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Ferry Sandra

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Anti-cancer Potency and Mechanism of Human Umbilical Cord Blood Stem Cell

Ferry Sandra

Department of Biochemistry and Molecular Biology, Division of Oral Biology, Faculty of Dentistry, Universitas Trisakti, Jl. Kyai Tapa No.260, Jakarta, 11440, Indonesia.

Corresponding author: ferrysandra@gmail.com

Abstract. Human umbilical cord blood (hUCB) as a useful source of stem cell, has been kept in the stem cell bank and serves as a useful source as the last treatment option for severe illness in the future. In regards to immunogenicity, it has been reported that hUCBSC has low expression of HLA class I and II. In general, stem cell mechanism is not only through the incorporation of stem cell into the tissue, but stem cell can also secrete factors that can affect the surrounding cells. hUCBSC can induce apoptosis in cervical and lung cancer cells. hUCBSC can inhibit the growth of leukemic, cervical cancer and glioma cells. In addition, hUCBSC can inhibit invasion of glioma and lung cancer cells. Most of the reports showed that hUCBSC transplants are aimed for hematologic malignancies. There were low rates of malignant relapse after hUCBSC transplantation, suggesting that for patients at high relapse risk, hUCBSC could be the better option. hUCBSC showed as a good source for both dendritic and NK cells. Due to its high potency, hUCBSC should be developed further for the treatment of breast and other types of cancers.

Keywords: cancer, cord blood stem cell, dendritic cell, HLA, immunogenicity, NK cell.

INTRODUCTION

Human umbilical cord blood (hUCB) as a useful source of stem cell, can be collected immediately after parturition. hUCB stem cell (hUCBSC) has been kept in the stem cell bank [1] and serves as a useful source as the last treatment option for severe illness in the future [2]. In regards to immunogenicity, it has been reported that hUCBSC has low expression of HLA class I and II [3]. Therefore, the umbilical cord blood stem cell is a potential choice for allogeneic treatment, although partially human leukocyte antigen (HLA) mismatched [4].

hUCBSC has been widely studied for regenerative purposes, but it is also known that hUCBSC homes to not just injured tissues but also tumors [5]. hUCBSC can be affected, and at the same time, hUCBSC can also affect the tumor cells. In general, stem cell mechanism is not only through the incorporation of stem cell into the tissue, but stem cell can also secrete factors that can affect the surrounding cells [6]. The secreted factors are also known as secretome. In secretome, a broad panel of proteins including growth factors, chemokines and cytokines can be found.

EFFECT OF HUCBSC ON CANCER CELL

A study on leukemic cells showed that hUCB mesenchymal stem cells (MSC) inhibited proliferation of HL60 and K562 cells without inducing apoptosis. Growth inhibition was shown at the G0/G1 cell cycle. The p38 mitogen-activated protein kinase (MAPK) is important for the growth inhibitory effect of hUCB-MSC on HL60 and K562 cells [7].

In cervical cancer, secretome derived from conditioned media (CM) of hUCB mesenchymal stem cell (MSC) significantly induced apoptosis of HeLa cervical cancer cells in a concentration and time-dependent manner through

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the mitochondrial apoptotic pathway [8]. Also, CM-hUCB-MSC secretome might inhibit HeLa cells growth as well. The MSC, can be derived from various tissues, such as bone marrow [9], umbilical cord blood, Wharton jelly [10, 11], adipose tissue [12, 13], dental pulp and periodontal ligament [14, 15], is one of potential stem cell types to be used for allogeneic treatment [16]. MSC has been reported the potential for allogenic treatment since it has lack expression of human leucocyte antigen (HLA) class II [17].

Meanwhile, in glioma cells, hUCBSC has been reported to play a role in controlling glioma cell cycle progression and invasion. hUCBSC was shown to regulate U251 and 5 310 cells progression at the G0-G1 level by downregulating extracellular signal-regulated kinase (ERK), c-Myc, cyclin D1, cyclin-dependent kinase (CDK) 4 and CDK 6 [18, 19]. In addition, hUCBSC induced expression of Myc associated factor X (Max) dimerization protein (Mad) 1, that competitively bound to Max to repress the c-Myc/Max-mediated gene transcription [19]. Therefore, hUCBSC could regulate the expression of glioma cell cycle and ERK-associated invasion.

For lung cancer, the effects of hUCB-MSC on H1299 cells invasion and proliferation were evaluated using a Matrigel-based Transwell assay and Cell Counting Kit-8 assay, respectively. Results showed that the hUCB-MSC significantly inhibited invasion and induced apoptosis of H1299 lung cancer cells. The hUCB-MSC significantly suppressed AKT, phosphoinositide 3-kinase (PI3K), signal transducer and activator of transcription (STAT) three and mammalian target of rapamycin (mTOR) [20].

Based on these three studies, several conclusions can be made. hUCBSC can induce apoptosis in cervical and lung cancer cells. hUCBSC can inhibit the growth of leukemic, cervical cancer and glioma cells. In addition, hUCBSC can inhibit invasion of glioma and lung cancer cells. The potency of hUCBSC in other cancer cells should be explored further.

HUCBSC-DERIVED DENDRITIC AND NK CELL

Targeted therapy based on the monoclonal antibody (mAb) has been developed for the treatment of cancers. However, some of the mAbs have limited efficacy and need additional or other treatments. For example, in Ras wild type (WT) colorectal cancer, treatment of IgG1 mAb cetuximab has been reported to have limited efficacy. Meanwhile, there is potential therapy based on specific cells, namely dendritic and natural killer (NK) cells.

The hUCBSC-derived dendritic cell has been reported to have the ability to induce stronger antigen-specific immunity and more potent anti-tumor effects than peripheral blood mononuclear cell (PBMNC)-derived dendritic cells. The surface markers expression of hUCBSC-derived dendritic cells was higher than those of PBMNC-derived dendritic cells. The hUCBSC-derived dendritic cells had better antigen-presentation abilities, induced higher numbers of interferon (IFN)-γ-secreting antigen-specific $CD8^+$ T-cells, and stimulated more potent antigen-specific cytotoxic T-cell (CTL) activities. In addition, hUCBSC-derived dendritic cells had higher expression of ERK and phosphorylated Akt, and lower expression of phosphorylated p38, than PBMC-derived dendritic cells [21].

hUCBSC-derived NK cell-induced significantly higher cytotoxicity in epidermal growth factor receptor (EGFR)-Ras WT, EGFR-RASmut, and EGFR-BRAFmut colon cancer cells compared to activated peripheral blood-derived NK (a-PBNK) cells and equaled the cytotoxic efficacy of the combination of a-PBNK cells and IgG1 mAb cetuximab [22]. Large volume hUCBSC-derived NK cell production under good manufacturing practice (GMP) has been established in a fully closed, large-scale, cell culture bioprocess. The cryopreserved $CD34^+$ hUCBSC can be expanded 2 000 fold and differentiated into $CD56^+$ $CD3^-$ NK cell [23].

hUCBSC showed as a good source for both dendritic and NK cells. Therefore, both hUCBSC-derived dendritic and NK cells could be a potential modality to treat cancer. The hUCBSC-derived dendritic and NK cells could be suitable to diminish particular cancer cells.

HUCBSC TREATMENT AND CLINICAL TRIAL

Most of the reports showed that hUCBSC transplants are aimed for hematologic malignancies. hUCBSC has been acquired as a standard practice in pediatrics, and nowadays hUCBSC has been expanded to be practiced in adults as well. hUCBSC has been used for the treatment of acute leukemia in children and adults, chronic myeloid leukemia, myelodysplastic syndrome and lymphoid malignancies [24]. There were low rates of malignant relapse after hUCBSC transplantation, suggesting that for patients at high relapse risk, hUCBSC could be the better option. In addition, hUCBSC transplantation has lower rates of chronic graft versus host disease (GvHD) when compared with PBSC transplant [25]. hUCBSC-derived NK cell has been reported for treatment of acute myeloid leukemia (AML). Patients received 3×10^6 per kg body weight to 30×10^6 per kg body weight hUCBSC-derived NK cells

after lymphodepleting chemotherapy [26]. This study suggested hUCBSC-derived NK cells as a promising, potential "off-the-shelf" translational immunotherapy for AML.

hUCBSC transplants for breast cancer patient has been reported. Patients received a median of 9.9×10^6 expanded and unexpanded nucleated cells per kg body weight [27]. The study suggested that the CD34 selection and *ex vivo* expansion of hUCBSC prior to transplantation of hUCBSC was feasible. Another study in metastatic breast cancer has been reported as well. An *ex vivo* expansion system for hUCBSC, in which $CD34^+$ hUCBSCs were cultured. The patient received 1.83×10^7 per kg of total nucleated hUCBSCs and 7.7×10^4 per kg of CD34+ expanded and unexpanded hUCBSCs. Results showed that there were not acute adverse effects after infusion of the cultured hUCBSCs [28].

CONCLUSION

hUCBSC can induce apoptosis and inhibit the growth of cancer cells. In addition, hUCBSC can also inhibit the invasion of cancer cells. hUCBSC can be a good source for both dendritic and NK cells so that it can be "off-the-shelf" translational immunotherapy for AML. hUCBSC has been used for the treatment of hematologic malignancies in children and adults. For patients at high relapse risk, hUCBSC could be the better option. Due to hUCBSC lack expression of HLA, despite hematologic malignancies, hUCBSC treatment should be developed further for breast and other types of cancers.

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