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The Therapeutic Potential of X-Irradiated Umbilical Cord Blood Cells in Neuroregeneration and Tissue Repair Mechanism

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Abstract

Since regenerative therapy with stem cells is believed to exert an effect based on their proliferation and differentiation potential, anything that would cause the loss of these capacities, such as irradiation, may negate the anticipated effect. In this study, X-irradiated (XR) mononuclear cells were prepared from umbilical cord blood. Even though hematopoietic stem/progenitor cell activity was diminished in the XR cells, the regenerative activity was surprisingly conserved and aided recovery from experimental stroke in mice. Here, we provide evidence indicating the possible therapeutic mechanisms by which damaged cerebrovascular endothelial cells may be rescued by low-molecular-weight metabolites supplied by injected XR cells *via* gap junctions as energy sources to improve blood flow in the infarcted area. Thus, XR cells may exhibit tissue repair capabilities through the activation of endothelial cells, rather than *via* cell-autonomous effects.

Keywords: Hematopoietic stem/progenitor cells • Umbilical cord blood • Regenerative therapy • Tissue repair ability • XR cells

About the Study

Umbilical Cord Blood (UCB) is utilized as a source of transplantable hematopoietic stem cells for patients with hematological or metabolic disorders and has also become an important source of cells for regenerative therapy against non-hematological diseases, such as ischemic brain injuries [1]. Taguchi demonstrated that UCB-derived $CD34^+$ cells (Hematopoietic Stem/Progenitor Cells; HSPCs) can significantly improve motor and cognitive function in mice with experimentally-induced stroke [2]. Recently, this regenerative effect of UCB was confirmed in an early clinical trial involving adult patients with stroke [3]. However, how UCB-derived HSPCs induce neurological recovery in mice and humans with ischemic brain injury remained unclear. Surprisingly, Kikuchi-Taura reported that UCB-derived HSPCs accumulated at the brain injury site in stroke mice and transferred small-molecule metabolites into the cerebrovascular endothelium within just 10 min after cell [4]. This novel discovery led us to hypothesize that UCB-derived HSPCs do not require their hematopoietic ability, that is, their proliferating and multilineage differentiation capabilities, to trigger nerve cell regeneration *via* angiogenesis shortly after infusion.

Through trial and error, we attempted to deprive UCB-derived HSPCs of their hematopoietic ability. We investigated the efficacy of X-ray irradiation, which is widely used for blood component preparation for the prophylaxis of transfusion-related graft-versus-host experiments [5]. We determined that the optimal X-ray irradiation dose for the whole UCB sample was 15 Gy. Surprisingly, Mononuclear Cells (MNCs) isolated from UCB irradiated with a dose of 15 Gy or higher (named XR cells) exerted a significant effect on neurofunctional recovery in mice after experimental stroke similar to that of the parental pre-irradiated MNCs. We observed the transfer of low-molecular-weight materials from the injected XR cells to cerebrovascular endothelial and perivascular non-endothelial cells in the ipsilateral cortex 10 min after cell administration. This indicates that the therapeutic activity of UCB-derived MNCs is unlikely to change upon X-ray irradiation. Interestingly, the therapeutic effect of XR cells was not significantly attenuated even after freeze-thawing suggesting that XR cells can be frozen in a cell bank for storage [6].

To clarify how the initial small metabolic substance transfer described above promotes neuroangiogenesis, we analyzed short-term changes in the metabolic state of the brains of mice. XR cell-treated mice with experimental stroke showed significantly higher levels of glycolytic metabolites than those in PBS-treated mice 24 hrs after cell administration. In addition, energy metabolism was significantly activated in the XR cell-treated group *via* alternative pathways to glycolysis, such as gluconeogenesis. HSPCs remain in a high-energy state in an activated glycolytic system [7]. Accordingly, it is presumed that the transfer of metabolites derived from XR cells,

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particularly HSPCs, to damaged cerebrovascular endothelial cells activates energy metabolism in the brain. Concurrent with metabolic activation, cerebral blood flow markedly increased around the infarcted area. Surprisingly, the substances released from the injected XR cells were observed not only in cerebrovascular endothelial cells, but also in perivascular astrocytes (3 hrs after administration) across the blood-brain barrier, which likely contributes to that significant increase in the number of branches and dendritic spines at the border of the infarction area.

Based on these findings, the following conclusions can be made regarding the mechanisms underlying the therapeutic effects of XR cells on ischemic brain injury: 1) The action targets of XR cells are cerebrovascular endothelial cells; 2) XR cells may rescue damaged endothelial cells resulting from the disruption of energy metabolism under ischemic conditions by delivering low-molecular-weight metabolites that can be utilized as energy sources; 3) these metabolic changes may promote neo-angiogenesis followed by improved cerebral blood flow in the infarction area; and 4) XR cells also supply low-molecular-weight metabolites to perivascular neural cells such as astrocytes, enabling rapid restoration of neurological functions. Notably, these rapid mechanisms of action do not require the administered cells to remain in the infarcted area for an extended period.

After determining the mechanism of action, the safety of the XR cells was examined. The proliferative capacity of T lymphocytes was completely abolished by 15 Gy X-ray irradiation. When $CD34^+$ cells purified from either XR cells or pre-irradiated MNCs were infused into immunodeficient mice, the pre-irradiated $CD34^+$ cells efficiently reconstituted the human hematopoietic system in all recipients, as expected, whereas the X-irradiated $CD34^+$ cells did not, even after increasing the number of XR cells administered by 20 times that of the pre-irradiated cells. In addition, no abnormal findings, such as tumorigenesis or inflammation, were observed in any organ in any of the recipients after cell therapy. Collectively, these results show that X-ray irradiation of whole UCB samples achieved complete deprivation of both the lympho-hematopoietic capacity of HSPCs and the transforming ability of T-lymphocytes, preventing the risk of adverse alloimmune reactions as well as tumorigenicity, which are associated with XR cell administration. These preclinical outcomes support the safety of XR cells, which is crucial for their clinical application. As indicated by the findings of the present study, the promotion of tissue regeneration is an intrinsic property of HSPC, in addition to their conventional self-renewal and multilineage-differentiation capacities. However, there are still some unknown aspects of HSPCs in UCB (Figure 1).

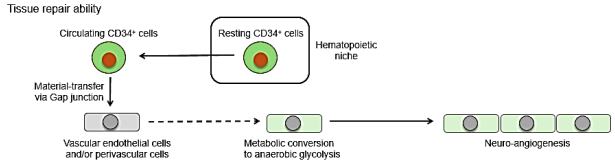

Figure 1: Tissue repair ability of HSPCs. HSPCs can repair tissues independently of their conventional hematopoietic activity. The direct binding of HSPCs to vascular endothelial cells, mainly *via* GAP-junctions, serves as a foundation for the intercellular transport.

of small sub-1.5 kDa molecules from HSPCs to endothelial cells. Anaerobic glycolytic metabolism in HSPCs may induce cell-to-cell chain reactions during metabolic conversion in vascular endothelial cells, eventually promoting angiogenesis, that is autonomous replication. However, the physiological role of circulating HSPCs in neonatal and adult survival remains unclear.

What is unclear

- Do circulating $CD34^+$ cells in UCB reach the bone marrow to act as hematopoietic stem/progenitor cells under physiological condition?
- Is the cell-to-cell movement of microRNAs, high molecular weight proteins, mitochondria and other cell organelles through tunneled nanotubes also involved in tissue repair?
- The $CD34^+$ cells in UCB are very effective for subacute stroke treatment, but are they equally effective in the chronic phase?
- Does this neuro-angiogenesis-promoting effect also apply to the repairs in other tissues?

What is the mechanism by which HSPCs exit neonatal bone marrow into the peripheral bloodstream? What is the physiological role of circulating HSPCs during the neonatal period? Are circulating HSPCs involved in tissue maintenance in steady-state adulthood? XR cells may provide important clues for solving these questions.

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