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Exploring and Engineering Stem Cells and their Niches

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Stem cells were originally discovered in mouse bone marrow in the landmark work of Becker, Till, and colleagues in the 1960s. In the intervening and in particular recent years, this field has enjoyed a number of fundamental advances in new directions ranging from the discovery of new niches of stem cells in numerous adult tissues to the derivation of human embryonic stem cells (hESCs). As a result, it is poised to offer both the next generation of therapeutics, as well as better means to ensure the safety and efficacy of current generations of therapeutics.

Stem cells in vivo reside in a highly complex microenvironment or niche in which they are continuously courted by signals including small molecules, soluble proteins, signals immobilized within the extracellular matrix and in some cases mineralized tissue, signals immobilized on the surface of adjacent cells, and mechanical properties of the surrounding microenvironment. Realizing their therapeutic potential, and further developing experimental systems to analyze basic mechanisms of their regulation, will often hinge upon the ability to extract cells from their comfortable niches and sustain them in culture. Therefore, there has been considerable effort to identify key regulatory signals from the stem cell niche, develop or synthesize culture systems that emulate the natural niche's presentation of these signals, and evaluate or analyze cellular identity and response to these signals. These efforts in identification, synthesis, and analysis place stem cells at the intersection of biology, engineering, and chemical biology.

This issue of *Current Opinion in Chemical Biology* provides a broad, state of the art view of the field of stem cells from a chemical biology perspective. It is composed of three complementary groups of articles that focus on signal identification, microenvironment synthesis, and cellular analysis. In addition to responding to individual signals, it is becoming increasingly clear in general that cells can respond to combinations of factors in an unpredictable and nonlinear fashion. Given the complex milieu of signals that the stem cell niche presents, identifying single signals and mixtures of signals that promote self-renewal or lineage-specific differentiation rapidly becomes a combinatorially intractable problem. Fortunately, in recent years microarray technologies have been extended to generate dense arrays of cells, in which individual features on the array expose cells to cDNA libraries, immobilized factors, or combinations of immobilized and soluble factors. As discussed in Underhill and Bhatia, these high throughput technologies have led to the identification of novel regulatory signals as well as the realization that combinations of signals, previously well characterized individually, can have counterintuitive effects on cell function.

Additional efforts to identify novel regulatory factors have been motivated by the problem of developing conditions that enable stem cell to grow in culture. The development of defined

cultures conditions, as opposed to poorly defined factors present in serum or secreted by feeder cell layers, will greatly aid both scientific and eventual therapeutic stem cell endeavors. As reviewed by Chase and Firpo, empirical candidate-based studies, high throughput small molecule screens, and analysis of feeder cell properties have led to the identification of key signaling factors that support the self-renewal of important stem cells such as hESCs. As reviewed by Lanctot et al., new technological capabilities in chemical biology have made another set of regulatory signals, glycans, increasingly amenable to investigation. For a number of years, glycans have served as essential markers for the analysis and purification of different stem cell populations, including for example stage-specific embryonic antigens and tumor-rejection antigens (SSEAs and TRAs) for embryonic stem cells. Furthermore, it has been discovered that glycans can modulate signaling pathways important for stem cell function, including the fibroblast growth factor and Notch systems. Finally, foreign oligosaccharide structures can elicit immune responses, further highlighting the need to further explore and understand the roles of glycans in stem cell biology as a foundation to enable future clinical translation efforts.

Basic efforts to identify key regulatory factors can be translated towards the synthesis of stem cell culture microenvironments. For example, many stem cell populations require substrate or extracellular matrix signals for viability, maintenance, and differentiation. As reviewed by Lanctot et al., there has been strong progress in the development of defined media for stem cell culture; however, significant work is still required to define key substrate matrix signals. Extracellular matrix proteins are a highly diverse and complex set of molecules, each of which engages multiple cellular receptors. Furthermore, recent work has demonstrated that the mechanical properties of the substrate can exert profound effects on stem cell function. Saha et al. discuss progress in the synthesis of biomaterials for stem cell cultures, with a focus on the creation of fully synthetic systems with defined biochemical and mechanical signaling properties. In concert with defined media conditions, these efforts promise to synthesize a fully defined microenvironment to support stem cell self-renewal and differentiation. Mei et al. describe the development of high throughput array technologies to identify optimal synthetic material formulations to regulate human embryonic stem cell function, as well as further highlight the capabilities of high throughput array technologies in general to identify key stem cell regulatory signals. The highly promising biomaterial array technology promises to aid in the future development of bioactive substrates in defined soluble culture conditions.

Furthermore, various stem cell applications under development will require large numbers of cells, necessitating the development of scaleable technology platforms for stem cell expansion and differentiation. As reviewed by Miller and King, there has been considerable progress in developing bioreactor technologies that maintain the cellular microenvironment in a scaleable fashion for some stem cell types, particularly ones that can be grown in suspension. This collective work has also led to recognition of the importance of additional conditions such as dissolved O₂ concentration and pH in controlling stem cell function. Furthermore, additional development of defined soluble and substrate conditions for challenging cell types such as hESCs may make them amenable to large scale bioreactor expansion.

Novel technologies from biology and chemical biology are also aiding in the analysis of stem cell populations. Stanton and Bakre describe the application of genomics and proteomics towards the stem cell study. These technologies can provide a high resolution, diagnostic fingerprint of cell state. Additionally, they can aid in the analysis of key regulatory genetic and signaling networks that control key stem cell functions. Finally, the potential use of stem cells in tissue engineering efforts, where the cells directly serve as the therapeutic for disease or injury, is the most recognized biomedical application of the field. However, as discussed by Cesar, stem cells also have potential in the analysis and enhancement of the therapeutic potential of current generations of therapeutics. Many small molecule lead compounds fail due

to toxicology problems, and the development of enhanced preclinical models to analyze cytotoxicity (particularly to the liver and heart) has the potential to greatly facilitate pharmaceutical drug development. Human stem cells have the capacity to provide in theory limitless quantities of well-defined, differentiated human cells for use in high throughput screens to assess drug pharmacology and toxicology. It is arguable that these important applications will realize the shortest term benefits of stem cells for human healthcare.

In addition to highlighting many recent advances, these articles indicate the need for future work. The continual identification of regulatory signals will benefit both developmental biology and biomedical application, the development of fully synthetic microenvironments for cell expansion and differentiation where both the soluble conditions and the substrate are fully defined will enable a range of applications, and the application of stem cells in the short term towards pharmacology/toxicology screens and in the longer term towards disease therapy will deliver on their full promise. The recognition of stem cells as an important and exciting field will continue to draw investigators with diverse backgrounds, including chemical biology, and further enable progress in these and other new directions.

David Schaffer is an Associate Professor of Chemical Engineering at University of California, Berkeley, and the Lawrence Berkeley National Lab. He graduated from Stanford University with a B.S. degree in Chemical Engineering in 1993. Afterward, he attended Massachusetts Institute of Technology and earned his Ph.D. also in Chemical Engineering in 1998 with Professor Doug Lauffenburger. While at M.I.T., Dave minored in Molecular and Cell Biology. Finally, Dave did a postdoctoral fellowship in the laboratory of Fred Gage at the Salk Institute for Biological Studies in La Jolla, CA before moving to UC Berkeley in 1999. At Berkeley, Dr. Schaffer applies engineering principles to enhance stem cell and gene therapy approaches for neuroregeneration. This work includes mechanistic investigation of stem cell control, as well as molecular engineering of viral gene delivery vehicles. David Schaffer has received an NSF CAREER Award, Office of Naval Research Young Investigator Award, Whitaker Foundation Young Investigator Award, and was named a Technology Review Top 100 Innovator. He was also awarded the Biomedical Engineering Society Rita Shaffer Young Investigator Award in 2000.