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MEETING REPORT

THE STANDPOINT OF STEM CELL RESEARCH

A REPORT ON THE 9TH ANNUAL MEETING OF THE INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

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SUMMARY

The 9th Annual Meeting of the International Society for Stem Cell Research (ISSCR) focused particularly on topics related to the engineering and characterization of induced pluripotent stem cells through reprogramming of mammalian somatic cells, embryonic and adult stem cells of different species, tissue regeneration, stem cell transplant and cancer stem cells. This report summarizes the standpoint of stem cell research programs based on the proceedings of the meeting.

INTRODUCTION

This year, the 9th Annual Meeting of the International Society for Stem Cell Research (ISSCR) was held on June 15-18, 2011, in Toronto, Canada. The meeting was very well organized and attended by investigators from all over the world. Several topics were presented and discussed. A major emphasis was placed on the production and characterization of induced pluripotent stem (iPS) cells through artificial reprogramming of human and murine somatic cells, the biology of embryonic and adult stem cells of various species, tissue regeneration, stem cell transplant and cancer stem cells (the ISSCR meeting website is available at http://www.isscr.org/meetings/index.cfm). For practical reasons, this commentary can only discuss the reports that best represent the current standpoint of stem cell research programs and possibly lead to novel discoveries.

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INDUCED PLURIPOTENT STEM CELLS

The possibility of reprogramming human somatic cells into iPS cells has attracted a great deal of interest in the field of stem cell research (1-7). Undoubtedly, the use of iPS cells has circumvented the ethical issues and controversies associated with the use of human embryonic stem (ES) cells. In addition, iPS cell-derived cells and/or tissues can be utilized from autologous transplant therapy in patients, in contrast to human ES cell-derived cells and/or tissues (1-4).

At least three defined factors are required to reprogram the epigenetic pattern of human and murine somatic cells into a pluripotent state. Such defined factors are octamer-binding protein 4 (Oct-4), Krueppel-like factor 4 and transcription factor SOX-2 (1, 2). Initially, proto-oncogene c-Myc was also included in the pool of reprogramming factors (1-3). Studies are currently in progress to address the issue of the development of iPS cell-derived malignancies and to better elucidate the mechanism of somatic cell epigenetic reprogramming, which is still not completely understood (1-9). It was observed that even a single iPS cell clone might be heterogeneous, although it is derived from a single somatic mammalian cell. This can be explained by the fact that the induction into a pluripotent state requires several cell divisions, which cannot be completed by the four exogenous reprogramming factors alone (3). In fact, a number of other cellular factors are thought to come into play in order to achieve a full reprogramming of somatic mammalian cells (3), including: transcription activator BRG1 (9); specific microRNA molecules (10); inhibition of tumor suppressor proteins such as p53 (11, 12), retinoblastoma-associated protein (pRb) (11) and ribonuclease P protein subunit p21 (12); TGF-β inhibitors or vitamin C (13); histone

deacetylase (HD) inhibition (13); and the protein Wnt signaling system (13, 14). Naturally, a better elucidation of the mechanism for the reprogramming of somatic cells may optimize the production of more homogeneous iPS cell populations (3, 9-14). The necessity to inhibit tumor suppressor genes for the reprogramming of somatic cells into a pluripotent state was already discussed at the 8th ISSCR meeting that was held last year in San Francisco (3).

Interestingly, one report showed that it is possible to reprogram dermal murine fibroblasts directly into chondrogenic cells without the establishment of an intermediate iPS cell line (15). In this study, two reprogramming factors (c-Myc and Krueppel-like factor 4) were cotransduced into murine dermal fibroblasts along with transcription factor SOX-9, which is a chondrogenic factor. This combination allowed for the direct in vitro production of chondrogenic cells from fibroblasts (15).

Another important application of iPS cells consists of generating useful patient-specific cell culture models for the study of various pathological conditions. In this respect, studies were conducted for cystic fibrosis (16), Rett syndrome (17), chronic infantile neurological, cutaneous, and articular (CINCA) syndrome (18), type 1 diabetes (14), cardiovascular disorders (19), retinal ischemic diseases (20) and familial dysautonomia (21). These studies hold great potential in terms of elucidating the pathogenesis of human disorders for which there are no suitable animal models, establishing novel diagnostic systems, the development of novel therapeutic approaches and screening for drug discovery.

EMBRYONIC STEM CELLS

Some reports were presented on the characterization of the biology of human and murine ES cells. The majority of these studies focused on the mechanism of self-renewal (22).

The canonical homeobox protein NANOG–Oct-4–SOX-2 axis was described in the context of human ES cell self-renewal and/or differentiation into specific cell lineages. Each of these three factors was inhibited with a specific siRNA in order to determine the effects in terms of cell differentiation program. It was found that NANOG inhibition resulted in the induction of neuroectodermal markers in progeny cells, whereas other germ cell layer markers were not detectable. Instead, Oct-4 inactivation exhibited two distinct patterns of cell differentiation. Human ES H9 cells were induced along the neuroectodermal lineage, whereas human ES H1 and many other human ES cell types were induced into trophectoderm and endoderm. Silencing of SOX-2 did not result in any specific cell differentiation program in human ES cells (23).

Studies on murine ES cell self-renewal and/or transcriptional programs investigated the role of DNA methylation (24-26), chromatin modification (27), histone variant H2A.X (28) and the ubiquitin proteasome system (29). The latter is an innovative research project aiming at characterizing the role of post-transcriptional modifications in regulating murine ES cell differentiation. This study showed that the expression of E3 ubiquitin-protein ligase F-box/WD repeat-containing protein 7 is dynamically associated with murine ES cell differentiation. Moreover, siRNA-mediated silencing of F-box/WD repeat-containing protein 7 resulted in inhibition of murine ES cell differentiation (29).

SOMATIC STEM CELLS

The mechanism of self-renewal and/or differentiation programs was also investigated in the context of somatic stem cells of various tissues, such as the nervous system (30), the hematopoietic compartment (31, 32) and muscle tissues (33). Typically, these studies focused on the following factors: the Wnt pathway in muscle stem cells (33); environmental factors, such as growth factors and cytokines in neural stem cell lineage progression (34); collagen alpha-1(XVII) chain (*COL17A1/BP180/BPAG2*), which is a component of the niche for melanocyte stem cells (35) and is also required for the maintenance of hair follicle stem cells via regulation of self-renewal program; the role of metabolism-induced reactive oxygen species (ROS) and hypoxia-inducible factor 1-α (HIF-1-α) stimulation in regulating the induction and expansion of hematopoietic stem cells (36); the role of the *Flamingo* gene family member *CELSR2* (cadherin EGF LAG seven-pass G-type receptor 2) in maintaining hematopoietic stem cells (37); the α-catenin downstream effector termed Yorkie homolog (*YAP1*) in controlling the epidermal stem cell proliferative program (38); the function of subdermal adipocytes as components of the microenvironment for epidermal stem cells (39); and the protein Wnt–PGE_2 pathway in the hematopoietic stem cell self-renewal program (40).

The study of ROS and HIF-1-α stimulation in regulating hematopoietic stem cell fate may represent a very useful model for the investigation of metabolic-related disorders, such as obesity, diabetes and the clinical complications that are associated with these pathological conditions (36).

CANCER STEM CELLS

The isolation and characterization of cancer stem cells from various types of malignancies changed entirely the focus of cancer research (3, 41-45). Tumors originate from highly specialized, rare subpopulations of malignant cells that are termed cancer stem cells, which are also responsible for the maintenance and reconstitution of the tumor mass following chemo- and/or radiotherapy. Cancer stem cells derive from the malignant transformation of tissue-specific somatic stem cells (Fig. 1) (3, 41-44). On these grounds, cancer stem cells retain most of the somatic stem cell properties, such as self-renewal and differentiation programs, multidrug resistance (41, 42) and enhanced resistance to apoptosis induced either by chemo- or radiotherapy (3, 41-44).

Reports discussed the role of a variety of factors in the biology of cancer stem cells, such as: the protein Wnt target gene *LGR5* in colon cancer stem cells (45); the requirement for histone deacetylase 6 (HD6) for the expression of the cancer stem cell marker CD133 (46); and the role of polycomb repressive complex 2 (PRC2) in the development of hematopoietic and solid tumors (47). Other studies are addressing the complex issue of determining the genetic factors that are required by cancer stem cells to give rise to tumors in the context of human primary basal-like breast cancer stem cells (48), human leukemia (49) and human neoplastic neural stem cells (50).

The targeting of the CD133/HD6/Wnt axis and/or PRC2 may allow for the development of novel therapeutic approaches for the treat-

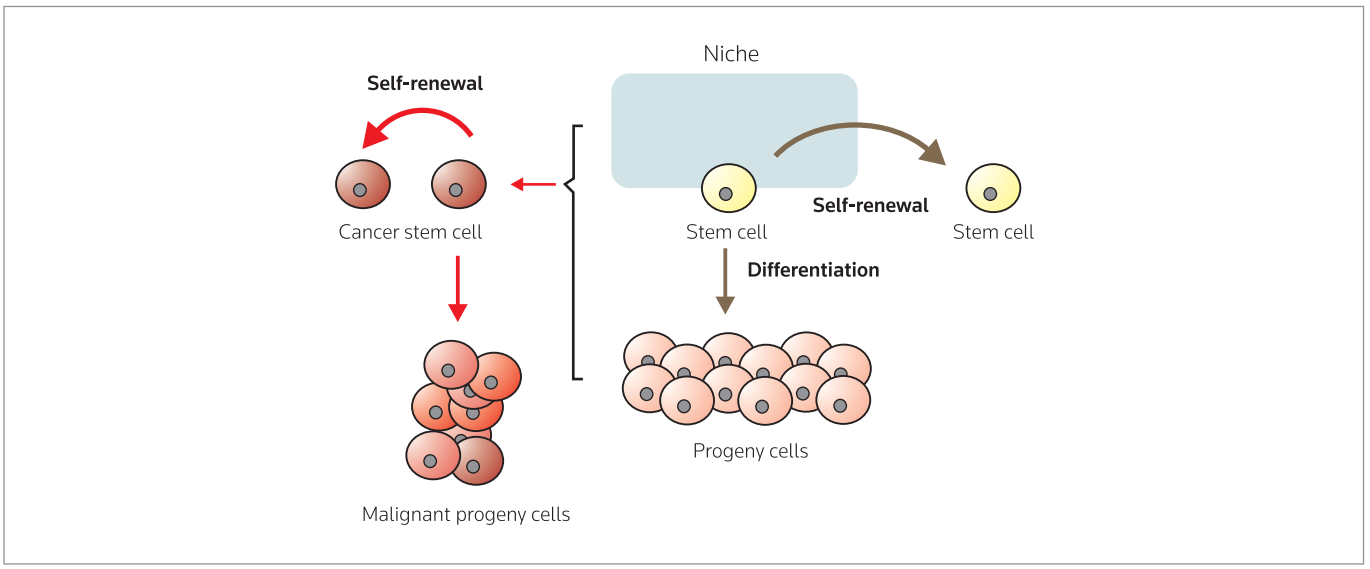

Figure 1. The niche, or microenvironment, is a critical component for controlling the fate of adult stem cells, which can either undergo symmetric cell division for a self-renewal program, or asymmetric cell division with self-renewal and differentiation. On the other hand, the deregulation of the factors involved in the control of the biology of adult stem cells may lead to malignant transformation, which gives rise to a so-called cancer stem cell, which in turn generates a very heterogeneous cancer cell population.

ment of multiple types of malignancies, whereas genetic studies on cancer stem cells may identify new targets in cancer therapy.

CONCLUSIONS

The 9th Annual Meeting of the ISSCR reported certain progress in the field of stem cell research. Nevertheless, the investigation of stem cell biology still demands an enormous effort from investigators.

The possibility of reprogramming human somatic cells into iPS cells may circumvent the ethical issues associated with the use of human ES cells. In addition, iPS cells have the potential to generate patient-specific cells and/or tissues for autologous transplant therapy, for the study of a wide variety of human maladies and for screening new drugs. Indeed, iPS cell technology has had a profound impact in the field of stem cell research.

Cancer stem cell biology is another very important research field in the sectors of oncology and stem cell biology. The isolation and characterization of cancer stem cells from various types of human malignancies shed very useful insight into the mechanisms of carcinogenesis and progression of the disease. Lastly, the study of cancer stem cell biology may lead to the development of novel diagnostic tools and therapeutic approaches.

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DISCLOSURES

The author states no conflicts of interest.

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