HANDBOOK OF STEM CELLS

VOLUME 2

Adult and Fetal

干细胞手册

第二卷：成体和胎儿干细胞

EDITORS
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北京

图字:01-2006-0538 号

This is an annotated version of
Handbook of Stem Cells
Robert Lanza et al. eds.

ISBN 0-12-436643-0

Published by arrangement with **Elsevier Pte Ltd.**

图书在版编目(CIP)数据

干细胞手册=Handbook of Stem Cells/(美)兰扎(Lanza,R.)等编. —北京:科学出版社,2006
(Elsevier 英文原版名作中文导读系列)
ISBN 7-03-016709-0
Ⅰ.干… Ⅱ.兰… Ⅲ.干细胞-手册-英文 Ⅳ.Q24-62
中国版本图书馆 CIP 数据核字(2005)第 155558 号

责任编辑:马学海 盖 宇
责任印制:钱玉芬/封面设计:耕者设计工作室

科学出版社 出版
北京东黄城根北街16号
邮政编码:100717
http://www.sciencep.com
中国科学院印刷厂 印刷
科学出版社发行 各地新华书店经销
*
2006 年 1 月第 一 版 开本:889×1194 1/16
2006 年 1 月第一次印刷 印张:116 1/2 插页:4
印数:1—2 500 字数:2 749 000
定价:320.00 元(全二卷)
(如有印装质量问题,我社负责调换〈科印〉)

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Preface

New discoveries in the field of stem cells increasingly dominate the news and scientific literature. Wave upon wave of papers has led to an avalanche of new knowledge and research tools that may soon lead to new therapies for cancer, heart disease, diabetes, and a wide variety of other diseases that afflict humanity. The *Handbook of Stem Cells* integrates this exciting area of biology, combining in two volumes the prerequisites for a general understanding of adult and embryonic stem cells; the tools, methods, and experimental protocols needed to study and characterize stem cells and progenitor populations; as well as a presentation by the world's experts of what is currently known about each specific organ system. No topic in the field of stem cells is left uncovered, including basic biology/mechanisms, early development, ectoderm, mesoderm, endoderm, methods (such as detailed descriptions of how to derive and maintain animal and human embryonic stem cells), application of stem cells to specific human diseases, regulation and ethics, and patient perspectives from Mary Tyler Moore (diabetes) and Christopher Reeve (spinal cord injury). The result is a comprehensive two-volume reference that will be useful for students and experts alike. It represents the combined effort of 12 editors and more than 300 scholars and scientists whose pioneering work has defined our understanding of stem cells.

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序　言

干细胞领域的新发现越来越影响着新闻和科学文献。大量文章的出现引发的新知识和研究手段的涌现，最终将产生针对肿瘤、心脏病、糖尿病，以及影响人类健康的许多其他疾病的新的治疗手段。《干细胞手册》这部书分为上下两册，整合了该领域有关成体干细胞和胚胎干细胞必备的生物学知识、手段、方法、研究和描述干/祖细胞的特征所用的实验方案，以及国际专家对于每一个特定的器官系统相关知识发展现状的介绍。干细胞领域的所有主题无一例外地收录其中，包括基础生物学/机制、早期发育、外胚层、中胚层、内胚层、方法（例如如何分离和培养动物和人胚胎干细胞的具体描述）、针对特定人类疾病的干细胞的应用、法规与伦理，以及分别来自 Mary Tyler Moore（糖尿病患者）和 Christopher Reeve（脊髓损伤患者）的观点。这两册书将成为学生和科研人员必备的全面的参考书目，它们凝集了 12 位编辑和超过 300 位学者和科学家的共同努力，正是他们开拓性的工作使得我们对干细胞有了精确的理解。

Robert Lanza，MD
波士顿，马萨诸塞州

前　言

众所周知，关于细胞移植的事件都源自于二战结束之后。最初发现小鼠经过注射脾或骨髓细胞之后能够抵御致命的辐射损伤。起初假设这些是由于脾脏或者骨髓内体液因子的保护作用，可是这些保护作用可能源自于活细胞的假设被一些实验结论所推翻。细胞遗传学和皮肤移植的研究证实保护辐射损伤的原因是细胞假说而不是体液假说。

早期的研究者意识到在脾脏和骨髓内一定存在着某种类型的种子细胞，它们能够形成再生的骨髓组织。这些细胞被称为干细胞，但是找到干细胞存在的证据是一个长期的艰巨过程；之后在近交系小鼠内进行了数以千计的实验以阐明成功的细胞移植所需的条件，并且描述了其中涉及的免疫学现象。狗成为了一个补充近交系和杂交系动物品系之间空缺的实验模型，因为大多数情况下，医生总是试图通过从动物实验结果中获取的知识用于解决人类疾病，然而应用这些通过动物实验结果获取的知识解决骨髓移植问题时却导致患者出现了严重的并发症，包括免疫缺陷疾病、白血病和再生障碍性贫血等；到了 20 世纪末，骨髓、外周血以及脐带血来源的造血细胞移植已经成为治疗许多类型疾病的主要手段。

随着研究工作的深入，干细胞被成功地分离和鉴定。尽管进行了很多实验，人类干细胞的体外扩增培养依旧非常困难。人类干细胞的基因治疗研究充满了吸引力但是困难重重。长期以来一直假定造血干细胞只能产生造血细胞，但是最近令人振奋的实验数据提示骨髓干细胞能够产生其他组织类型的细胞包括肝、心脏甚至是中枢神经系统细胞。实验结果表明骨髓、肝、心脏等组织器官有它们自己的干细胞，而且这些干细胞不是组织特异性的。干细胞的可塑性、或者说横向分化研究已经成为干细胞领域的一个主要的研究课题。从胚胎组织中获取干细胞的技术不断进步并且提供了更广阔的应用前景。应用这些干细胞治疗那些难以治愈疾病成为可能。

因此，在 21 世纪之初，我们开始着手完成这项工作——编写《干细胞手册》。这本分上下两卷的手册汇集了干细胞研究不同领域的很多研究者辛勤的工作积累。很明显地，干细胞研究是飞速发展的学科，需要更多的工作去验证目前的假说，这本手册为那些致力于这项工作的人们提供了最基本的信息。

E. Donnall Thomas，(Hon)

Foreword

Almost everything we know about cell transplantation dates to the end of World War II. It was found that mice could be protected against otherwise lethal irradiation by an injection of spleen or marrow cells. At first it was hypothesized that the protection was caused by a humerol factor in the spleen or marrow preparations. That the protection might be caused by living cells seemed to be ruled out by several experiments. However, cytogenetic and skin transplant studies made it clear that the cellular hypothesis rather than the humoral hypothesis was the explanation for the irradiation protection phenomenon.

The early investigators recognised that there must be some kind of seed cell or cells in the spleen or marrow preparations that generated the repopulated marrow. These cells came to be called stem cells, but the search for the elusive stem cell became a long and complicated one. There followed thousands of experiments in inbred mice that clarified the requirements for successful cell transplants and described the immunological phenomena involved. The dog became a model for bridging the gap of knowledge between inbred mice and outbred species. As is often the case, physicians were driven to attempt to alleviate human disease by the application of knowledge gained from studies of animal systems. Application of this knowledge to human marrow transplantation began to produce results in patients with fatal disorders such as immunodeficiency disease, leukemia, and aplastic anemia. By the end of the twentieth century, transplantation of hematopoietic cells from marrow, blood, or cord blood had taken its place in the therapeutic armamentarium against an ever-increasing number of diseases.

As work continued, stem cells were isolated and characterized. Despite many studies, the expansion of human stem cells by *in vitro* culture proved to be difficult. Gene therapy of human stem cells remained an attractive but elusive goal. It had long been assumed that hematopoietic stem cells would produce only hematopoietic cells, but intriguing data began to suggest that marrow stem cells might generate other tissues such as a liver, a heart, or even a central nervous system. These and other tissues and organs seemed to have their own stem cells, and these stem cells might not be lineage specific. The plasticity of stem cells, or transdifferentiation, became a major subject of study. Techniques for obtaining stem cells form embryonic tissues were developed and seemed to offer even greater utility. Application of these stem cells to a variety of otherwise incurable human diseases became a possibility.

Thus, at the beginning of the twenty-first century, the stage was set for this work, *Handbook of Stem Cells*. This two-volume book is a much-needed attempt to bring together the cumulative work of many investigators in widely diverse aspects of stem cell studies. Clearly, this field is a work in progress. Much more work will be needed to fulfill the exciting promise of stem cell research. This handbook provides essential information for those who undertake this challenge.

E. Donnall Thomas, (Hon)

胚胎干细胞和成体干细胞的比较：一些看起来简单的问题

由于得到了很多研究者对本书的大力帮助，使得我们能够阐明很多干细胞领域的研究进展。然而仍有很多看起来很简单的问题却难以解释和回答。

怎样定义干细胞

教科书上的定义是干细胞是一群这样的细胞，它们能够分裂产生一个子代的干细胞和另一个产生分化细胞的子代细胞。这个定义适用于解释受精卵以及在发育过程中的一些现象。全能性的胚胎干细胞（ES 细胞）很容易从内细胞团或胚体的生殖嵴中获得。但是获得 ES 细胞的时间段在内细胞团仅仅限制在 4～6 天，而在鼠胚胎生殖嵴中获取 ES 细胞的时间稍稍靠后，那么获取永生化的 ES 细胞的时间窗关闭之后，它们的子代细胞又在哪里呢？我们也许被 ES 细胞能在适当的培养条件下无限繁殖这一现象所迷惑，在体内它们有着有限的生命周期，而且随着胚胎的发育它们逐渐消失。一个更引起兴趣的简单答案是它们可能成为了造血系统的干细胞和那些成体脊椎动物非造血系统中最近发现的干细胞样的细胞。

成体组织中干细胞样的细胞和 ES 细胞有什么区别

一个答案是 ES 细胞很容易分化为所有的细胞表型，然而大多数的从骨髓基质、脂肪、肌肉和神经组织中分离得到的成体干细胞只有有限的分化能力，而且大多数的成体干细胞和 ES 细胞相比有着有限的生命周期。这些观察到的区别足以证实从事成体干细胞分化潜能和扩增能力研究的科学家具有足够的聪明智慧。但是我们有那么聪明吗？将一个完全分化细胞的细胞核移植入去核的胚体中发生重编程的核移植实验又说明了什么？尽管很多核移植实验失败，但那些成功的核移植实验说明任何细胞只要将细胞浆的正确信号发送给细胞核都可以成为干细胞。因此从一个受精卵发育到 ES 细胞到成体干细胞再到任何分化的细胞这一连续的过程中可能是可逆的；如果这个观点是正确的，那么在 ES 细胞、成体干细胞以及完全分化的细胞之间的分化区别又可能转变为哪些步骤是可逆的以及由分化细胞逆转再生为多能和永生化细胞的难度有多大。

ES 细胞或者成体干细胞哪一个能更好地用于治疗和组织工程研究？

一些非常杰出的科学家已经针对这个问题作出了简单的答案：一些合适的 ES 细胞和某些特定类型的成体干细胞可以用于治疗和组织工程研究。随着时间的推移，有必要进行深入的研究来回答这个问题。应用异体 ES 干细胞有导致瘤性以及免疫反应的危害。成体干细胞没有出现明确的致瘤性，而且一些类型的成体干细胞可以通过一定手段扩增获得合适的数量以应用于自体治疗。然而，没有一种干细胞可以非常理想地应用于所有的实际应用。ES 细胞被证明是个理想的选择用于器官再生研究并且有效解决伦理和技术上的难题。成体干细胞能够更有效地修复由于损伤、疾病和老龄性改变导致的组织和器官损伤。最近的实验研究不断有证据支持成体干细胞是人体用于组织修复的天然组成部分的观点。研究表明：对于组织损伤最初的反应似乎是内源性干细胞样细胞的增殖和分化。当内源性的干细胞样细胞枯竭的时候，来源于骨髓的非造血系统的干细胞就会聚集到损伤部位行使修复功能。而且，实验结果

显示聚集到损伤部位的成体干细胞行使修复功能有以下机制：分化为适合的细胞表型；提供细胞因子和其他类型的因子以增强内源性细胞的修复功能；以及细胞融合，一种可以提供干细胞快速分化的机制。

总结

我们目前处在胚胎干细胞和成体干细胞研究的快速发展阶段。势必会出现相关的概念和教条推陈出新的现象。目前干细胞的分化潜能研究和临床应用仍有很多受限制的地方，但是我们远未充分认识这些限制，尤其是因为我们还不能准确地把握干细胞的关键性的生物学特征，所以我们仍将依赖现有的复杂的生物系统去深入研究这个课题。

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