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COMMUNICATION

Proteome biology of stem cells

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Abstract The notion that integration of cutting-edge technologies in stem cell research would be enhanced by proteomic analyses has emanated from rapid advances in proteome technology. These advances have increased the probability that basic properties of stem cells will be elucidated more effectively, leading to acceleration toward novel stem cell therapies. We have therefore sought to establish a world-wide alliance of proteomics and stem cell researchers, which has resulted in the foundation of an initiative supported by the Human Proteome Organisation (HUPO) and the International Society for Stem Cell Research (ISSCR) called the Proteome Biology of Stem Cells Initiative. Here we report on the rationale and goals of this initiative.

Stem cells

Stem cells are an area of biomedical research receiving broad attention in the scientific literature and in the media elsewhere. This attention has been inspired by the notion that human embryonic stem cells have the unique property to form all cells in the human body, once they receive the proper signals. The control of this property in vitro would offer tremendous opportunities to develop treatments of diseases that cannot be cured today, especially in the area of regenerative medicine where the aim is to replace damaged tissue, particularly in organs where capacity for repair is inherently low (e.g., pancreas, heart, nervous system). The approach is of proven value in the clinic, in that hematopoietic stem cells offer curative options in a number of diseases. But there is requirement for other kinds of cell types for cellular therapies and there is a great deal of promise that these can be derived from human embryonic stem cells. Thus, intensive efforts have been and are being put into multiple approaches aimed at developing stem cell therapies, from defining standardized culture conditions for expansion of stem cell lines, to designing and optimizing strategies for directed differentiation to specific cell lineages, and, in the long term, to finding ways to implant cells with the required properties in animals and humans without challenging the immune system. Apart from these clinically orientated applications, there is great interest in using human stem cells and their differentiated derivatives in drug and toxicology screening. Our understanding of most of the basic cellular process underlying stem cell self-renewal, maintenance, and differentiation is still very

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limited, and it will be essential to expand our knowledge if stem cells are also to reach their full potential in this area.

Our increased understanding of hematopoietic stem cell biology (such as the role of HoxB4 in stem cell expansion) was derived from basic research programs and offers new options for deriving populations for cell-based therapies. The same basic understanding derived from embryonic stem cell research will similarly support clinical developments. As such, applying the most advanced systematic techniques to embryonic stem cell studies is an essential adjunct to current research approaches.

Proteomics

Proteomics is a technology platform that aims to characterize proteins in their biological context in a medium- to high-throughput scenario. This field was mainly technology-based, driven initially by the development of mass spectrometers with the speed and sensitivity amenable to large-scale analysis of peptides, followed by sophisticated miniaturized chromatographic systems. Proteomics has more recently been complemented by an expanding toolbox of bioinformatic applications that have allowed the interpretation of large sets of mass spectrometric data. As a result, proteomics today includes a multitude of techniques, such as fractionation strategies for cell organelles and enrichment steps for the selective isolation of specific classes of proteins or peptides (e.g., to identify specific posttranslational modifications critical in regulating cell fate). A wide variety of mass spectrometers are now available for the confident identification of proteins using either commercial or open source software tools. The strength of this set of techniques is its flexibility in being adapted to the biological question that needs to be addressed. Most importantly, the ability to relatively or absolutely quantify proteins in different cell populations allows proteomics to move to a new level. With a large body of effective technology in place (and more sensitive instruments in the pipeline), the true challenge now is to integrate proteomics into the full spectrum of biological and biomedical research, challenging the creativity of both the biologist and the analytical chemist and demanding a dialogue between these research communities.

Proteome biology of stem cells

Considering the many challenges in stem cell biology, there is a pressing need for the implementation of cutting-edge approaches such as proteomic applications. This need is beginning to be realized by a growing number of scientists who have started to chart the proteome of individual primary stem cells and stem cell lines and their differentiated derivatives, to define a subset of stem-cell-specific proteins, or to identify differentiation-specific proteins that can be used as benchmarks for the intermediate or terminal steps of differentiation of cells. Critically, these approaches are also providing clues to the signal transduction pathways and transcription factor cascades that drive each differentiation step. Importantly, recent work on stem cells using proteomics has shown that transcriptome analyses do not give a full guide to developmental change in stem cells and protein interactions (which can only be discovered systematically using proteomic approaches). Thus, certain concepts of processes regulating development will only be determined by analysis at the proteome level. However, stem cell biology and proteomics are both highly specialized scientific domains, so they are currently rarely united in the work of one person, or even one lab or one institute. The only way to bridge this gap and derive optimal benefit from what each field has to offer is to bring together the specialists from both fields to discuss needs, possibilities, requirements, and conditions that will have to be resolved before collaborative efforts can be successful. This union has been the imperative driving the launch of the HUPO (see Box 1) initiative Proteome Biology of Stem Cells. The consortium consists of more than 15 leading scientists across the globe from both the proteomics and stem cell communities. From the beginning the initiative has also been strongly supported by the International Society for Stem Cell Research (ISSCR), which hosted the inauguration of the initiative at its annual meeting in Cairns, Australia, in June 2007. Future HUPO and ISSCR meetings will be used as platforms to further shape the initiative. To this end, joint HUPO/ISSCR stem cell proteomics sessions have already been scheduled for the HUPO meetings in Seoul (October 6th – 10th, 2007) and Amsterdam (August 16th – 21st, 2008), while a dedicated meeting is being considered to bring together all participants involved. Issues being discussed at present include short-term goals of an initial, relatively small-scale collaborative project and possibilities for funding enabling larger efforts in the longer term. Progress on these activities, further documentation on the background of the initiative, and a list of participating groups so far is available at www.hupo.org/research/stemcells.

Box 1
Human Proteome Organisation (HUPO)

The Human Proteome Organisation (HUPO, www.hupo.org) is an international scientific organization, launched in 2001, representing and promoting proteomics through international cooperation by fostering the development of new technologies, techniques, and training. It coordinates the development of standard operating procedures, and promotes global collaboration in major proteomics projects by gathering leading international laboratories in life sciences, bioinformatics, mass spectrometry, and systems biology. To achieve this, HUPO has facilitated the establishment of global consortia in HUPO Initiatives, each focusing on specific aspects of the development of proteomic techniques and their application to biology and medicine. Over the past few years 9 initiatives have been launched, of which Proteome Biology of Stem Cells is the latest addition.