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Editorial

When biology bursts into the clinic: stem cells and their potential

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Introduction

During the last 20 years, the great development of new biological technologies has set stage for novel human therapeutic methods. In particular, the knowledge reached about stem cell biology has offered a new key-lecture for human physiology and pathology, opening unsuspected perspectives for prevention and treatment of several human diseases, with obvious ethical and political implications[1,2].

The purpose of this review is to analyse the "state of the arts" about stem cell biology and to discuss its main future applications in Medicine.

Carcinogenesis Mirrors Stem Cell Proliferation and Differentiation

Stem cells exist in all multicellular organisms from the first steps of embryogenesis. "Stemness" is a complex of properties whose expression is strictly regulated to guarantee organ homeostasis. The main characterstics of a stem cells are two: multipotency, as the ability to give rise to multiple tissues and cell-phenotypes during the differentiation process and self-maintenance, that is the maintenance of a stable stem cell population, switching between symmetrical and asymmetrical divisions, in response to environmental conditions[3,4].

The first stem cells to appear, from zygote to the blastocyst stage, are "totipotent", but, after the implantation and the development of the three fundamental germ layers (endoderm, ectoderm and mesoderm) embryonic stem cells (ESCs) progressively differentiate, becoming multipotent, so losing the ability to give rise to all tissues. At the end of gestation, tissue-specific stem cells (TS-SCs or adult stem cells, ASCs) persist, as long-term elements (true stem cells), fewer in number but with a greater differentiation potential and a longer proliferative capacity, and short-term elements, that derive from the first ones as "committed-progenitors" and progressively maturate providing new functional elements[6]. TS-SCs have been identified in bone marrow, gastrointestinal tissue, skin, brain, muscle and liver, participating to tissue turnover, through the replacement of the continuous physiological cell loss, and providing to tissue regeneration in case of damage[6]. Besides, in the last years several studies showed that stem cells from one tissue could change into another, even of different origin, a process called "transdifferentiation"[7,8], suggesting an unsuspected degree of plasticity and heterogeneity for stem cell compartment[9].

A better knowledge of stem cell proliferation and differentiation might permit to perform new strategies for prevention and cure against malignancies, that afflict a large part of population worldwide. Cancer results from the dysregulation of proliferation and differentiation processes, caused by progres-

sive genetic mutations and epigenetic abnormalities in the expression of multiple genes, that occur in a single stem cell. Clarifying the complex of mechanisms involved in stem compartment maintenance and alterated in carcinogenesis, it will be possible to develop novel approaches to cancer therapy, aimed at limiting the proliferative capacity of mutant clones, through stem cell gene-therapy, antagonistic growth factors or immunotherapy against tumor specific antigens.

Stem cell Tissue Renewal and Regeneration: a Bridge Towards a Regenerative Medicine

Stem cells play a fundamental role for tissue homeostasis maintenance. Improving our knowledge about the environmental factors that drive tissue-stem cells towards proliferation and differentiation, it will be possible to facilitate tissue engeering and provide alternaltive sources for organ transplantation and/or restore. End–stage diseases, such as hepatic, cardiac or renal failure, could be treated with TS-SC transplantation or with tissues and organs produced in vitro using patient's stem cells, solving the problem of donor organ scarcity and the need for immune-compatibility and immunosuppression to avoid graft rejection[12].

Stem Cell Gene-Therapy and Allotransplantation: New Tools to Cure Metabolic Diseases

Inborn errors of metabolism are caused by inherited genetic disorders, resulting in enzyme deficiencies. Many of these pathologies involve the hepatic metabolism and can be resolutely treated only through the orthotopic transplantation of the whole donor liver (OLTx). However, few patients can benefit from this procedure, because of the limited availability of organs, its significant morbidity and mortality and the risk of rejection. For these reasons, many investigators have found in stem cell potential an alternative to OLTx. Crigler-Najjar syndrome, LDL-receptor defect, hereditary hemochromatosis, Wilson disease, and also acquired metabolic diseases, such as diabetes mellitus, could be successfully treated with allogeneic TS-SCs transplantation or, better, with patient's stem cells manipulated replacing the alterated genes with ex vivo or in vivo gene-therapy. The feasibility of these new treatments, demonstrated by several animal models, has recently permitted to perform the first clinical trials in humans[12,13].

Plasticity and Heterogeneity of the Hematopoietic Stem Cells: Actual and Future Clinical Applications

The first adult stem cells that were studied and found a clinical application were the haematopoietic stem cells (HSCs), the pluripotent cells that permanency generate all the component of blood[14]. The clinical applications of HSCs began in 1960s, in hematology and oncology, with the first cases of bone marrow transplantation (BMT). At present too, HSCs transplantants are used in patients with non-hematolymphoid and hematologic malignancies, to permit treatments based on high-doses of chemotherapy[15]. Besides, allogeneic transplantation is used to restore the haematopoietic system in several non-malignant haematologic diseases (haemoglobin disorders, primitive immunodeficiency, etc)[16], and to improve the survival of transplanted organs, through the co-transplantation of HSCs from the same donor (BM-allograft determines a condition of chimerism that permits a permanent tolerance towards donor tissue-antigens)[17,18]. Finally, HSCs transplantation seems to be able to solve also severe autoimmune diseases, as suggested by several clinical evidences[19].

Despite the classic wisdom that denied the existence of Stem Cells into the bloodstream and limited their poterntial to heamatopoiesis, recent studies demonstrated that HSCs circulate normally in the peripheral blood, reaching every organs, and that could differentiate into several phenotypes, including blood, cartilage, fat, tendon, lung, liver, muscle, marrow, stroma, brain[20], kidney[21] and heart cells[22]. This unsuspected degree of plasticity and heterogeneity sug-

gests that HSCs may be a reserve of stem cells for all tissues, representing a "pluripotent itinerant element" able to mobilize, circulate and engraft into every organ, to participate to its regeneration and renewal[6]. In future, it will be possible to use patient's circulating cells as source for the design of custom tissues and organs. The potential advantages are numerous, going from the ease of cell availability and the absence of any rejection risk, to the escape from the ethical issues springing with the use of nuclear-transplantation or embryonic stem cells[23]. Finally, co-transplantation of HSCs and non-haematopoietic tissue-specific stem or progenitor cells may represent a new approach to cure degenerative disorders, such as neurological diseases, cirrhosis, insuline-dependent diabetes mellitus, muscle loss conditions and heart failure, thanks to the capacity of HSCs to favour both immune tolerance and organ regeneration[5].

Conclusion

Stem cell biology has altered the way we think about the origin and regeneration of tissues and organs. However, several questions remain to be solved, such as the identification and characterization of the TS-SCs, the evaluation of their potential and the environment which drives their proliferation and differentiation, the development of techniques that will be able to guarantee the stability of manipulated cells, through a safe and effective gene-therapy, and to prevent ageing and oncogenicity of the transplanted cells. When we will solve these questions, stem cells biology will really burst into the clinic, making possible to find new therapies also for those pathologies, such as cancers, degenerative, autoimmune and genetic disorders, that at present cannot be successfully prevented and resolutely cured.

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