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Cancer Stem Cells as Therapeutic Target

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Abstract

Cancer is one of the most deadly diseases in the world. Many methods developed for the treatment of cancer but fail in the long or short term. Researches suggest that one of the causes of this failure may be cancer stem cells (CSC). CSCs, which are constituted a very small group of cells in the tumor mass, are resistant to chemotherapy and radiotherapy, which are traditional treatment methods. In addition, studies show that CSCs may be responsible for metastases and recurrences.. For all these reasons, new treatment strategies need to be developed to target CSCs as well as cancer cells. However, specifically targeting CSCs, without harm normal tissues and adult stem cells is very important. In this review, the origin of CSCs and their resistance to traditional treatment methods are briefly mentioned. In addition, it has been evaluated whether immunotherapy, which has successful results in many cancer types, is an effective option for CSCs. For that purpose, CSC markers have been reviewed to specifically target CSCs.

Keywords: *Cancer, Cancer therapy, Cancer stem cells (CSC), Therapeutic target*

Introduction

Cancers are the most deadly disease group after cardiovascular diseases worldwide. For this reason, numerous researches are being conducted to develop effective treatment strategies for cancer. However, many of these strategies fail. Evidence from several studies in recent years point to Cancer Stem Cells (CSC) as one of the reasons for this failure.

In 1971, Perce and Wallace observed aggressive cells capable of producing *in vivo* squamous cell carcinoma. After this study, a large number of researches have been made for these cell groups groups have been emerged to understand the this type of cells [1, 2]. The definition of CSC was in 1997 in Acute Myeloid Leukemia. This cell group, which is also detected in many solid cancers in the following years and defined as CSC. It is thought to be the cells that have the ability to initiate tumors and are responsible for metastases and recurrences [2]. In 2006, the American Cancer Research Association identified CSCs as a self-regenerating cell group that is responsible for the forming of heterogeneous cell lineage within the tumor mass [3].

Evidence of the presence of CSC in the tumor mass emerged the question of the origin of the CSC. For this purpose, many researches have been made and continued to be done. There are various considerations regarding the origin of CSCs.

According to the CSC model that developed after the identification of CSCs, it was supported by

numerous experimental and clinical studies in which CSCs are a group of cells that are capable of initiating tumor, responsible for resistance to chemotherapy and radiotherapy, capable of metastasis and also responsible for recurrences [4-7]. CSCs in the tumor mass are avoiding chemotherapy and radiotherapy with various mechanisms and they are effective in the development of relapses with a more aggressive process. Because of these characteristics, CSCs are a good target for new treatment strategies to be developed. In recent years immunotherapy which has shown positive results in many cancer types, it also targeting CSCs.

Targeting CSCs for effective treatment of cancer is very important. However, targeting CSCs specifically on this issue is a very sensitive point. For this purpose, various studies have been conducted to identify the markers of CSCs that are not expressed in somatic cells and/or adult stem cells.

In this review, the origins of CSCs, their possible roles that are thought to be effective in the failure of traditional treatment methods, and various researches on the development of new CSC-targeted treatment strategies are presented discussed.

The Origin of Cancer Stem Cells

There are various views on the origin of CSCs, which make up a small population within the tumor mass. One of these views is that CSCs arise from non-stem cancer cells within the tumor mass. According to this; CSCs are thought to develop by upregulation of pluripotency-associated pathways such as Hedgehog, Wnt / β-Catenin and Jagged2-Notch in non-stem cancer cells [8,9]. In addition, hypoxia occurs as a result of rapid growth in cancer cells. Accordingly, the hypoxia-related genes, Hif1α and Hif2α, are upregulated. This leads to the emergence of stem-like properties through upregulation of EMT-specific genes such as Notch-1, C-kit, Snaıl, Slug, Twist and N-Cadherin [9-11]. Another view of the origin of CSCs is that CSCs are derived from somatic stem cells. Accordingly, it is thought that one or more internal pathways such as Wnt, SHH (Sonic Hedgehog), Phosphatase and tensin homolog (PTEN), Bmi1 and Notch, which are active in adult stem cells, may cause the development of CSCs [5]. Another hypothesis about the origin and clonal evolution of CSCs is that it develops and progresses by fusion of normal stem cells and mutant somatic cells. According to this view, some mutations occur in somatic cells, stem or progenitor cells and accumulate over time. The fusion of stem cells with self-regeneration, high proliferation and differentiation ability cells containing this mutation causes genomic imbalance. This can initiate the conversion of CSCs [12]. Some studies have shown that circulating hematopoietic stem cells can fuse with cells found in specific tissues. Therefore, it is thought that CSCs may constitute a possible origin [12,13]. Another hypothesis about the formation of CSCs is horizontal gene transfer. Normally horizontal gene transfer is seen in prokaryotes. However, according to this hypothesis, in eukaryotes, DNA in apoptotic cells can pass into recipient cells. As a result, nuclear programming and the onset of cancer occur [12,14].

The microenvironment is also important for the formation and clonal selection of CSCs. Damaged and injured cells give signals to the environment and the tissue repair mechanism is activated as a response to these signals. In this context, cancer is also a formation that does not heal and constantly signals to the microenvironment with some cytokines and chemokines. As a result, the repair mechanism remains permanently active and causes the development of cancer [12].

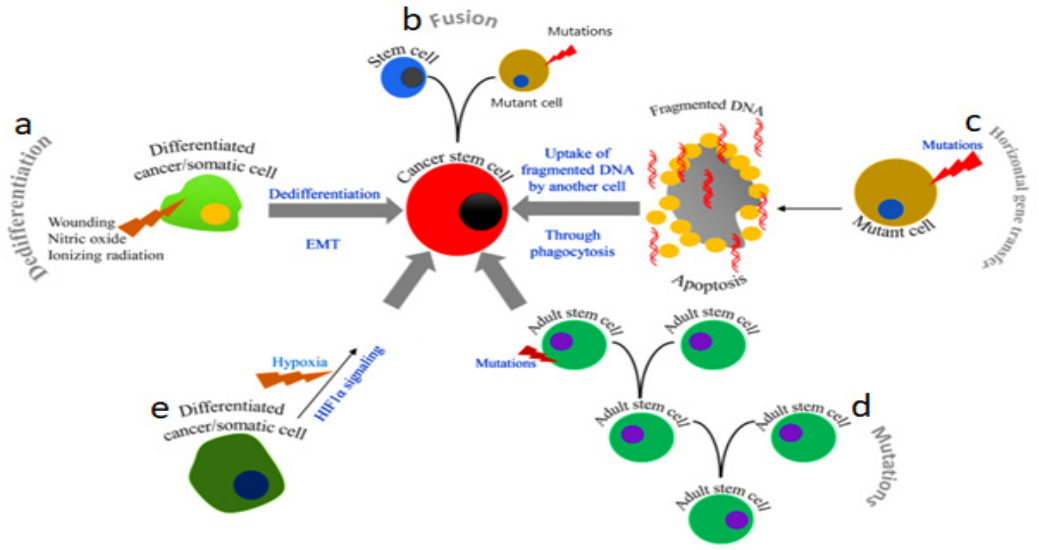

Figure 1. *Origin of Cancer Stem Cells. a. CSC formation from dedifferentiated somatic cells b. The fusion of stem cell and mutant cell for CSC formation. c. CSC formation by horizontal gene transfer due to the transition of DNA in apoptotic cells to receptive cells. d. CSC formation from an adult stem cell. e. Hypoxia-induced CSC formation [Modified from 15].*

Traditional Treatment Methods and Cancer Stem Cells

Cancer Stem Cells and Chemotherapeutic Resistance

One of the most important obstacles in the effective treatment of cancer is chemotherapy resistance. One of the factors causing this resistance is ABC (ATP-binding cassette) transporters. These transporters are expressed by multiple drug resistance (MDR) genes, which use the energy released by the hydrolysis of ATP to export drugs delivered into the cell. The most studied genes that are members of the ABC transporter superfamily encoding these transporter proteins are ABCB1, ABCG2 and ABCC1 [16]. In addition, P-glycoprotein (P-gp), multidrug resistance-associated protein (MRP1), lung resistance protein (LRP), and breast cancer resistance protein (BCRP) have been identified as MDR associated proteins. These transporter transmembrane proteins act in two ways by reducing the total uptake of drugs in the cell or by inhibiting their accumulation in and/or near the target organelles by dispersing the drugs in the cell [17, 18].

Some types of stem cells are known to have highly effective pumps against Hoechst 33342 dye. This dye, which binds to DNA, especially A-T rich regions, has little retention in cells with these pumps. Because of these characteristics, these cells are called 'side populations'. Verapamiland and Reserpinel are specific inhibitors of these transporters. CSCs also have drug delivery pumps connected to functional ATP [18-21].

Numerous inhibitors have been developed for ABC transporters to overcome this chemotherapy resistance barrier. However, the requested success was not achieved. Because even though inhibitors are effective in differentiated cancer cells, new cells encoding ABC transporters are supplemented by CSCs in the tumor mass [16]. Therefore, developing new strategies to target CSCs as well as differentiated cancer cells in tumor mass will increase the chances of success. However, another important issue is that normal stem cells are not affected when targeting CSCs.

Cancer Stem Cells and Radiotherapy Resistance

At the present time, the standard treatment for solid tumors is surgery and radiotherapy. However, because of the infiltrative properties of many cancer cells, it is not possible to completely remove them by surgical intervention. In addition, recurrence and a more

aggressive process develop in many cancer types after radiotherapy. CSCs are seen as responsible for this condition after therapy. In order to investigate the response of CSCs to radiotherapy, glioma and breast cancer cells were first studied. Accordingly, in a study with $CD133^+$ cells in glioma, radiotherapy resistance was found to be due to structural activation of DNA repair mechanism and inhibition of the responsible kinase at the control point in $CD133^+$ cells that became susceptible to radiation after radiation therapy [22,23]. In response to radiotherapy in breast cancer, it was seen that the expression of free radical cleaners in CSCs increased and consequently less reactive oxygen species were produced. In addition, in these CSCs in breast cancer, the Notch signaling pathway was activated by upregulation of Notch receptor ligand due to PI3K. This activation causes both the protection and the increase in the number of CSCs [23, 24].

Although radiotherapy is an effective method for eradicating differentiated cancer cells in the short term, its effect on CSCs within the tumor mass rather than destroying CSCs will contribute to their protection and even increase their number. In this case, it causes recurrences after therapy and a more aggressive process and treatment are ineffective.

Cancer Stem Cells and Immunotherapy

These failures in traditional treatment methods have led researchers to develop new treatment strategies. For this purpose, cancer immunotherapy studies have been intensified and successful results have been obtained. In addition, the effects of immunotherapy on CSCs, which are known for their resistance to chemotherapy and radiotherapy, are being investigated. Knowing the immunological characters of CSCs and their characteristics of the tumor microenvironment in which they are located will facilitate the immunotherapeutic targeting of these cells. The expression of MHC I molecule and NK receptors and other natural immune receptors is low in CSCs. This makes it easier for these cells to escape from cells with antitumor activity, such as NK cells and T cells [25].

The characteristics in the tumor microenvironment are also important in the effectiveness of immunotherapy. The tumor microenvironment includes cancer and CSCs as well as immune and stromal cells. Immune cells in the tumor microenvironment are tumor-associated macrophages (TAM), tumor-entering lymphocytes (TIL), regulatory T cells (Treg), myeloid-derived suppressor cells (MDSC), Dendritic Cells (DC), Natural killer cells (NK cells), and natural killer T cells derived from bone marrow. Stromal cells include blood and lymphatic endothelial cells and cancer-associated fibroblasts. These cells secrete various cytokines and chemokines that are responsible for antitumor immunity as well as suppress the efficacy of metastasis and anticancer therapies. Interactions between CSCs and other cell groups via these cytokines and chemokines, significantly suppress antitumor activity [25-29].

In recent years, immunotherapy methods for cancer have been targeted to cancer cells as well as CSCs. In addition, methods specifically targeting CSCs are being investigated. According to research, CSCs are targeted immunologically therapeutically in various ways. These methods are $CD8^+$ T cells with γδ T cells, NK cells and Cytokine Induced Killer Cells (CIK), DC-based vaccines, oncolytic virotherapy, immunological cell death by induced antitumor immunity, and activation of T cells and blockage of immune control points. In particular, DC-based vaccines, blockade of immune control points by oncolytic virotherapy are frequently preferred targeting strategies in recent years [25,30,31].

Specific Targeting of Cancer Stem Cells

The CSC hypothesis and CSCs as responsible for the failure of traditional treatment methods led researchers to develop strategies targeting CSCs. However, it is very important to target CSCs specifically without affecting normal cells and/or stem cells when performing this targeting. For this purpose, a study was conducted to compare the expression of 40 CSC surface markers in human embryonic stem cells, adult stem cells and normal tissue cells. In this study, 33 (83%) of 40 CSC markers were rarely expressed in normal tissue cells (Table 1). It has been reported that these CSC markers

may be a therapeutic target due to low cross-reactions in normal tissue cells. In addition, 9 of these markers were approved by the FDA as a molecular drug target (Table 2). However, 7 of the 40 CSC markers are highly expressed in normal tissue cells and are found all over the cells (Table 1). This indicates that the use of these markers as targets may cause serious side effects. It is also important to distinguish between CSCs and adult and embryonic stem cells. CSCs are very rare in tumor tissue and adult stem cells are very rare in mature tissues. Therefore, it is difficult to isolate and cultivate. The possibility that a method targeting CSCs may also damage adult stem cells should never be overlooked. Because damage to adult stem cells can cause serious damage to tissue regeneration in the organism. In addition, 21 (53%) of 40 CSC markers were expressed in embryonic stem cells (Table 1). These markers, which are expressed in undifferentiated embryonic stem cells and they are oncofetal features are rarely expressed in normal tissue cells. Therefore, these markers may be potential targets for CSCs [32].

Table 1. *Expression of CSC markers in normal tissues and embryonic stem cells [32]*

Markers Rarely Expressed in Normal Tissues	Highly Expressed Markers in Normal Tissues	Markers Expressed in Embryonic Stem Cells
SSEA3	CD29 (Integrin β1)	SSEA3
SSEA4	CD9	SSEA4
TRA-1-60	CD166 (ALCAM)	TRA-1-60
TRA-1-81	CD44 variants	TRA-1-81
SSEA1	ABCB5	SSEA1
CD133 (AC133)	Notch3	CD133 (AC133)
CD90 (Thy-1)	CD123 (IL-3R)	CD90 (Thy-1)
CD326 (EpCAM)		CD326 (EpCAM)
Cripto-1 (TDGF1)		Cripto-1 (TDGF1)
PODXL-1 (Podocalyxin- like protein 1)		PODXL-1 (Podocalyxin- like protein 1)
ABCG2		ABCG2
CD24		CD24
CD49f (Integrin α6)		CD49f (Integrin α6)
Notch2		Notch2
CD146 (MCAM)		CD146 (MCAM)
CD10 (Neprilysin)		CD10 (Neprilysin)
CD117 (c-KIT)		CD117 (c-KIT)
CD26 (DPP-4)		CD26 (DPP-4)
CXCR4		SSEA3
CD34		
CD271		
CD13 (Alanine aminopeptidase)		
CD56 (NCAM)		
CD105 (Endoglin)		
LGR5		
CD114 (CSF3R)		
CD54 (ICAM-1)		
CXCR1, 2		
TIM-3 (HAVCR2)		
CD55 (DAF)		
DLL4 (Delta-like ligand 4)		
CD20 (MS4A1)		
CD96		

Table 2. *FDA approved CSC markers [32]*

MARKERS APPROVED BY THE FDA
CD10 (Neprilysin)
CD117 (c-KIT)
CD26 (DPP-4)
CXCR4
CD114 (CSF3R)
CD54 (ICAM-1)
CD20 (MS4A1)
CD29 (Integrin β1)
CD44 variants

In addition to these protein structure markers, a few stem cell markers were found to be glycans bound to proteins or lipids. Developmental regulation of glycans and alterations in mostly tumor cells have led to the idea that they can be used as markers of CSC. Accordingly, many studies have been conducted on the Thomsen-Friedenreich (TF) antigen which is an oncofetal glycan (33-38). These studies have shown that TF may be an exceptionally specific tumor marker. Karsten and Goletz who research this topic suggest that CSCs markers will differ from their normal counterparts by expressing tumor-specific glycans [38].

These markers, both protein and glycan, are promising for therapeutic targeting of CSCs. However, further studies are needed to develop methods that specifically target CSCs to minimally affect normal tissue and stem cells.

Conclusion

CSCs are a small population of cells within the tumor mass. However, these cells are seen as a group of cells that are effective in the formation and development of cancer and also responsible for therapy resistance and metastasis and recurrence. Therefore, targeting of CSCs along with cancer cells is very important for the effective treatment of this disease. However, targeting CSCs specifically is very important. Therefore, investigations should be carried out to determine the characteristics of CSCs to distinguish them from normal somatic cells and adult stem cells.

Highlights

- The CSC;
  - capable of tumor initiation,
  - self-renewable,
  - causing chemotherapy and radiotherapy resistance,
  - is a group of cells that are responsible for metastases and recurrences.
- CSCs are a potential target for effective cancer treatment.
- Specific targeting of CSCs is essential.

References

[1] Lobo NA, Shimono Y Qian D, Clarke MF. The biology of cancer stem cells. Annual Review of Cell and Developmental Biology 2007;23: 675–699. Available from: doi.org/10.1146/annurev.cellbio.22.010305.104154.

[2] Turdo A, Veschi V, Gaggianesi M, Chinnici A, et al. Meeting the challenge of targeting cancer stem cells. Frontiers in Cell and Developmental Biology 2019;7: 16. Available from: doi.org/10.3389/fcell.2019.00016.

[3] Şeber S, Yetişyiğit T. Cancer stem cells: secret of failure. International Journal of Basic and Clinical Medicine. 2016; 4(2): 101-8.

[4] Takebe N, Harris PJ, Warren RQ, Ivy SP. Targeting cancer stem cells by inhibiting Wnt, Notch, and Hedgehog pathways. National Reviews Clinical Oncology. 2011;8: 97–106. Available from: 10.1038/nrclinonc.2010.196.

[5] Takebe N, Miele L, Harris PJ, Jeong W, et al. Targeting Notch, Hedgehog, and Wnt pathways in cancer stem cells: Clinical Update. National Reviews Clinical Oncology. 2015;12: 445–464. 10.1038/nrclinonc.2015.61.

[6] Shabbir A, Esfandyari T, Farassati F. Cancer stem cells, the ultimate targets in cancer therapy. OncoTargets and Therapy. 2018; 11: 183–184. Available from: 10.2147/OTT.S154431.

[7] Zhu P, Fan Z. Cancer stem cells and tumorigenesis. Biophysics Reports. 2018;4(4): 178-188. Available from: 10.1007/s41048-018-0062-2.

[8] Yanger K, Zong Y, Maggs LR, Shapira SN, et al. Robust cellular reprogramming occurs spontaneously during liver regeneration. Genes & Development. 2013;27: 719724. Available from: 10.1101/gad.207803.112.

[9] Das A, Dutta A, Paul S, Dutta A et al. Cancer stem cells, their origin and niche: a search for the therapeutic target. Journal of Stem Cell Research and Medicine. 2017;2(1): 1-11. Available from: 10.15761/JSCRM.1000118.

[10] Jögi A, Øra I, Nilsson H, Lindeheim A et al. Hypoxia alters gene expression in human neuroblastoma cells toward an immature and neural crest-like phenotype. Proceetings of the National Academy of Sciences of the United States of America. 2002;99: 7021-7026. Available from: 10.1073/pnas.102660199.

[11] Xing F, Okuda H, Watabe M, Kobayashi A et al. Hypoxia-induced Jagged2 promotes breast cancer metastasis and self-renewal of cancer stem-like cells. Oncogene. 2011;30: 4075-4086. Available from: 10.1038/onc.2011.122.

[12] Bu Y, Cao D. The origin of cancer stem cells. Frontiers in Bioscience S4 (Schol Ed). 2012;4: 819-830. Available from: 10.2741/s302.

[13] Rizvi AZ, Swain JR, Davies PS, Bailey AS et al. Bone marrow-derived cells fuse with normal and transformed intestinal stem cells. Proceetings of the National Academy of Sciences of the United States of America. 2006;103(16): 6321-5. Available from: 10.1073/pnas.0508593103.

[14] Sinkovics JG. Horizontal gene transfers and cell fusions in microbiology, immunology and oncology. International Journal of Oncology. 2009;35(3): 44 1-65. Available from: 10.3892/ijo_00000357.

[15] Nimmakayala RK, Batra SK, Ponnusamy MP. Unraveling the journey of cancer stem cells from origin to metastasis. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2018;1871(1): 50-63. Available from: 10.1016/j.bbcan.2018.10.006.

[16] Dean M, Fojo T, Bates S Tumour Stem Cells and Drug Resistance. Nature Reviews Cancer. 2005;5(4): 275. Available from: 10.1038/nrc1590.

[17] Tan B, Piwnica-Worms D, Ratner L. Multidrug Resistance Transporters and Modulation. Current Opinion in Oncology. 2000;12: 450–8. Available from: 10.1097/00001622-200009000-00011.

[18] Ishii H, Iwatsuki M, Ieta K, Ohta D et al. Cancer stem cells and chemoradiation resistance. Cancer science. 2008;99(10): 1871-1877. Available from: doi.org/10.1111/j.1349-7006.2008.00914.x.

[19] Goodell MA, Brose K, Paradis G, Conner AS et al. Isolation andfunctional properties of murine hematopoietic stem cells that are replicating in vivo. Journal of Experimental Medicine. 1996;183: 1797–806. Available from: 10.1084/jem.183.4.1797.

[20] Challen GA, Little MH. A side order of stem cells: the SP phenotype. Stem Cells. 2006;24: 3–12. Available from: doi.org/10.1634/stemcells.2005-0116.

[21] Polgar O, Robey RW, Bates SE. ABCG2: structure, function and role in drug response. Expert Opinion on Drug Metabolism & Toxicology. 2008;4: 1–15. Available from: doi.org/10.1517/17425255.4.1.1.

[22] Bao S, Wu Q, McLendon RE, Hao Y et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature. 2006;444: 756–760. Available from: doi.org/10.1038/nature05236.

[23] Vlashi E, McBride WH, Pajonk F Radiation responses of cancer stem cells. Journal of Cellular Biochemistry. 2009;108(2): 339-342. Available from: doi.org/10.1002/jcb.22275.

[24] Phillips TM, McBride WH, Pajonk F. The response of CD24-/low/CD44+ Breast cancer-initiating cells to radiation. Journal of National Cancer Institute. 2006;98: 1777– 1785. Available from: doi.org/10.1093/jnci/djj495.

[25] Badrinath N, Yoo SY. Recent advances in cancer stem cell-targeted immunotherapy. Cancers. 2019;11(3): 310. Available from: doi.org/10.3390/cancers11030310.

[26] Turley SJ, Cremasco V, Astarita JL. Immunological hallmarks of stromal cells in the tumour microenvironment. Nature Reviews Immunology. 2015;15: 669–682. Available from: doi:10.1038/nri3902.

[27] Klemm F, Joyce JA. Microenvironmental regulation of therapeutic response in cancer. Trends in Cell Biology. 2015;25: 198–213. Available from: doi.org/10.1016/j.tcb.2014.11.006.

[28] Nagarsheth N, Wicha MS, Zou W. Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. Nature Reviews Immunology. 2017;17: 559–572. Available from: doi.org/10.1038/nri.2017.49.

[29] Relation T, Dominici M, Horwitz EM. Concise review: An (im)penetrable shield: how the tumor microenvironment protects cancer stem cells. Stem Cells 2017;35: 1123–1130. Available from: doi.org/10.1002/stem.2596.

[30] Teitz-Tennenbaum S, Wicha MS, Chang AE, Li Q. targeting cancer stem clls via dendritic-cell vaccination. Oncoimmunology. 2012;1: 1401–1403. Available from: doi.org/10.4161/onci.21026.

[31] Badrinath N, Heo J, Yoo SY. Viruses as Nanomedicine for Cancer. International Journal of Nanomedicine. 2016;11: 4835–4847. Available from: doi:10.2147/IJN.S116447.

[32] Kim WT, Ryu CJ. Cancer stem cell surface markers on normal stem cells. BMB Reports. 2017;50(6): 285. Available from: doi: 10.5483/BMBRep.2017.50.6.039.

[33] Springer GF, Desai PR, Banatwala I. Blood group MN antigens and precursors in normal and malignant human breast glandular tissue. Journal of National Cancer Institute. 1975;54: 335–339. Available from: doi.org/10.1093/jnci/54.2.335.

[34] Springer GF. T and Tn, general carcinoma autoantigens. Science. 1984;224: 1198–1206. Available from: doi: 10.1126/science.6729450.

[35] Clausen H, Stroud M, Parker J, Springer G et al. Monoclonal antibodies directed to the blood group a asociated structure, glactosyl-a: specificity and relation to the Thomsen-Friedenreich antigen. Molecular Immunology. 1988;25: 199–204. Available from: doi.org/10.1016/0161-5890(88)90068-5.

[36] Karsten U, Butschak G, Cao Y, Goletz S, et al. A new monoclonal antibody (A78-G/A7) to the Thomsen-Friedenreich Pan-tumor Antigen. Hybridoma 1995;14: 37–44. Available from: https://doi.org/10.1089/hyb.1995.14.37.

[37] Goletz S, Cao Y, Danielczyk A, Ravn P, Schöber U, et al. ThomsenFriedenreich antigen: the "hidden"tumour antigen. Advances in Experimental Medicine and Biology. 2003;535: 147–162. Available from: DOI:10.1007/978-1-4615-0065-0_10.

[38] Karsten U, Goletz S. What makes cancer stem cell markers different?. Springer Plus 2013;2(1): 301. Available from: doi.org/10.1186/2193-1801-2-301.

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