

Center for Stem Cell Biology and Regenerative Medicine

Division of Cell Engineering

幹細胞基盤技術研究分野

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Our studies focus mainly on investigation of stem cell biology using the hematopoietic stem cell (HSC) as a research model. Recent identification of a variety of stem cell sources including embryonic and somatic (tissue-specific) stem cells has brought about substantial progress in the field of stem cell research.

1. Purging myeloma cell contaminants and simultaneous expansion of peripheral blood-mobilized stem cells

Kantaro Ishitsuka, Hidekazu Nishikii, Takaharu Kimura, Ayano Sugiyama-Finnis, Satoshi Yamazaki

Human hematopoietic stem cells (HSCs) are widely used as a cellular source for hematopoietic stem cell transplantation (HSCT) in the clinical treatment of hematological malignancies. After transplantation therapy, delays in hematopoietic recovery due to insufficient donor-derived HSCs can lead to increased risks of life-threatening infections and bleeding. Our previous studies developed an efficient ex vivo expansion culture medium (3a medium) for umbilical cord blood-derived HSCs (CBSCs), offering a potential solution to this problem. Nevertheless, the broader applicability of our culture method to alternative cell sources and, of greater significance, its efficacy in eliminating potentially disease-associated contaminated tumor cells, especially in autologous transplantation, raise critical clinical questions. In this study, we modified the 3a medium by incorporating UM729 to replace UM171, adding FMS-like tyrosine kinase 3 (Flt3) ligand, and adjusting the concentrations of butyramide, 740Y-P, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (PCL-

PVAc-PEG, Soluplus) to create the modified-3a medium. This sophistication allowed the efficient expansion of not only CBSCs but also peripheral blood-mobilized HSCs (PBSCs). Additionally, we successfully removed contaminated myeloma cells by adding bortezomib and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) at appropriate concentrations, although we maintained HSCs through the addition of lenalidomide. Our research findings present the potential for widespread clinical application of the modified-3a medium and suggest a safe ex vivo culture technique for expanding human HSCs within peripheral blood-derived donor grafts used for autologous HSCT.

2. Activated mesenchymal stem/stromal cells promote myeloid cell differentiation via CCL2/CCR2 signaling

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Myeloid cells, which originate from hematopoietic stem/progenitor cells (HSPCs), play a crucial role in mitigating infections. This study aimed to explore the impact of mesenchymal stem/stromal cells (MSCs) on

the differentiation of HSPCs and progenitors through the C-C motif chemokine CCL2/CCR2 signaling pathway. Murine MSCs, identified as PDGFR α ⁺Sca-1⁺ cells (PaS cells), were found to secrete CCL2, particularly in response to lipopolysaccharide stimulation. MSC-secreted CCL2 promoted the differentiation of granulocyte/macrophage progenitors into the mye-

loid lineage. MSC-derived CCL2 plays an important role in the early phase of myeloid cell differentiation in vivo. Single-cell RNA sequencing analysis confirmed that CCL2-mediated cell fate determination was also observed in human bone marrow cells. These findings provide valuable insights for investigating the in vivo effects of MSC transplantation.

Publications

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