Center for Experimental Medicine and Systems Biology

Division of Cell Regulation
細胞制御研究分野

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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. Understanding genetic heterogeneity in gene-edited hematopoietic stem cell products

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CRISPR/Cas gene editing has transformed genetic research and is poised to drive the next generation of gene therapies targeting hematopoietic stem cells (HSCs). However, the installation of the "desired" edit is most often only achieved in a minor subset of alleles. The array of cellular pathways triggered by gene editing tools produces a broad spectrum of "undesired" editing outcomes, including short insertions and deletions (indels) and chromosome rearrangements, leading to considerable genetic heterogeneity in gene-edited HSC populations. This heterogeneity may undermine the effect of the genetic intervention since only a subset of cells will carry the intended modification. Also, undesired mutations represent a potential safety concern as gene editing advances toward broader clinical use. Here, we will review the different sources of "undesired" edits and will discuss strategies for their mitigation and control.

2. Purging myeloma cell contaminants and simultaneous expansion of peripheral blood mobilised stem cells.

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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, raises critical clinical questions. In this study, we modified the 3a medium by incorporating UM729 to replace UM171, added Flt3 ligand, and adjusted the concentrations of butyzamide, 740Y-P, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (PCL-PVAc-PEG, Soluplus®) to create the modified 3a medium. This sophistication allowed efficient expansion of not only CBSCs but also peripheral blood mobilized HSCs (PBSCs). Additionally, we successfully removed contaminated myeloma cells by adding bortezomib and TNF-related apoptosis inducing ligand (TRAIL) at appropriate concentrations, while maintaining 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.

Publications

Becker HJ, Yamazaki S. Understanding genetic heterogeneity in gene-edited hematopoietic stem cell products. Exp Hematol. 2023 Nov 29:S0301-472X(23)01770-8. doi: 10.1016/j.exphem.2023.11.007. Online ahead of print.PMID: 38036097

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