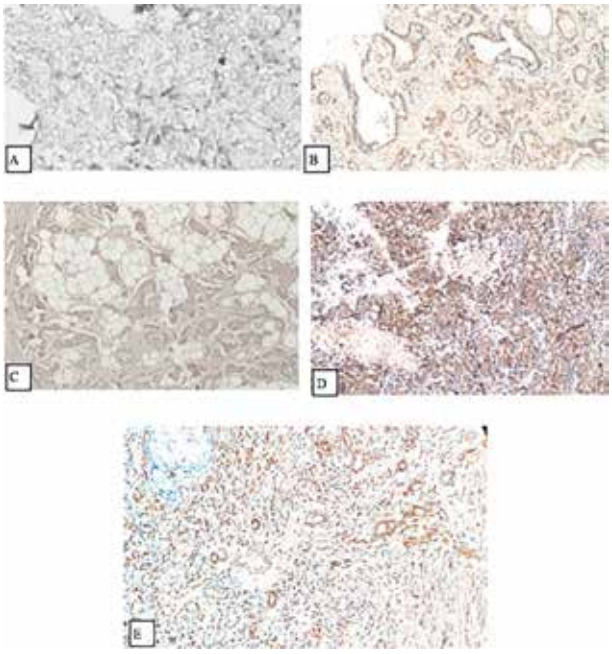

Figure 3. Immunohistochemisty staining of Twist (A), CD24 (B), CD44 (C), Claudin 7 (D), and Vimentin (E) (x200).

$CD44^{+}CD24^{-}$ expression showing stem cell-like subtypes were very heterogeneous and divided into SC-1, SC-2, and SC-3. SC-1 is an early stem cell-like subtype, in which Twist and Claudin-7 were not expressed. SC-2 showed an ontogeny level above SC-1. In SC-2, Twist and Claudin-7 expressions were positive, meanwhile in SC-3 Twist was negative but Claudin-7 positive. This showed a higher cell differentiation level than SC-2. In this study, we also found that both stem cell-like and non-stem

cell-like subtypes of TNBC commonly had low vimentin. This showed that both stem cell-like and non-stem cell-like subtypes did not tend to have mesenchymal morphology.

Identification of BCSCs gets special attention to date because of has implications for its treatment. Standard chemotherapy often fails because BCSCs have low proliferation and are resistant to chemotherapy which also causes the enhancement of stem cell count. This is one important cause of therapy failure and recurrence in TNBC. Therefore, validation of stem cells in TNBC is mandatory. This is one of the critical steps to developing an effective targeted therapy in TNBC.

Table 1

Classification of stem cell-like subtypes based on immunohistochemical staining

No	CD44	CD24	Claudin 7	Twist	Vimentin	Classification of stem cell-like subtype
1	+1	+2	0	3	0	SC
2	+1	0	0	0	2	SC
3	1+	+3	7	0	1	SC
4	1+	+3	8	2	1	SC
5	1+	0	7	2	2	SC
6	1+	0	4	3	4	SC
7	1+	3+	8	5	9	SC
8	1+	3+	8	3	3	SC
9	1+	0	8	2	2	SC
10	1+	0	8	2	6	SC
11	1+	3+	8	2	0	SC
12	1+	0	8	0	0	SC
13	1+	0	8	0	1	SC
14	1+	3+	8	2	2	SC
15	1+	3+	5	0	4	SC
16	3+	0	8	0	6	SC
17	2+	0	8	4	0	SC
18	1+	0	7	4	1	SC
19	1+	3+	8	4	2	SC
20	0	+3	8	4	2	NSC
21	0	+3	8	4	2	NSC
22	0	+1	0	3	2	NSC
23	0	+3	8	0	1	NSC
24	0	+3	8	3	0	NSC
25	0	+3	8	2	1	NSC
26	0	+3	7	0	0	NSC
27	0	0	7	0	1	NSC
28	0	+3	8	4	2	NSC
29	0	+3	6	0	1	NSC
30	0	0	7	0	1	NSC
31	0	0	8	0	2	NSC
32	0	+3	8	0	3	NSC
33	0	+3	0	0	0	NSC
34	0	+3	8	2	0	NSC
35	0	+3	8	0	2	NSC
36	0	+3	8	0	1	NSC
37	0	+3	4	0	3	NSC
38	0	+3	8	0	3	NSC

Continue pag S92…

…continuation of Table 1.

No	CD44	CD24	Claudin 7	Twist	Vimentin	Classification of stem cell-like subtype
39	0	+3	0	0	0	NSC
40	0	2+	0	0	0	NSC
41	0	3+	8	2	2	NSC
42	0	3+	7	0	2	NSC
43	0	3+	0	0	1	NSC
44	0	3+	8	0	2	NSC
45	0	3+	7	2	2	NSC
46	0	3+	8	2	1	NSC
47	0	3+	7	3	2	NSC
48	0	3+	8	0	1	NSC
49	0	3+	8	2	2	NSC
50	0	3+	7	0	2	NSC
51	0	0	8	3	0	NSC
52	0	3+	8	4	3	NSC
53	0	0	8	2	9	NSC
54	0	2+	8	0	2	NSC
55	0	0	8	3	2	NSC
56	0	2+	8	0	6	NSC
57	0	1+	8	3	6	NSC
58	0	0	8	3	2	NSC
59	0	3+	8	0	3	NSC
60	0	0	7	2	9	NSC
61	0	0	8	0	0	NSC
62	0	0	6	6	6	NSC
63	0	3+	8	0	1	NSC
64	0	0	7	0	2	NSC
65	0	0	5	4	0	NSC
66	0	3+	7	5	9	NSC
67	0	2+	8	0	2	NSC

SC: Stem cell like; NSC: non-stem cell-like

Several studies show that CD44 expression was correlated with high histological grade, tumor growth, lymph node invasion, and visceral metastases (5). These results are in accordance with our study. Mesenchymal-like CSCs characterized as $CD24^{-}$ $CD44^{+}$ are primarily quiescent and are located at the tumor's invasive front. This condition has high invasive capacity. EMT may be regulated by the tumor microenvironment, such as TGFβ and IL-6 (29). But in this study, researchers found that only 3 cases (12.5 %) of stem cell-like and 6 cases (14 %) of non-stem cell-like subtypes were found with high vimentin.

CONCLUSION

TNBC is heterogeneous breast cancer. By using immunohistochemical staining panels, TNBC can be classified into stem cell-like and non-stem cell-like subtypes. Stem cell-like subtypes are resistant to therapy. To classify non-stem cell-like subtypes, other immunohistochemical stains are needed. Vimentin should be included in immunohistochemical staining panels to determine the EMT phenomenon. The importance of this study was to identify stem-cell-ness/stemness which will influence therapy.

Table 2

Classification of stem cell-like subtypes based on clinicopathological characteristics

Variables	Classification of stem cell-like				Total
	Stem cell-like	%	Non-stem cell-like	%	
Status menopausal					
Premenopause	17	32.7	35	67.3	52
Postmenopause	2	13.3	13	86.7	15
Tumor size					
2-5 cm	1	33.3	2	66.7	3
>5 cm	18	28.1	46	71.6	64
Stage					
II	6	28.6	15	71.4	21
III	13	28.3	33	71.7	46
Grade					
II	13	31	29	69	42
III	6	24	19	76	25
Subtype histology					
IC-NST	17	30.9	38	69.1	55
ILC	1	25	3	75	4
Mucinous carcinoma	0	0	1	100	1
Carcinoma with medullary features	1	20	4	80	5
Metaplastic carcinoma of no special type	0	0	2	100	2
Vimentin					
Low	16	27.6	42	72.4	58
High	3	33.3	6	66.7	9
Total	19	28.4	48	71.6	67

ACKNOWLEDGMENTS

Thank you to the Ministry of Research, Technology, and Education, Universitas Sumatera Utara, Research and Community Service Institute, Research Field with contract number 21/UN5.2.3.1/PPM/KP-TALENTA USU/2018.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Wabula I, Yunitasari E, Wahyudi AS. Supportive Care Needs of Women with Breast Cancer: A Systematic Review. J Ners. 2020;15(2):142-148.
2. Fatimah S, Rahaju AS, Rahniayu A. Role of claudin-4 and matrix metalloproteinase-2 in tumor invasion of colorectal adenocarcinoma. Res J Pharm Technol. 2021;14(9):4795-800.
3. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics. CA Cancer J Clin. 2010;60:277-300.
4. Sukartini T, Dewi LC, Nihayati HE, Laili NR, Nandaka IKT, Nugraheni A. The lived experience of women with breast cancer. Int J Innov Creat Chang. 2020;13(6):249-262.
5. Bhoo-Pathy N, Yip CH, Hartman M, Uiterwaal CSP, Devi BCR, Peeters PHM, et al. Breast cancer research in Asia adopt or adapt Western knowledge? Eur J Cancer. 2013;49(3):703-709.
6. Shiu KK, Tan DS, Reis-Filho JS. Development of therapeutic approaches to "triple-negative" phenotype breast cancer. Expert Opin Ther Targets. 2008;12:1123-1137.
7. Dent RA, Lindeman GJ, Clemons M, Wildiers H, Chan A, McCarthy NJ. Safety and efficacy of the oral

PARP inhibitor olaparib (AZD2281) in combination with paclitaxel for the first- or second-line treatment of patients with metastatic triple-negative breast cancer: Results from the safety cohort of a phase I/II multicenter. J Clin Oncol. 2010;28(15):10-18.

8. Schneider BP, Wine EP, Foulkes WD, Garber J, Perou CM, Richardson A. Triple-negative breast cancer: risk factors to potential targets. Clin Cancer Res. 2008;14(24):8010-8018.
9. De Laurentiis M, Cianniello D, Caputo R, Stanzione B, Arpino G, Cinieri S. Treatment of triple-negative breast cancer (TNBC): Current options and future perspectives. Cancer Treat Rev. 2010;36(Suppl 3):S80-86.
10. Putra A, Riwanto I, Putra ST, Wijaya I. Typhonium flagelliforme extract induce apoptosis in breast cancer stem cells by suppressing survivin. J Cancer Res Ther. 2020;16(6):1302-1308.
11. Lim E et al. Transcriptome analyses of mouse and human mammary cell subpopulations reveal multiple conserved genes and pathways. Breast Cancer Res. 2010;12:R21.
12. Prayogo AA, Wijaya AY, Hendrata WM, Looi SS, I'tishom R, Hakim L, et al. Dedifferentiation of MCF-7 breast cancer continuous cell line, development of breast cancer stem cells (BCSCs) enriched culture and biomarker analysis. Indones Biomed J. 2020;12(2):115-123.
13. Kirtishanti A, Siswodihardjo S, Sudiana IK, Suprabawati DGA, Dinaryanti A. Inhibition of Ras and STAT3 activity of 4-(tert-butyl)-N-carbamoylbenzamide as antiproliferative agent in HER2-expressing breast cancer cells. J Basic Clin Physiol Pharmacol. 2021;32(4):363-371.
14. Taube JH et al. Core epithelial-to-mesenchymal transition interactome gene-expression signature is associated with claudin-low and metaplastic breast cancer subtypes. Proc Natl Acad Sci USA. 2010;107:15449-15454.
15. Prat A, Parker JS, Karginova O, Fan C, Livasy C, Herschkowitz JI, et al. Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer. Breast Cancer Res. 2010;12:R68.
16. Takebe N, Warren RO, Ivy SP. Breast cancer growth and metastasis: Interplay between cancer stem cells, embryonic signaling pathways and epithelial-to-mesenchymal transition. Breast Cancer Res. 2011;13:211.
17. Neve RM et al. A collection of breast cancer cell lines for the study of functionally distinct cancer subtypes. Cancer Cell. 2006;10:515-527.
18. Matulessy RY, Purwanto H, Danardono E. Breast cancer subtypes and disease-free interval in early-stage breast cancer. EurAsian J Biosci. 2020;14(1):2539-2544.
19. O'Brien CA, Kreso A, Jamieson CH. Cancer stem cells and self-renewal. Clin Cancer Res. 2010;16:3113-3120.
20. Ricardo S, Vieira AF, Gerhard R, Leitao D, Pinto R, Cameselle-Teijeiro JF, et al. Breast cancer stem cell markers CD44, CD24 and ALDH1: Expression distribution within intrinsic molecular subtype. J Clin Pathol. 2011;64:937-946.
21. Bernardi MA, Logullo AF, Pasini FS, Nonogaki S, Blumke C, Soares FA, et al. Prognostic significance of CD24 and claudin-7 immunoexpression in ductal invasive breast cancer. Oncol Rep. 2011;27(1):28-38.
22. Ferguson NL, Bell J, Heidel R, Lee S, VanMeter S, Duncan L, et al. Prognostic Value of Breast Cancer Subtypes, Ki-67 Proliferation Index, Age, and Pathologic Tumor Characteristics on Breast Cancer Survival in Caucasian Women. Breast J. 2013;19(1):22-30.
23. Kyo S, Sakaguchi J, Ohno S. High Twist expression is involved in infiltrative endometrial cancer and affects patient survival. Hum Pathol. 2006;37:431-438.
24. Zhao M et al. Expression and correlation of Twist and gelatinases in breast cancer. Exp Ther Med. 2013;6:97-100.
25. Kagara N, Huynh KT, Kuoetal C. Epigenetic regulation of cancer stem cell genes in triple-negative breast cancer. Am J Pathol. 2012;181(1):257-267.
26. Visvade JE, Stingl J. Mammary stem cells and the differentiation hierarchy: Current status and perspectives. Genes Dev. 2014;28:1143-1158.
27. Idowu MO, Kmieciak M, Dumur C. CD44+/CD24–/low cancer stem/progenitor cells are more abundant in triple-negative invasive breast carcinoma phenotype and are associated with poor outcomes. Hum Pathol. 2012;43(3):364-373.
28. Kuilman T, Michaloglou C, Mooi WJ, Peeper DS. The essence of senescence. Genes Dev. 2010;24:2463-2479.
29. Liu S, Cong Y, Wang D, Sun Y, Deng L, Liu Y, et al. Breast Cancer Stem Cells Transition between Epithelial and Mesenchymal States Reflective of Their Normal Counterparts. Stem Cell Reports. 2014;2:78-91.