Chapter 5
Immunogenicity of Stem Cells

Franz Ricklefs
University Heart Center Hamburg, Germany

Sonja Schrepfer
University Heart Center Hamburg, Germany

ABSTRACT

Current medical research is focused on two particular types of stem cells, adult stem cells and embryonic stem cells. Both cell types demonstrate a tremendous potential as the source for regenerative medicine due to their paracrine and pluripotency effects, respectively. Therefore, stem cells are expected to have an enormous impact on clinical therapy. However, allogeneic approaches using "off-the-shelf" stem cells from healthy donors are the only financially and ethically feasible pathway. The long-standing assumption that stem cells are not recognized by the recipient's immune system was recently disproved not only by our group. Therefore, specific knowledge of the immunologic properties of pluripotent and multipotent stem cells is a prerequisite for safe application of stem cell-based therapy. This chapter will discuss the involvement of the innate and adaptive immune system and summarize state-of-the art approaches to overcome the immunological barrier.

INTRODUCTION

In December 1905 the early days of modern medicine began with the first reported tissue transplantation (cornea transplantation) performed in Olmutz, Moravia (now Czech Republic). Around 5 decades later the first milestone in organ transplantation had been established when a team of physicians in Boston, USA, performed the first successful kidney transplantation ever reported. Since these early days, immune rejection of the transplanted tissue had been known, except when performed between identical twins. Due to extensive research efforts, scientists have revealed that the differences in itLA proteins between allogeneic (genetically not-identical) individuals trigger the rejection by an immunocompetent host. Large diverse groups of molecules involved in immune recognition were discovered and defined as histocompatibility antigens, divided into three groups:

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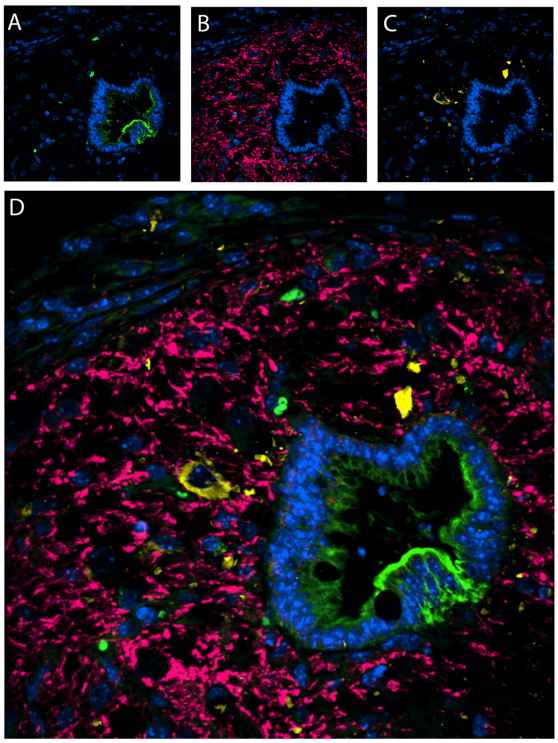
1) Major Histocompatibility Complex (MHC) molecules, in humans: Human Lymphocyte Antigen (HLA); 2) minor Histocompatibility complex Antigens (mHAgs); 3) ABO blood group antigens (Tang & Drukker, 2011). Hence, even nowadays, an immunosuppressive therapy is still mandatory and is included in protocols when organs or tissues are transplanted between allogeneic individuals.

Since transplantation medicine started, it became crucial to overcome the lack of available organs needed due to the high number of patients, waiting on the organ-lists all over the world. To overcome this hurdle a novel strategy was offered when Embryonic Stem Cells (ESCs) had been first isolated (murine ESC in 1981 [Kaufman, Robertson, Handyside, & Evans, 1983]; human in 1994 [Bongso, Fong, Ng, & Ratnam, 1994]) and also their adult partners, Adult Stem Cells (ASCs) with the first bone marrow transplantation in a 2-year old patient with Wiskott Aldrich syndrome (Bach, Albertini, Joo, Anderson, & Bortin, 1968). Their directed differentiation into a variety of tissue specific cell types seemed and still seems very appealing for organ restoration and cell-based therapies. However, up to today a successful transfer of the therapeutic promises of ESCs into the clinic is absent. Undefined growth of ESCs leading to teratoma formation (Figure 1) and immune rejection of transplanted ESCs are still major problems that need to be resolved before a successful clinical translation can be made. Therefore, current medicine is not only focused on ESCs but rather on ASCs, since they are already tissue-specific and lack the ability to form a teratoma. Nevertheless, an allogeneic approach for ASCs-therapy leads to a rejection of the transplanted cells by an immunocompetent recipient.

The purpose of this book chapter is to reveal the current knowledge of the involvement of the innate and adaptive immune system and to summarize state-of-the art approaches to overcome the immunological barrier.

Figure 1. Verification of pluripotency of ESCs by teratoma formation in vivo. Teratoma formation seven weeks after injection of 1x10^6 pluripotent ESCs into SCID beige mice. Teratomas are stained with germlayer specific antibodies and visualized using confocal microscopy. Cell nuclei are stained in blue (DAPI); A: green = Cytokeratin 8 indicating the endodermal cell lineage; B: far red = GFAP identifying ektodermal cell types; C: yellow = Brachyury indentifying mesenchymal derived cell types; D: merged (magnification: 400x). (Courtesy by Xiaoqin Hua)



TOTIPOTENCY/PLURIPOTENCY/ MULTIPOTENCY

All mammalia life derives from the fusion of an egg cell and spermatocyte resulting in the zygote. During the progression to a fully living organism, the cell proceeds from a state of totipotency, specialty of the zygote and blastomeres, to cells that are limited in their developmental potential.