ABSTRACT

Regenerative medicine is a rapidly evolving research field whose main aims are to provide new therapeutic approaches and to repair or replace injured tissues with functional cells derived from stem cells. In the past few years, research breakthroughs have revolutionized the field by showing that all somatic cells have the potential to re-acquire stem cell-like properties. Thus, it appears possible to generate relevant cell types starting from cells easily obtained from affected individuals. The obtained differentiated cells could eventually serve as in vitro tools for the study of disease-associated mechanisms and for performing customized drug screenings. Moreover, in the context of cellular transplantation, these cells represent the ideal cell source given that they possess the same genetic code and thus will avoid the occurrence of unwanted immune reactions. Overall, this revolutionary technique called cellular reprogramming might provide substantial support for the future development of personalized medicine. In this chapter, I describe the recent advances in the field of stem cell-based regenerative medicine applications. Parkinson’s disease is chosen as a paradigmatic example in which the use of stem cells for study and therapy could have a relevant impact and potentially represent a future cure for this debilitating disorder.

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INTRODUCTION

Regenerative medicine aims at repairing or replacing lost or injured tissues and organs due to diseases, aging, or congenital defects with living and functional cells derived from stem cells. Stem cells are a special cell type that can be found in every multi-cellular organism. Their unique features include two key properties, i.e. indefinite propagation (self-renew) and the capability to generate a diverse range of specialized cell types through differentiation (potency). Stem cells are classified according to their degree of potency. Embryonic stem cells (ESCs), derived from early-stage embryos are pluripotent, i.e. they retain the ability to differentiate into virtually any cell type of the body derived from any of the three germ layers. On the other hand, somatic stem cells, which are found in developed organisms, are usually multipotent, since their differentiation is restricted to one specific lineage.

Regenerative-based applications are historically divided into two branches. The first utilizes cellular transplantation of ex vivo-cultured stem cells, while the second seek to activate the endogenous stem cell population. The latter route appears less achievable in the near future, as it requires complex chain of events capable of selectively stimulate the resident stem cell population without inducing unwanted unspecified responses, which might lead to cancerogenic transformations. Thus, most of research studies are currently focused on in vitro stem cell cultures and on the optimization of distinct protocols for the generation of specialized cell types, which could be then used for cellular transplantation. To this end, ESCs represent the most plastic type of stem cells.

ESCs were first discovered in mice by Martin Evans in 1981 (Evans & Kaufman, 1981), who has been awarded the Nobel Prize for his landmark discovery in 2007. The derivation of human ESCs was reported by James Thomson in 1998 (Thomson, et al., 1998). Since then, the field has rapidly evolved and considerable advances have been made to define specific differentiation protocols able to efficiently generate functional relevant cell types. These include cardiomyocytes and hepatocytes, which might prove to be useful for drug-screening studies, and dopamine-producing neurons, which could be used in cell-based therapeutic applications aiming at replacing the loss of this specific neuronal population in patients affected by Parkinson’s disease.

Despite all these promising results, numerous drawbacks are associated with ESC-mediated regenerative medicine. Indeed, the derivation of human ESCs requires the use of embryos, which can raise ethical concern. Moreover, in a similar fashion to organ transplants, stem cell transplants can give rise to immune rejections, since they are derived from a different individual with a different genetic background (allogenic). Patients should then be subject to immuno-suppressive therapy, which may in turn produce several clinical complications.

Generation of Patient-Derived Pluripotent Stem Cells

One way to circumvent the issues related to the use of human ESCs for disease treatment is the generation of genetically equivalent stem cells, directly obtained from the own cells of the patients (isogenic). All the cells of multi-cellular organisms possess the same genetic code but are functionally heterogeneous, due to their distinct epigenetic status. Through the modulating of their epigenetic profile, differentiated somatic cells can be reverted to stem cell-like cells capable of acquiring the two key properties of ESCs, i.e. self-renewal and pluripotency.

Somatic Cell Nuclear Transfer (SCNT)

The first demonstration of this reversion was obtained by somatic cell nuclear transfer (SCNT), which removes the nucleus of a somatic cell and transplants it into an enucleated oocyte. In the late
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