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The transplantation of neural stem cells and predictive factors in hematopoietic recovery in irradiated mice

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Abstract

A number of surprising observations have shown that stem cells, in suitable conditions, have the ability to produce a whole spectrum of cell types, regardless, whether these tissues are derived from the same germ layer or not. This phenomenon is called stem cell plasticity, which means that tissue-specific stem cells are mutually interchangeable. In our experiments, as a model, we used neural stem cells (NSCs) harvested from fetal (E14–15) neocortex and β-galactosidase positive. In the first experiment we found that on days 12 and 30 after sub-lethal irradiation (LD 8.5 Gy) and (β-galactosidase$^+$) NSCs transplantation all mice survived, just as the group with bone marrow transplantation. Moreover, the bone marrow of mice transplanted NSCs contained the number of CFU-GM colonies with β-galactosidase$^+$ cells which was as much as 50% higher. These differences were statistically significant, $p < 0.001$. In the second experiment, we studied kinetics of (β-galactosidase$^+$) NSCs after their transplantation to sub-lethally irradiated mice. Histochemistry of tissues was performed on days 12 and 30 post-transplantation, and β-galactosidase$^+$ cells were detected with the help of histochemical examination of removed tissues (lung, liver, spleen, thymus, and skeletal muscle). In tissues removed on day 12 post-transplantation, we found a significantly higher number of β-galactosidase$^+$ cells in the spleen and thymus on day 30. While we presumed the presence β-galactosidase$^+$ cells in the spleen, as spleen and reticuloendothelial system represent an important retaining system for different cell types, the presence of β-galactosidase$^+$ cells in the thymus was rather surprising but very interesting. This indicates a certain mutual and close interconnection of transplanted stem cells and immune system in an adult organism. In the third experiment, we verified the mutual interchange of Sca-1 surface antigen in the bone marrow cells and NSCs before transplantation. Analysis of this antigen showed 24.8%

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Sca-1 positive cells among the bone marrow cells, while NSCs were Sca-1 negative. Our experiments show that NSCs share hemopoietic identity and may significantly influence the recovery of damaged hematopoiesis but do not have typical superficial markers as HSCs. This result is important for the determination of predictive factors for hemopoiesis recovery, for stem cell plasticity and for their use in the cell therapy.

Keywords: Neural stem cells; Hematopoietic stem cells; Hematopoiesis; Plasticity; Sca-1 antigen; Predictive factors; Cell therapy

1. Introduction

Stem cells represent a unique population of cells designed to create the infrastructure for individual organs and tissues, to maintain their structures and functions in a multicellular organism. They are generated at the very beginning of ontogenesis and persist in tissues even in adulthood. Stem cells are undifferentiated but possess the capacity to renew themselves indefinitely [1].

Hematopoiesis is the most studied system of cell function. At present, we already know that of 10 000–15 000 cells in the bone marrow there is one hematopoietic stem cell (HSC). Terminally differentiated cells of the hemopoietic system produce at least eight lines, each having different functions, morphology and cellular kinetics [2]. Terminally differentiated cells do not develop from hemopoietic stem cells directly but through proliferating progenitor populations. Previously, it was presumed that in this way, a relatively small number of stem cells may give rise to 0–4% cells of total bone marrow cell population [3]; but a newer estimation is much lower 0.01–0.1% [4]. Although the existence of hemopoietic stem cells is well documented, it has been shown that their identification is difficult. The strategies for stem cell isolation were based on separation of stem cell sub-populations according to their density (buoyant density), sensitivity to antimitotic agents, or on the expression of cellular surface antigens, eventually, on enrichment of population with stem cells produced by suitable culture methods or marrow reconstitution. Mouse hemopoietic stem cells show following characteristics: They do not express granulocyte or macrophage markers, nor markers of B- and T-lymphocytes [5], but bind agglutinin WGA (wheat germ agglutinin) [6], express surface antigen Sca-1 (stem cell antigen-1) [7] and low levels of Thy-1 [5–7]. In humans, about 1–4% of marrow cells bear CD34 antigen [7]. A group of these cells also contains stem cells found in assays in vitro. Stem cells are found, for example, in the population of cells Sca-1^{+} lin^{-} or also $CD117^{high}$ lin^{-} that do not contain differentiation markers of individual blood lines. Post-transplantation, they are able to colonise the recipient's bone marrow and are responsible for long-term transplant engraftment. Stem cells show plasticity which enables their transdifferentiation into cells of many other tissues, such as heart muscle and other tissues [8,9].

A number of surprising observations indicated that stem cells have the ability, in suitable conditions, to produce a whole spectrum of cell types, regardless, whether the tissues are derived from the same germinal layer or not. This phenomenon is called stem cell plasticity which means that tissue-specific stem cells are mutually interchangeable [10,11] through transdifferentiation [12] or fusion [13].

Following bone marrow transplantation, donor cells were found in non-hemopoietic tissues, such as vascular tissues [14], astroglia in the brain [15], skeletal muscle [16], and bone [17]. In addition, it is known that stem cells from non-hemopoietic tissues differentiate into hemopoietic cells. There is one example, when clonal population of neural stem cells repopulated hemopoietic system after transplantation [18].

When designing these experiments, we started from our published results, as well as results of others [18–20]. From the first experiment we know that NSCs transplantation protects sub-lethally irradiated mice when compared with controls not given cell transplantation [20]. In the second experiment, where NSCs kinetics was studied after their