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REVIEW

Stem cell sources for regenerative medicine: the immunological point of view

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Abstract Stem cell transplantation consists in the introduction of stem cells or derived products in a diseased organism. Because of the differentiation properties of stem cells, the goal is to replace damaged cells or tissues. Numbers of stem cell were identified and isolated from embryos, fetuses, or adult organs, harboring different properties, and thus providing multiple strategies of regenerative medicine for different diseases. More recently, the artificial induction of stemness properties in adult somatic cells has proposed a new way to generate stem cells. One important concern of stem cell therapy is the possible risk that transplanted stem cells could be rejected by the recipient's immune system. Depending on their source, stem cell transplantation is associated with diverse immunological situations. If some sources allow autologous transplantation, others cannot bypass an allogeneic context between the donor and the recipient. This review summarizes all of the stem cell sources for regenerative medicine and the immunological questions associated to their use. Regarding the emerging strategies compatible with autologous transplantation, this article points notably the complexity of the choice between the immunological safety and the specific advantages of allogeneic stem cells.

Keywords Stem cell transplantation · Immune rejection · Pluripotent stem cells · Adult stem cells · Induced pluripotent stem cells

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Introduction: stem cells and stem cell therapy

Stem cells are found in all multicellular organisms. The classical definition of a stem cell requires that it possess the following two properties (i) self-renewal, which indicates the ability to go through numerous cycles of cell division while maintaining the undifferentiated state and (ii) potency, i.e., the capacity to differentiate into specialized cell types. Potency can cover various properties. Totipotency indicates the capacity to differentiate into all embryonic and extra-embryonic cell types. Such cells can construct a complete and viable organism. Pluripotency indicates the ability to differentiate into nearly all cells derived from any of the three germ layers. Multipotency is restricted to a closely related family of cells (e.g., neural stem cells differentiate into cells of the central nervous system). The two broad types of stem cells found in vivo are: embryonic stem cells that are isolated from the inner cell mass of early embryos [1] and stem cells that are found in adult tissues and called adult stem cells. In the developing embryo, embryonic stem cells are dedicated to differentiate into all of the specialized tissues. Adult stem cells act as a repair system for the body, replenishing specialized cells, but also maintain the normal turnover of regenerative organs. Induced pluripotent stem cells are a type of pluripotent stem cell artificially derived from a non-pluripotent cell, typically an adult somatic

cell, by inducing a forced expression of specific genes [2, 3]. Induced pluripotent stem cells resemble their natural embryonic stem cell equivalent.

Stem cell therapy is a type of intervention strategy that introduces new cells into damaged tissue in order to treat disease or injury. The ability of stem cells to self-renew and give rise to subsequent generations with variable degrees of differentiation capacities offers significant potential for generation of tissues that can potentially replace diseased and damaged areas in the body. Some adult stem cells from umbilical cord blood and bone marrow are routinely used in medical therapies. In the future, researchers anticipate being able to use technologies derived from stem cell research to treat a wider variety of diseases including, e.g., neurodegenerative disorders and brain and cardiac injury amongst a number of other impairments and conditions. Depending on their source, stem cells with a therapeutic potential could or could not originate from the treated patient. As profiling of the antigens expressed on stem cells and their derivatives has revealed that they can express rejection antigens, an immune reaction can occur when the donor is unrelated to the recipient.

Different sources of stem cells for regenerative medicine and their immunological potential

Embryonic stem cells

Embryonic stem cells are cell lines derived from the inner cell mass of a blastocyst. A blastocyst is an early-stage embryo (approximately 4 to 5 days old in humans) consisting of 50–150 cells. It contains the trophectoderm which gives rise to the placenta and the inner cell mass which is dedicated to generate the embryo proper. Embryonic stem cells result from the in vitro culture of the inner cell mass, resulting in the proliferation of pluripotent cells in culture [1]. Human embryonic stem cell lines require a specific environment in order to maintain them in vitro in an undifferentiated state. Pluripotent cells of the inner cell mass give rise during in vivo development to all derivatives of the three primary germ layers: ectoderm, endoderm, and mesoderm [1]. Thus, human embryonic stem cells can be differentiated in vitro into various cell types of the body, opening the possibility of various transplantations. The currently most-studied applications using embryonic stem cells are heart failure [4], neurodegenerative disorders, brain injury including Parkinson's disease and spinal cord injury [5–8], and diabetes [9]. Due to the systematic unrelated genetic origin between embryonic stem cells and the recipient, there is a potential risk of transplant rejection.

Adult stem cells

The term adult stem cell refers to any cell which is found in a developed organism that has the two fundamental properties of stem cells: the ability to divide and create another cell like itself and also the ability to create a more differentiated cell. Pluripotent adult stem cells are rare and generally small in number, but can be found in a number of tissues. Most adult stem cells are multipotent (lineage-restricted) and are generally referred by their tissue origin.

Hematopoietic stem cells are found in the bone marrow and give rise to all the blood cell types. Hematopoietic stem cell transplantation has been successfully used for many years to treat bone marrow disorders. In the case of allogeneic adult stem cell transplantation, there are immunological questions related to graft/recipient rejection that must be considered [10]. However, in some instances, hematopoietic stem cells can be obtained from the intended recipient. In these autograft situations, the risk of rejection is essentially non-existent. Adipose-derived stem cells have been isolated from human fat, usually by liposuction. Human adipose-derived stem cells have been shown to differentiate into bone, cartilage, fat, and muscle, which make them a possible source for future applications in the clinic [11]. There are no immunological barriers for these cell types if they are isolated from the recipient. Multipotent stem cells have been successfully recovered from dental pulp, the soft living tissue inside a tooth [12]. This particular type of stem cell has the future potential to differentiate into a variety of other cell types including cardiac cells, neural cells, and bone and cartilage cells. They are not associated with an immunological barrier if they are isolated from the recipient. Mesenchymal stem cells have been isolated from the placenta, adipose tissue, lung, bone marrow, blood, and the umbilical cord [13]. They are of stromal origin and can differentiate into a variety of tissues. Mesenchymal stem cells are particularly attractive for clinical therapy not only due to their ability to differentiate into various cell types, but also for their immunosuppressive properties [14]. They are not systematically associated with an immunological barrier since they can be isolated from the recipient. The existence of stem cells in the fetal or adult brain has been discovered following the observation that the process of neurogenesis, the birth of new neurons, continues into adulthood. Neural stem cells are commonly isolated and cultured in vitro as so called “neural spheres”—a kind of cell aggregate containing a large proportion of neural stem cells. They can be propagated for extended periods of time and differentiated into cells of the central nervous system including neurons, astrocytes, and oligodendrocytes [15]. Neural stem cells can be isolated from either the fetal central nervous system or from very restricted neurogenic regions now known to

persist in two niches in the adult brain: one in the subventricular zone lining the lateral ventricles and the other in the dentate gyrus of the hippocampus [16, 17]. Lineage-restricted neural stem cells have been shown to be able to integrate into the brain [18] and to elicit repair in animal models, including Parkinson's disease [19], multiple sclerosis [20], and ischemic stroke [21]. Neural stem cells for replacement therapy applications are systematically unrelated to the recipient because they originate in general from aborted fetuses or surgical pieces from the brain of cadavers. Thus, there is an immunological barrier for their use. Olfactory stem cells have been successfully harvested from the human olfactory mucosa, which are found in the lining of the nose and are involved in the sense of smell. If they are given to the right chemical environment, these cells have the same ability to develop into many different cell types [22]. Olfactory stem cells hold the potential for therapeutic applications and, in contrast to neural stem cells, can be harvested with ease without harm to the patient context. Thus, there are no immunological barriers associated with this stem cell source.

Induced pluripotent stem cells derived from adult somatic cells

It has been described in 2006 that the expression of a set of only four genes (Klf4, Sox-2, Oct-4, and c-Myc) transformed mouse somatic cells back into a pluripotent-like state [3]. In cell culture, these first induced pluripotent stem cells behaved like embryonic stem cells. Soon after was described the successful generation of human induced pluripotent stem cells by the same set of genes, with an alternative gene combination composed of Oct-4, Sox-2, Nanog, and Lin28 [2]. While the potential use of human embryonic stem cells for therapeutic applications comes with immunological problems similar to those encountered during organ transplantation, reprogramming of somatic cells theoretically promises to provide custom-made pluripotent cells from individual patients.

Multipotent or pluripotent stem cell transplantation?

Pluripotent stem cells have theoretically the capacity to generate all of the existing cell types in the body, whereas multipotent stem cells are more restricted to defined lineages. One inconvenience of some multipotent stem cells is their availability. It is notably the case for fetal or adult neural stem cells for which the number of aborted fetuses or brain samples is limited. Moreover, several aborted fetuses are generally required for one transplanted patient [23]. In both cases, fetal or adult samples are a non-standardized source of neural stem cells, leading to high variability in the quality of transplants. On the contrary, pluripotent stem cells have the advantage to be an indefinite and more standardized source of cells for transplantation. However, despite this advantage, pluripotent stem cells do not share the same efficiency than multipotent stem cells for differentiation. To date, it is still more complicated to trigger pluripotent stem cells toward a defined cell type than multipotent stem cells. Indeed, pluripotency is a very immature stage. Thus, highly defined exogenous and endogenous cues are required for the specific decision to differentiate towards a precise cell type. As a consequence, in vitro differentiation of pluripotent stem cells generally requires more complicated and less controlled culture conditions with a high risk of dedifferentiation or incomplete differentiation. Unsuited undifferentiated cells or foreign cells are dangerous for the recipient because of a risk of tumors [24] or inefficient transplantation. On the contrary, multipotent stem cells are more mature and have already been naturally specified towards a defined direction, rendering them more suitable for the targeted differentiation in vitro, with a lower risk of dangerous cell generation. Thus, there is still a balance between the advantages and inconvenience of pluripotent versus multipotent stem cells, opposing the availability of stem cells to the possibility to efficiently differentiating them (Table 1).

Stem cell transplantations: multiple immunological situations

Multiple strategies of stem cell transplantation are currently studied. Some of them open the possibility of autologous transplantations, whereas others are associated with allogeneic situations. Several situations do not expose the transplant to rejection because the donor is also the recipient. A simple approach consists in the isolation and transplantation of stem cells in the same individual, without any differentiation process ex vivo (Fig. 1a). This approach is currently used in medicine in the context of autologous hematopoietic stem cell transplantation, where the transplanted stem cells differentiate towards the bone marrow in vivo after their injection. Numerous approaches consist of the same principle, with the addition of an in vitro stem cell differentiation step. In this context, stem cells are isolated, differentiated in vitro towards the suited cell type, and re-injected in the same patient (Fig. 1b). It is notably the case for multipotent adult stem cells which have to be further matured towards a defined cell type. Another autologous context consists of the in vitro reprogramming of recipient somatic cells towards induced pluripotent stem cells. The reprogrammed cells are then differentiated towards the suited cell type and transplanted (Fig. 1c). Theoretically,

Table 1 Advantages and disadvantages of pluripotent versus multipotent stem cells

	Autologous transplantation	Allogeneic transplantation	Advantages	Disadvantages
Pluripotent embryonic stem cells	Not possible	In all cases	Unlimited and standardized source, can generate all cell types	Complexity of in vitro differentiation, allogeneic source: risk of immune rejection, risk of tumor, ethical questions
Induced pluripotent stem cells	Possible	Possible	Allows autologous transplantation, can generate all cell types, optimal for cell banking according hla	Complexity of in vitro differentiation, risk of tumor, genetic modifications
Adult neural stem cells	Rare	Possible	Easier differentiation towards suited cells, tumors are rare	Low availability of cells, non-standardized source, allogeneic source: risk of immune rejection
Fetal neural stem cells	Not possible	Possible	Easier differentiation toward suited cells, tumors are rare	Low availability of cells, non-standardized source, strong risk of immune rejection
Hematopoietic stem cells	Possible	Possible	Availability of transplants, autologous or allogeneic context, low manipulation of transplanted cells	Restricted differentiation potential
Adipose-derived stem cells	Possible	Possible	Easy availability of transplants, autologous or allogeneic context	Restricted differentiation potential
Mesenchymal stem cells	Possible	Possible	Availability of transplants, autologous or allogeneic context	Restricted differentiation potential
Olfactory adult stem cells	Possible	Possible	Availability of transplants, autologous or allogeneic context	Restricted differentiation potential
Dental pulp stem cells	Possible	Possible	Availability of transplants, autologous or allogeneic context	Restricted differentiation potential

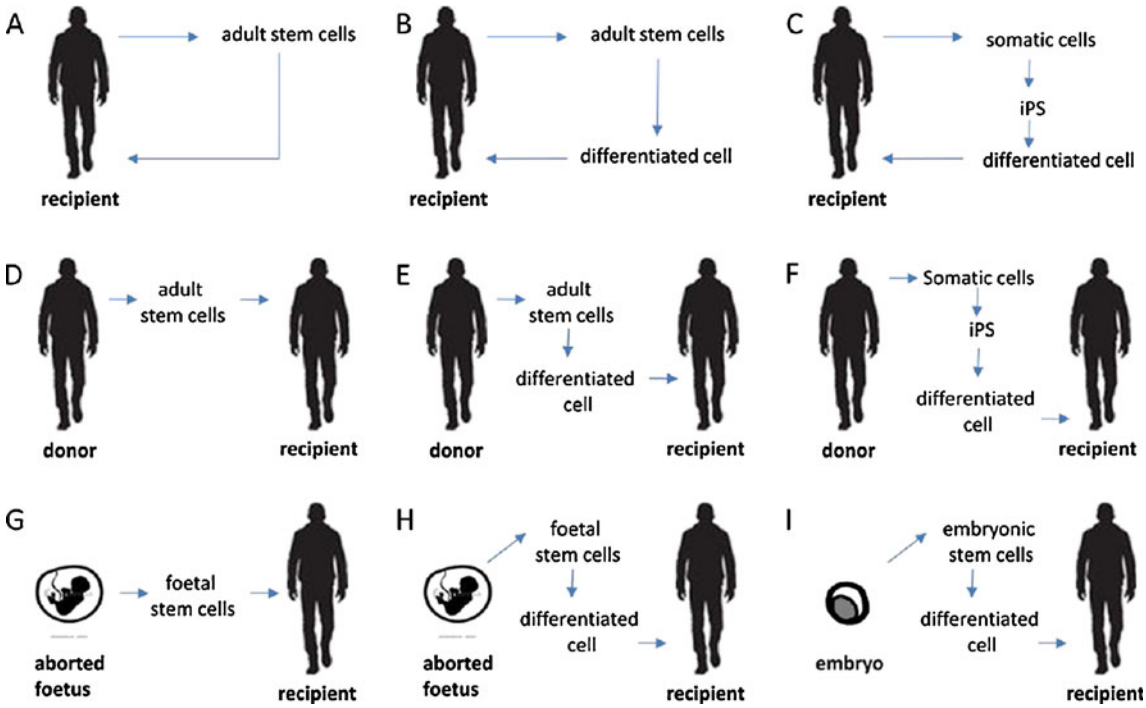

Fig. 1 Multiple strategies of stem cell transplantation. **a** Isolation and transplantation of stem cells in the same individual, without any differentiation process ex vivo. **b** Stem cells are isolated, differentiated in vitro towards the suited cell type, and re-injected in the same patient. **c** The reprogrammed cells are then differentiated towards the suited cell type and transplanted. In the allogeneic context, **d** adult stem cells can be transferred from a donor to a recipient. **e** Allogeneic adult stem cells can either be transplanted directly or further differentiated in vitro towards the suited cell type before transplantation. **f** They also can be generated from a donor, differentiated, and transplanted to a recipient. **g** Other allogeneic contexts of cell transplantation are the use of stem cells **h** or differentiated stem cells. **i** Embryonic stem cells cannot be directly injected into patients because of the risk of teratomas [24], but need to be differentiated towards the suited cell types

this approach opens the possibility of autologous transplantation of any cell types without any immune barriers.

The other concepts of stem cell therapy are associated with an allogeneic context (Fig. 1). First, adult stem cells can be transferred from a donor to a recipient (Fig. 1d). This situation is necessary when adult stem cells cannot be obtained from the recipient. It is the case for hematological malignancies where the diseased bone marrow has been destroyed to be replaced by hematopoietic stem cells from a donor. It is also the case for adult neural stem cells that generally cannot be isolated from the recipient. Allogeneic adult stem cells can either be transplanted directly or be further differentiated in vitro towards the suited cell type before transplantation (Fig. 1e), depending on the application. Although induced pluripotent stem cells have opened the possibility of autologous transplantation, they also can be generated from a donor, differentiated, and transplanted to a recipient (Fig. 1f). There are indeed several arguments to prefer allogeneic transplantation of induced pluripotent stem cells (discussed in the next paragraph). The other allogeneic contexts of cell transplantation are the use of stem cells (Fig. 1g) or differentiated stem cells (Fig. 1h) from aborted fetuses. It has been notably widely tested in neurodegenerative disorders such as Parkinson's disease where neural stem cells were isolated from the fetal mesencephalon and transplanted into the diseased striatum of patients [23]. One inconvenience of this approach was the need of a high number of cells for each transplanted patient, requiring the use of several aborted fetuses. In this situation, the immunological risk is very high because of the diversity of major and minor rejection antigens in the transplant. Finally, embryonic stem cells are systematically from an allogeneic origin because of the use of spared embryos to generate lines. Embryonic stem cells cannot be directly injected into patients because of the risk of teratomas [24], but need to be differentiated towards the suited cell types (Fig. 1i).

Patient-specific or characterized stem cell lines?

Autologous stem cell transplantation has the advantage of immunological safety. Does it mean that this option must be systematically preferred when the nature of stem cells offers this possibility? In fact, there are some reasons to doubt this assumption because autologous transplantation is also associated with some risks.

First, stem cells isolated or generated from a donor are not systematically efficient to differentiate and cure the disease. Indeed, a high variability in the differentiation potential of different pluripotent stem cell lines is well known [25–28]. It means that, for example, a unique induced pluripotent stem cell line derived from a patient could be inefficient to produce a defined cell type for transplantation. Second, stem cells for transplantation must be highly characterized. Numbers quality controls to ensure the safety of therapeutic cells must be performed before transplantation, including, e.g., the microbial safety and the control of their tumorigenic potential. Validation of these safety controls takes time and involves numerous laboratories. To solve these limitations, numerous stem cell lines should be derived from one patient and then fully characterized before the selection of the most safe and efficient ones. However, in the context of autologous transplantation, such heavy and long procedures would be difficult to adapt to clinical-grade conditions and would not be compatible with cell therapy applications for which stem cells must be transplanted in a very short delay after injury (e.g., spinal cord lesions) [29]. Thus, if autologous transplantation is theoretically possible for some stem cell sources, there could be more advantages to favor allogeneic approaches for which characterized, efficient, and safe lines have been stored and are readily available. Finally, the genetic status of transplanted cells must also be considered in the context of autologous stem cell transplantation. Because of the genetic origin of some diseases, the following question is opened: Does autologous stem cell transplantation consist in the reintroduction of diseased cells in the same patients? In other words, is there a risk of relapse of the disease in the graft? If progression of the disease within the graft has been reported independently of the genetic status of transplanted cells [30], there are still no data to answer to this question, and further studies are needed to address this point.

Stem cell transplantation and immunosuppressive drugs

Because of the situations associated with a risk of immune rejection, the question of pharmacological immune suppression after stem cell transplantation is relevant. Immunosuppressive agents are drugs that inhibit or prevent activity of the immune system. Because the majority of them are very active on cell physiology and act non-selectively on the immune system, there are generally strong side effects on the patients. For example, ciclosporin or glucocorticoids interfere with the transcription of numerous genes, cytostatic agents inhibit cell proliferation, etc.

In addition to side effects on the patient and because of their generally strong activity on cells, immunosuppressive drugs could also be associated with side effects on the grafted cells. Indeed, in numerous situations, undifferentiated or pre-differentiated stem cells, depending on their source, must continue and finish their differentiation program after transplantation. As this terminal maturation

of cells requires multiple intracellular events combining transduction pathways and gene expression, it cannot be excluded that some immunosuppressants will alter this process and decrease graft efficiency. A recent study showed that ciclosporin and dexamethasone strongly inhibited in vitro the terminal maturation of neural progenitor cells toward mature neurons [31], confirming that the possible interference between drugs and transplanted cells needs to be carefully evaluated.

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