

Unleashing the Genome: Maintaining, Reinstating and Exploiting Pluripotency

Oliver Brüstle

During ontogeny, stem and progenitor cells experience a continuous restriction of their developmental potential. Controlled by stringent epigenetic mechanisms, the progeny of a fertilized oocyte sojourns in a pluripotent stage before embarking on a long route of germ layer and tissue-specific differentiation. Until recently, this concept of continuous lineage-segregation was considered a fundamental and, above all, irreversible process of development.

While some tissues such as skin and the hematopoietic system maintain an active stem cell pool for regeneration throughout adulthood, others mature into terminally differentiated cells with no or little residual progenitor cells. This irreversible exhaustion of the endogenous stem cell pool has been a major bottleneck for cell-based repair strategies in, e.g., heart and the nervous system.

The ability to derive continuously self-renewing human embryonic stem cells (hESC) from in vitro fertilized human oocytes, first demonstrated by James Thomson in 1998, has provided a first perspective to tackle the restricted access to precursor cells of non-regenerative tissues and organs. Since then, a steadily increasing number of studies demonstrate that numerous mature somatic cell types can be obtained from hESC.

Recent advances show that it is not only possible to maintain pluripotency of early embryonic cells but to actively reinstate this property in nuclei and cells derived from adult tissues. The demonstration by Shinya Yamanaka in 2006 that overexpression of a few transcription factors in adult fibroblasts suffices to generate induced pluripotent stem cells (iPSC) has opened new perspectives for generating large numbers of somatic cell types from individual patients. An enormous potential of these pluripotent stem cell-derived somatic cells lies in autologous regenerative approaches, but they also represent an attractive system for the study of disease mechanisms and the evaluation of potential therapies in human cells. Such a strategy is particularly relevant for diseases which i) cannot be adequately modeled in animal systems and ii) involve human cell types not readily accessible to experimentation.

More recent data from neurobiology indicate that pluripotent stem cells may themselves serve as source of more restricted, tissue-specific stem cells. These long-term self-renewing hESC-derived neural stem cells (lt-hESNSC) can be extensively proliferated, show multipotentiality at a clonal level and may thus be exploited as continuous source of human neurons and glia. Due to their stability, lt-hESNSC can be subjected to complex genetic modification, including neuronal lineage selection and Cre-mediated recombination. Combining long-term stability and phenotypic plasticity, lt-hESNSC represent a useful tool to study mechanisms of human neural stem cell self-renewal, lineage segregation and functional in vivo integration. In conjunction with appropriate standardization, automation and cryopreservation techniques they might also be exploited for modeling neurological disease, compound development and neural repair.