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Functional Genomics on Stemness and Plasticity of Human Stem Cells

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Stem cells are unique cell populations with the ability to undergo both self-renewal and differentiation into specific cell types simultaneously. Currently, excitement is increasing in a stem cell research area since stem cells can provide a promising tool not only for basic research but also for clinical applications in regenerative medicine. Primarily, two kinds of stem cells are generated from animals and humans: embryonic stem cells and adult stem cells. Each type has different functions and characteristics. Embryonic stem cells (ESCs) are derived from early stage embryos and retain the pluripotency to differentiate into all cell types. Adult stem cells are undifferentiated cells found among differentiated cells in a tissue or organ and show multipotency to differentiate into the major specialized cell types of the tissue or organ. A wide variety of stem cells has been isolated, among which embryonic, neural, and hematopoietic stem cells are well characterized in vertebrates and their transcriptional profiles have been analyzed in mice. Although a wide variety of stem cells including human embryonic stem cells (hESCs) is identified and stem cell plasticity is recently reported, neither detailed molecular mechanisms underlying nor fate signaling genes involved in stemness and plasticity are known. To identify genes involved in the control of stemness as well as to characterize each stem cell specific gene, we carried out gene expression profiling of three types of human stem or immature progenitor cells using cDNA microarray: Embryonic, hematopoietic (CD34+ and CD133+), and mesenchymal stem cells (MSCs). The universal human reference RNA (Clontech) was employed as a reference for microarray gene profiling experiments. Comparative analyses of their expression identified putative genes that were differentially expressed in specific stem cell populations. Particularly we were able to identify potential hESC signature-like genes that encode transcription factors (TFAP2C and MYCN) and RNA binding protein (IMP-3). The overlapping sets of 22 enriched or 141 down-regulated genes identified in this study among all three human stem cell types may also provide molecular clues to understand the developmental mechanisms shared in all human stem cells. Furthermore, our comprehensive analyses of gene expression profiles of various adult stem cells might generate insight into genetic pathways involved in self-renewal as well as milti-lineage specific differentiation, which will be very informative for future application of hESCs to cell therapies. The expression pattern of several candidate clones was further characterized in several cell lines as well as in differentiating stem cells by semi-quantitative RT-PCR. To systematically characterize the functional role of each candidate gene for the maintenance of stemness or differentiation, we employed a tetracycline-inducible lentiviral knockdown strategy. We have demonstrated that RNA interference is effective to induce gene silencing using lentivrus in hESCs. Knockdown of POU5F1, Nanog, and Sox2 promotes differentiation, thereby demonstrating a role for these factors in human embryonic stem cell self-renewal. Knockdown of JAK2 and STAT3 did not promotes differentiation in human stem cells, thus JAK/STAT signaling is not play functionally conserved roles in human embryonic stem cells. In this presentation, we will also discuss putative functional roles of candidate genes including, WDHD1, GDF3, Stellar, and Znf217 in human ESC, MSC, and/or CD133+ HSC. Our results may open the door to fully understand the nature of the stem cells and molecular mechanisms of mammalian development and differentiation. Further functional studies of the identified other candidate genes may provide crucial data in understanding stem cell development in vivo, and useful tools for controlled hESC development into specific adult stem cells.