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Effects of extracellular modulation through hypoxia on the glucose metabolism of human breast cancer stem cells

I Yustisia¹, S W A Jusman² and S I Wanandi^{2*}

¹Doctoral Program in Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

²Department of Biochemistry and Molecular Biology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

*E-mail: septelia.inawati@ui.ac.id

Abstract. Cancer stem cells have been reported to maintain stemness under certain extracellular changes. This study aimed to analyze the effect of extracellular O₂ level modulation on the glucose metabolism of human CD24-/CD44+ breast cancer stem cells (BCSCs). The primary BCSCs (CD24-/CD44+ cells) were cultured under hypoxia (1% O₂) for 0.5, 4, 6, 24 and 48 hours. After each incubation period, HIF1 α , GLUT1 and CA9 expressions, as well as glucose metabolism status, including glucose consumption, lactate production, O₂ consumption and extracellular pH (pHe) were analyzed using qRT-PCR, colorimetry, fluorometry, and enzymatic reactions, respectively. Hypoxia caused an increase in HIF1 α mRNA expressions and protein levels and shifted the metabolic states to anaerobic glycolysis, as demonstrated by increased glucose consumption and lactate production, as well as decreased O₂ consumption and pHe. Furthermore, we demonstrated that GLUT1 and CA9 mRNA expressions simultaneously increased, in line with HIF1 α expression. In conclusion, modulation of the extracellular environment of human BCSCs through hypoxia shifted the metabolic state of BCSCs to anaerobic glycolysis, which might be associated with GLUT1 and CA9 expressions regulated by HIF1 α transcription factor.

1. Introduction

Many studies on the effort to increase the effectiveness of breast cancer therapy have found that the approach to cancer therapy should consider the role of tumor microenvironment. The environment is defined as the surroundings of cancer cells that comprises two main components: the cellular components, which are composed of tumor stromal cells such as epithelial cells, endothelial cells, fibroblasts, macrophages, immune/inflammatory cells, and mesenchyme stem cells; and the non-cellular components, which comprise structural proteins, extracellular matrix-forming polysaccharides, and soluble factors such as cytokines, chemokines, and growth factors [1,2]. The tumor microenvironment has its own chemical environment that is composed of oxygen tension (O₂), pH, molecule concentration, and small metabolites such as NO, glucose, glutamine, and lactate [3]. The tumor microenvironment is known to have a variation of O₂ tension that depend on the location and quality of nearby blood vessels. Although the tumor can induce angiogenesis, the quality of new blood vessels in tumor tissues are usually poor and the rapid growth of tumors often surpasses the pace of blood vessel formation by endothelial cells. Oxygen supply to the tumor is low and creates a hypoxic state [4,5].



Inside a tumor mass, there is a cancer cell subpopulation that has the pluripotency property similar to that of normal stem cells. This cancer cell population is known as cancer stem cells (CSCs). CSCs are hypothesized as the cell responsible for determining tumor growth (tumorigenic) because of its self-renewal and pluripotency [6,7]. The role of a hypoxic microenvironment in the regulation of the transcription factor, hypoxia inducible factor (HIF), the maintenance of CSCs is partly known. However, the role of metabolic state in maintaining stemness and survival of human breast cancer stem cells (BCSCs) in a hypoxia still needs to be examined because of the lack of consistent findings in previous studies. Some previous studies showed that BCSCs depend on oxidative phosphorylation, but other studies asserted that BCSCs depend on glycolysis to maintain their stemness [8-13]. The present study is part of a series of research investigating the influence of microenvironment changes on the BCSC metabolic state and how the metabolism affects the survival, tumorigenicity, and stemness of BCSCs.

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2. Materials and Methods

2.1. Culture of human BCSCs and hypoxia exposure

In our previous study, the primary culture of human breast cancer cells was sorted using magnetic-activated cell sorting conjugated with anti CD24 and anti CD44 antibody, thus resulting in CD24⁺/CD44⁺ cells for BCSCs and CD24⁻/CD44⁻ cells for non-BCSCs (Patent registration from the General Directorate of Intellectual Property Right, Ministry of Law and Human Right, Republic of Indonesia; No. P0021300369). BCSCs were initially seeded at 5×10^5 cells/well in a six-well plate, cultured in 3 mL/well of DMEM-F12 medium (pH = 7.4) containing HEPES buffer, 1% penicillin/streptomycin, 1% amphotericin B, 0.2% gentamycin sulfate, and 14.5 mM NaHCO₃, and then incubated at 37 °C in a humidified atmosphere of 5% CO₂ and 20% O₂ for 24 h. For the hypoxia exposure, seeding medium was replaced with a fresh medium, and the incubation was continued at 37 °C, 1% O₂, 5% CO₂, and 94% N₂ for 0, 4, 6, 24, and 48 h, respectively. We conducted a normoxic culture for each incubation period as the control. After each incubation period, the pH of the cell culture medium (pHe) was immediately measured using a pH electrode with a Micro Bulb for a 96-well plate (Hanna®) connected with a pH meter (HI 2210®, Hanna). The BCSCs were harvested by centrifugation at 1000 rpm for 10 min to obtain the cell pellet and culture supernatant for various analyses.

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2.2. Quantitative reverse transcription polymerase chain reaction (qRT-PCR)

Total RNA was extracted from the cell pellets using Tripure® RNA Isolation Kit (Roche) according to the manufacturer's protocol. The total RNA concentration was quantified using a spectrophotometer (Varioskan Flash). Samples with an A260/A280 ratio of 1.6–2.0 were considered to be free from DNA and proteins. qRT-PCR was performed using KAPA SYBR FAST® qPCR (KAPA BIO SYSTEMS) in the Exicycler™ 96 (Bioneer). The PCR primer sequences used in this study were HIF1 α : 5'-GGCGCAACGACAAGAAAAAG-3' and 5'-GTGGCAACTGATGAGCAAG-3'; GLUT1: 5'-GCTTCCAGTATGTGGAGCAAC-3' and 5'-GGTCCGGCCTTTAGTCTCAG-3'; CA9: 5'-GGTACAGCTGAACCTCCGA-3' and 5'-GCCAAAAACCAGGGCTAGGA-3'; 18S RNA: 5'-AAACGGCTACCACATCCAAG-3' and 5'-CCTCCAATGGATCCTCGTTA-3'. The Ct value for each gene was determined, and $\Delta\Delta C_t$ was normalized to the designated reference sample. The gene expression values were calculated using the Livak method ($2^{-\Delta\Delta C_t}$).

2.3. HIF1 α protein level

Total protein was extracted from 3×10^5 cells. The HIF1 α protein level was assayed using the HIF1A Human ELISA kit (Abcam) according to the manufacturer's protocol. Data were presented per total protein.

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2.4. Glucose consumption, lactate production, and lactate dehydrogenase (LDH) activity assay
Glucose consumption was determined by subtracting the glucose concentration in DMEM-F12 (17.5 mM) before incubation from with that remaining in the medium after a certain incubation period. The glucose level was measured using O-toluidine colorimetric assay (Sigma) and a spectrophotometer at 625 nm. To determine the extracellular lactate production, the amount of lactate present in the supernatant of the BCSC culture was determined using the L-Lactate Assay Kit (Abcam) and a spectrophotometer at 450 nm. The LDH activity of BCSCs was analyzed using the Lactate Dehydrogenase Activity Assay Kit (Sigma) according to the manufacturer's procedure.

2.5. Extracellular oxygen concentration assay

Oxygen consumption was determined using sensitive phosphorescent probes that were quenched at the excited state in the presence of oxygen (Extracellular O₂ probe, Abcam). Briefly, after culturing BCSCs for a certain incubation period, the cells were harvested and then transferred to a fluorescence 96-well plate with density of 8×10^4 cells/well. The 10 μ l probes from a 1 μ M stock solution were dispensed into each well, and 100 μ l of preheated mineral oil (30 °C) was added to each well to enhance the assay sensitivity by minimizing interference from ambient oxygen. Probe signals were measured by a fluorescence plate reader equipped with a time-resolved mode preset to 37 °C at 1.5 min intervals for 60 min using excitation and emission wavelengths of 380 nm and 650 nm, respectively.

15 **2.6. Statistical analysis**

All data were presented as $m \pm$ standard error means (SEM) of at least triplicates. A p-value of at least <0.05 in the independent t-test was considered statistically significant.

3. Results and Discussion

3.1 Results

3.1.1. mRNA HIF1 α expression

To evaluate the success of the hypoxia procedure, the expression of mRNA HIF1 α , which is an HIF protein subunit coding gene that is responsive to the decrease in O₂ concentration, was analyzed. Quantification using qRT-PCR shows that the expression of BCSCs CD24/CD44⁺ HIF1 α mRNA incubated in a hypoxic state significantly increases compared with the cells incubated in a normoxia. This increase in quantity is parallel with the increase in incubation time. After 48 h of incubation, the HIF1 α mRNA expression in hypoxia decreases compared with that in the first incubation time frame but is still higher than the HIF1 α mRNA expression in a normoxia (Figure 1A). Lysate examination from BCSCs CD24/CD44⁺ incubated in hypoxia shows an increase in HIF1 α protein concentration compared with that in the normoxia up to 48 h of incubation (Figure 1B). The increase in mRNA HIF1 α expression and HIF1 α protein concentration shows that BCSCs CD24/CD44⁺ is indeed responsive to hypoxia. To evaluate the effect of HIF1 α mRNA expression and HIF1 α protein concentration from BCSCs CD24/CD44⁺ in a hypoxic state on the genes under its regulation, the CA9 and GLUT1 mRNA expressions are quantified. These genes encode pH regulator enzyme, carbonic anhydrase 9, and glucose transporter, respectively. This test is conducted on these genes because hypoxia affects cell metabolism to anaerobic glycolysis, which then causes a decrease in extracellular pH and an increase in glucose consumption by the cells. The results of this study show that the increase in GLUT1 and CA9 mRNA expression of BCSCs CD24/CD44⁺ in a hypoxic state is correlated with the increase in HIF1 α mRNA expression (Figure 2A and 2B).

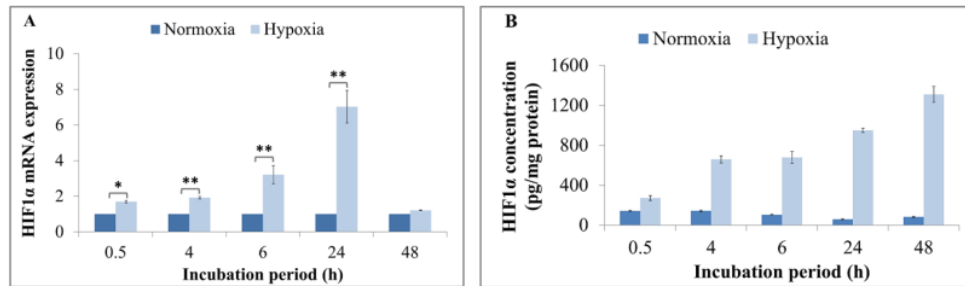


Figure 1. HIF1 α mRNA expression and HIF1 α protein concentration in BCSCs CD24/CD44⁺ increase in hypoxia. **A.** The HIF1 α mRNA expression increases as the incubation period increases and decreases after 48 h. **B.** The HIF1 α protein concentration in BCSCs CD24/CD44⁺ lysate cultured in a hypoxia increases. Data are shown as means \pm SEM, with T test * $p < 0.05$; ** $p < 0.01$; $n=4$

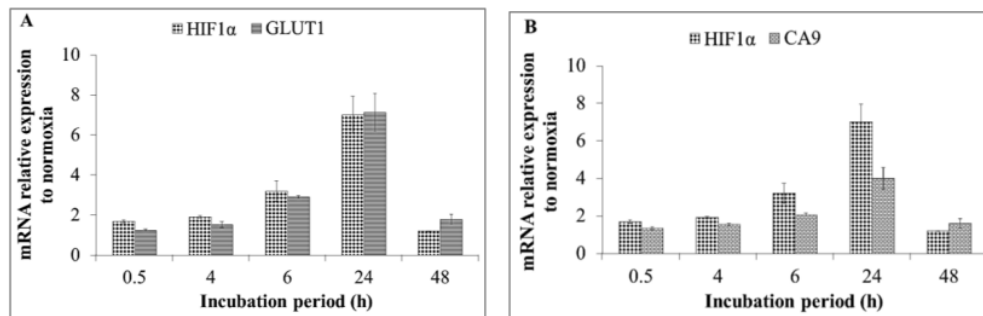


Figure 2. The HIF1 α mRNA expression pattern is similar to the GLUT1 and CA9 mRNA expression in hypoxia. **A.** HIF1 α and GLUT1 mRNA expression of hypoxic BCSCs CD24/CD44⁺ have the same pattern, with a correlation test result $r=0.984$ and $p=0.002$. **B** HIF1 α and CA9 mRNA expression of hypoxic BCSCs CD24/CD44⁺ also have the same pattern, with a correlation test result $r = 0.983$ and $p = 0.002$. Data are shown as mean \pm SEM

3.1.2. BCSCs CD24/CD44⁺ metabolic state in hypoxia

Glucose concentration in the supernatant decreases as the incubation time increases both in hypoxia and normoxia. However, hypoxia causes a faster decrease in glucose concentration than normoxia, particularly after 24 h and 48 h of incubation. The decrease in glucose concentration in the medium shows glucose consumption by the cells. In this study, glucose consumption increases more significantly in hypoxia than in normoxia (Figure 3A). The quantification of lactate concentration in the supernatant shows a difference in lactate production pattern from hypoxic BCSCs CD24/CD44⁺ compared with the normoxic. During 30 min, 4 h, and 6 h of incubation, lactate production in the normoxic group is higher, but not significantly, than that in the hypoxic group. After 24 h and 48 h of incubation, lactate production increases significantly in the hypoxic group. These findings coincide with the quantification of glucose consumption, which experiences an increase after 24 h and 48 h of incubation (Figure 3B). The increase in lactate production is supported by the increase in LDH activity. The results show that the intensity of intracellular O₂ probe of BCSCs CD24/CD44⁺ incubated in hypoxic condition for 0.5, 24, and 48 h is lower than the group incubated in a normoxic condition. An exception is observed in the 48 h normoxic group, which also shows a low O₂ probe intensity. A low probe intensity exhibits a high intracellular O₂ concentration [34]. These results indicate that BCSCs experience anaerobic metabolism during hypoxia. An increase in cell proliferation after 48

h of incubation in normoxia causes the cell metabolism to shift to anaerobic metabolism, which is the characteristic of cancerous cells (Figure 3C). A decrease in pH in the BCSC CD24/CD44⁺ culture medium occurs as the incubation period increases in the hypoxic group (Figure 3D). A decrease in pHe is also observed in the normoxic group. This result shows that BCSCs have a high metabolism rate and that metabolic products such as H⁺, lactic acid, and CO₂ cause a decrease in pHe. However, the pHe decrease in the hypoxic group is greater than that in the normoxic group because of an increase in anaerobic glycolysis, which significantly increases acidic metabolism products.

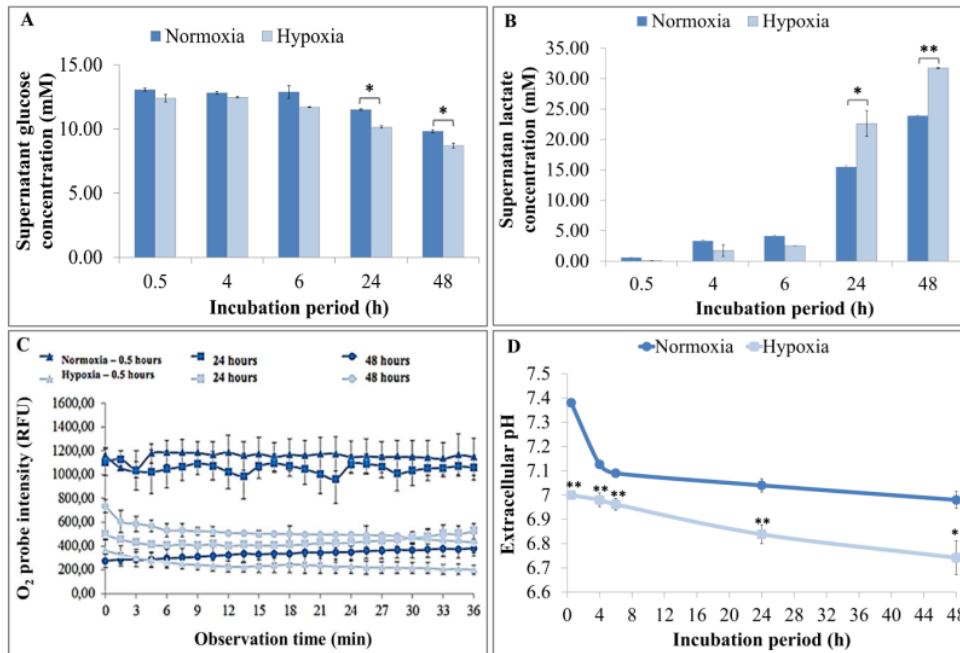


Figure 3. Hypoxia increases the anaerobic metabolism in BCSC CD24/CD44⁺. **A.** Glucose consumption, **B.** Lactate production, **C.** O₂ consumption, and **D.** Extracellular pH. Data are shown as means \pm SEM, with T-test results * $p < 0.05$; ** $p < 0.01$; $n=3$. RFU: relative fluorescence units.

3.2 Discussion

In primary tumors, the microenvironment is the main regulator of the CSCs stemness. The interaction between CSCs and the microenvironment is supported by the fact that a disturbance in the environment causes a disturbance in the CSCs [14]. The characteristics of the CSC tumor microenvironment specifically affect its metabolic state. Generally, stem cells show low oxidative phosphorylation activity and high glycolytic activity in synthesizing adenosine triphosphate (ATP) [15]. Therefore, CSCs in a hypoxic environment are predicted to depend on glycolysis as their main energy metabolism pathway. This pathway is considered to have an important role in sustaining the stem cell characteristics of CSCs [14,15]. To examine and prove the role of hypoxia in the glucose metabolism status, survival, and stem cell characteristics of CSCs, this study cultured BCSCs CD24/CD44⁺ in a hypoxia with 1% O₂. These conditions were intended to mimic the BCSC microenvironment in a cancer tissue.

The results of this study show that HIF1 α is the main regulator of BCSCs CD24/CD44⁺ in a hypoxia. This is observed with a significant increase in HIF1 α mRNA expressions and HIF1 α protein concentration after exposure to hypoxia but not to normoxia. The increase in HIF1 α expression and

stability affects glucose metabolism in two ways. First, HIF1 stimulates energy production through the glycolytic pathway by activating the genes involved in glucose transport into cells (e.g., GLUT1) and enzymes (e.g., such as PFK and aldolase) responsible for intracellular glucose breakdown. Second, HIF1 decreases the oxidative phosphorylation regulation in the mitochondria through the transactivation of genes, such as pyruvate dehydrogenase kinase 1. Both effects reduce the tumor cells' dependence on O_2 when exposed to hypoxia but can still sustain enough energy for the cells [16].

The results of this study indicate a gene expression increase in GLUT1 BCSCs CD24/CD44⁺ in hypoxia, which is correlated with the increase in HIF1 α expression. This increase in GLUT1 expression is followed with an increase in glucose consumption after 24 h and 48 h. Although this study did not measure the activity of the four key enzymes of glycolysis (i.e., hexokinase, glucokinase, phosphofructokinase, and pyruvate kinase), most of the pyruvates produced were transformed into lactate, as indicated by the increase in LDH activity and lactate production from the cells. These results show that in a hypoxia, HIF1 α regulates glucose metabolism in BCSCs CD24/CD44⁺ by increasing the anaerobic glycolytic activity. This action is supported by the decrease in mitochondrial activity exhibited by a low O_2 probe intensity and increased acid production, which lowers the pHe significantly. This study also measured the CA9 gene, which is regulated by HIF1. The results show that in hypoxia, the CA9 gene expression in BCSC CD24/CD44⁺ increases and correlates with the increase of HIF1 α mRNA expression. Previous studies found that CA9 in breast cancer cells increased in hypoxia (1% O_2) under the regulation of HIF1 α and possibly HIF2 α [17,23]. Other studies on esophagus cancer found that CA9 could be an intrinsic marker in hypoxia and play a role in tumor growth and survival [18].

In hypoxia, the glycolytic metabolism is predominant. That is, cells put in effort to sustain intracellular pH in the physiological range. CA9, as an extracellular anhydrase, plays a role in regulating extra- and intracellular pH. CA9 activity facilitates pH changes that are expelled by the cells as CO_2 and lactic acid is its conjugate (HCO_3^- and lactate) [19,20]. This CA9 activity is primarily determined by metabolic activities inside the cell to sustain an intracellular pH of 7.2, which is the pH needed for cells to grow [21]. The BCSCs CD24/CD44⁺ CA9 mRNA expression observed in this study might be an effort from cells to convert high acid production (H^+), the product of anaerobic glycolytic metabolism, through rehydration reaction of CO_2 to HCO_3^- . The HCO_3^- is then transported to the cell by a sodium bicarbonate co-transporter (NBC) or by a Na^+ dependent Cl^-/HCO_3^- exchange [20,21]. These conditions continue to lower the pHe as the incubation period extends.

4. Conclusion

The extracellular microenvironment modulation by hypoxia exposure increases the anaerobic glycolysis metabolism in BCSCs CD24/CD44⁺ by increasing glucose consumption, lactate production, LDH activity, and rapid decrease of pHe. The increase in anaerobic glycolysis is regulated by HIF1 α . These results show that the metabolic response to environmental change of BCSCs CD24/CD44⁺ is similar to that of normal cells. Therefore, the impact of BCSCs CD24/CD44⁺ metabolic changes as the response to the microenvironment disturbance toward stemness and survival must be studied further.

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