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EDITORIAL

Stem cells, a two-edged sword: Risks and potentials of regenerative medicine

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Abstract

The recent advancements in stem cell (SC) biology have led to the concept of regenerative medicine, which is based on the potential of SC for therapies aimed to facilitate the repair of degenerating or injured tissues. Nonetheless, prior to large scale clinical applications, critical aspects need to be further addressed, including the long-term safety, tolerability, and efficacy of SC-based treatments. Most problematic among the risks of SC-based therapies, in addition to the possible rejection or loss of function of the infused cells, is their potential neoplastic transformation. Indeed, SCs may be used to cure devastating diseases, but their specific properties of self-renewal and clonogenicity may render them prone to generate cancers. In this respect, 'Stemness' might be seen as a two-edged sword, its bright side being represented by normal SCs, its dark side by cancer SCs. A better understanding of SC biology will help fulfill the promise of regenerative medicine aimed at curing human pathologies and fighting cancer from its roots.

Key words: Stem cells; Regenerative medicine; Gastrointestinal diseases; Chronic liver diseases; Cell-based therapy

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A LESSON FROM THE PAST: STEM CELLS AND TUMORS

The recorded history of human cancer begins with an Egyptian papyrus, dating between 3000 and 2000 B.C., which describes breast tumors in humans. The nomenclature 'cancer' was first proposed by Hippocrates. The term derives from the Greek words carcinos and carcinoma, both literally meaning crab. Galen offered a possible explanation for this name based on similitude with either the morphology of cancer or with its tenacious and parasitic behavior. According to legend, Celsus attempted to classify pathologic masses into three categories: secundum naturam, associated with pregnancy; propter naturam, the tumefaction which develops following traumas and leads to tissue repair; and contra natura, synonymous with cancer[1,2]. After two millennia, this classification has found renewed perspective based on recent advancements in cell biology, with particular emphasis on the concepts of stemness and SCs.

In multicellular organisms, tissues are organized in a hierarchical manner, with SCs residing at the apex of the developmental pathway. SCs are defined as undifferentiated cells capable of self-renewal and differentiation into diverse mature progenies[3,4]. Therefore, SCs play a central role in tissue genesis, regeneration and homeostasis by providing new elements to increase tissue mass during pre- and post-natal growth, and replacing cell loss due to senescence or damage[5,6]. SCs are thought to alternate symmetric and asymmetric divisions, hence maintaining the property of self-renewal[7]. SCs possess a hierarchy of potentialities: from the totipotency of the zygote and its immediate progeny, to the pluripotency of embryonic SCs (ESCs), and the multi/unipotency of adult SCs (ASCs)[5,8,9]. ESCs are pluripotent cells derived from the inner cell mass of the blastocyst. ESCs can generate

any differentiated phenotype of the three primary germ layers by a process called determination[9,10]. At the end of embryogenesis, each tissue contains a heterogeneous population of cells at different stages of maturation, including relatively undifferentiated, self-renewing cells, termed adult SCs (ASCs). ASCs have a limited differentiation potential and are responsible for turnover and repair within the tissue of origin. ASCs have been identified in several organs, such as bone marrow (BM), gastrointestinal epithelium, skin, brain, muscle, and liver[8,11,12]. SCs colocalize with supporting cells in a physiologically limited and specialized niche, that varies in nature and location depending upon the tissue type[13,14]. The reciprocal interactions between SCs and their niche influence SC behavior: a complex network of developing signals regulates the balance between quiescence and the dividing state, leading ASCs toward self-renewal or differentiation[15,16]. According to the hierarchical model, long-term SCs (true SCs, extremely rare, with high differentiation potential and proliferative capacity) can give rise to short-term SCs (transit-amplifying or committed progenitors), which in turn are able to differentiate into mature elements providing tissue-specific functions[5,17]. Despite the paradigm of unidirectional cell determination, recent studies have shown that ASCs are endowed with an unexpected plasticity, as circulating adult progenitor cells can differentiate into mature cells of other tissue types[10,14,18]. A particularly high degree of plasticity is shown by bone marrow SCs (BM-SCs), which *in vivo* and *in vitro* studies have proved to be able to differentiate into a wide range of non-hematopoietic phenotypes[19-22]. It has also been demonstrated that BM-SCs normally circulate in the peripheral blood, and that the number of circulating SCs committed toward neuronal and hepatic differentiation increases following treatment with mobilizing agents[23]. This phenomenon has led to speculation about the existence of BM-derived pluripotent SCs, which could migrate from the peripheral blood into various tissues and contribute to normal turnover and repair following injury[5,15,24].

REGENERATIVE MEDICINE BASED ON STEM CELLS

The recent advancements in SC biology have led to the concept of regenerative medicine, which is based on SC potential for therapies aimed to facilitate the repair of degenerating or injured tissues[6]. SC-based therapies could be used to cure degenerative disorders associated with the loss of ASC functions, such as hematologic, cardiovascular, muscular and neurological diseases, gastrointestinal pathologies and chronic hepatopathies. SCs can be obtained from various sources, including embryos, fetal tissues, umbilical cord blood and adult organs. Once isolated, these cells may be forced to expand and differentiate into functional progenies suitable for cell replacement and tissue engineering[24]. ESCs, which have been isolated from humans and mice, can be maintained in an undifferentiated state indefinitely, though they seem to develop genetic abnormalities over long periods in culture[15,25]. ESCs and their derivatives might constitute an easily available source to obtain a large number of transplantable cells for regenerative treatments. Nevertheless, the possibility of immune rejection and teratoma/teratocarcinoma formation in the recipients represent major obstacles to the success and safety of ESC clinical applications[26]. A promising alternative source for SC-based treatments may be represented by cells established from fetal organs and placental tissues, which do not seem to form teratomas/teratocarcinomas in humans. In particular, several studies have indicated that umbilical cord blood SCs (CBSCs) are an easily accessible source of multipotent SCs, which may be readily available for transplantation, or for further expansion and manipulation prior to cellular therapies[8]. The plasticity and accessibility of CBSCs has provided the rationale for creation of CBSC unit banks, where these cells can be collected and stored for future use[24]. Finally, the manipulation and/or stimulation of ASCs seems to be the most promising tool for SC-based treatments, as it could improve the endogenous regenerative potential without risk of rejection and overcome the ethical and political issues related to embryonic and fetal SCs[6,8,24].

Focusing on ASC-based therapies in Gastroenterology, first attempts to translate regenerative medicine from theory to clinical practice have been made for various diseases, including celiac disease and inflammatory bowel disorders (IBD). In particular, following autologous BM transplantation, in a selected group of refractory celiac patients, significant histological improvement associated with impressive clinical progresses has been recorded[27,28]. Crohn's disease (CD) and ulcerative colitis (UC) are characterized by a status of chronic inflammation, mainly as a result of local immunological imbalance[29]. Several studies have suggested that either allogeneic or autologous BM-SC transplants may be effective in inducing CD and UC remission[30]. Various authors report their experience with IBD patients who underwent BM-SC transplantation for haematological malignancies and maintained a complete remission of their intestinal disease following transplantation[30]. The specific pathways and molecular mechanisms underlying the beneficial effects of HSC transplantation in IBD are still largely undefined. The immune system ablation followed by allogeneic transplantation of BM-SCs might provide a reset of the host immune system imbalance. Moreover, BM cells might contribute to tissue repair by facilitating neoangiogenesis and might also differentiate into epithelial cells and myofibroblasts[30,31]. The potential of BM-derived SCs in the treatment of IBD is currently being analyzed in clinical trials[30]. SCs might be used to cure other gastrointestinal pathologies, such as gastric ulcers, gastrointestinal motility disorders, and diabetes mellitus (DM)[32,33]. Regarding the latter, a major challenge in the treatment of DM is to provide patients with an insulin source that regulates glucose levels on a mandatory minute-to-minute basis[34,35]. In recent decades, new therapeutic strategies for the treatment of DM type I have been proposed, such as growth factor

administration, islet cell transplantation and also SC infusion to replace the dysfunctional beta-cells[35]. Different adult sources of extra-pancreatic SCs have been investigated, including CBSCs, whose efficacy for the treatment of DM has been shown in diabetic mice[36-39]. Another candidate for DM regenerative therapy is represented by BM-SCs. Numerous reports have showed that the infusion of BM-SCs can restore chemically-induced DM in mice[40,41]. Along with extra-pancreatic SC-based therapies, other researchers have focused their interest on endogenous pancreatic SCs (PSCs). The quest for an organ-bound PSC has received growing attention by the scientific community, because PSCs hold several advantages over extra-pancreatic sources, combining the ability for prolonged proliferation with an already established pancreatic commitment[35,42]. Finally, recent reports have demonstrated that extra-pancreatic, organ-bound SCs, such as liver SCs[43-46], human adipose tissue-derived mesenchymal SCs[47] and gastrointestinal SCs[48] can differentiate into islet cells. Unfortunately, there are still no functional studies that show biphasic insulin release upon glucose challenge by these cells.

In Hepatology, the most appealing application for SC-based therapies consists in the treatment of end-stage hepatic diseases. Chronic liver pathologies affect almost a fifth of the general population, often requiring an orthotopic liver transplantation (OLT)[49]. Given the donor organ shortage, various alternatives to OLT have been evaluated, including cell-based therapies which are currently under investigation all over the world. Cell-therapies in hepatology have numerous advantages when compared to OLT: the cells can be expanded *in vitro*, genetically manipulated, cryopreserved, obtained from the same patient and infused without major surgery. Possible cell-based treatments consist of hepatocyte transplantation and the development of bio-artificial liver systems (BALs). BALs have been mainly applied as supportive devices in patients excluded from or waiting for OLT and hepatocyte transplantation has limited overall success, related to the large amount of cells required to achieve acceptable function[50,51]. Therefore, SC-based therapies are emerging as new alternatives to OLT for end-stage liver pathologies. The most promising source for SC-based therapies is currently represented by BM-SCs and/or by mobilizing/proliferating agents, such as granulocyte-colony stimulating factor (G-CSF), which is able to both enhance the BM-SC mobilization into the peripheral blood and facilitate the endogenous liver SC activation[52,53]. BM-SCs seem to be physiologically involved in the processes of liver repair in humans[54,55]. The possible therapeutic potential of these cells has been investigated by intraportal autologous transplantation of BM-SC, which achieved some clinical improvement[56,57]. However, some authors reported negative results regarding BM-SC-therapies for end-stage liver disorders[58]. Other clinical approaches have been based upon the administration of G-CSF alone or in combination with the reinfusion of the mobilized BM-SCs. The feasibility, safety, and pattern of BM-SC mobilization following G-CSF treatment in patients affected by cirrhosis has been evaluated in a few clinical trials[59-64].

Overall, the use of ASCs for the treatment of gastrointestinal and hepatic disorders holds several advantages, such as easy accessibility, unlimited supply (given the possibility to expand the collected cells *in vitro*) and no risks of rejection or need for immunosuppressive therapies when autologous cells are employed. Nonetheless, some conceptual issues still limit the diffusion of such treatments into clinical practice. Firstly, on the basis of preclinical data, BM cells seem to facilitate gastrointestinal and hepatic regeneration mainly by a microenvironment modulation, which is likely to be transitory. In such a case, multiple treatments would presumably be required to achieve significant and lasting clinical results. Moreover, it has been observed that in some models of apparent transdifferentiation, SCs may actually be fusing with cells in the host tissue. Fusion phenomena between BM-SCs and other cells (Purkinjie cells, cardiomyocytes and hepatocytes) have been shown both *in vitro* and *in vivo*[15,24]. The implications of this discovery are notable: fusion and transdifferentiation are not synonymous, since transdifferentiation requires that a specific SC program be activated on the basis of extracellular signals, whereas in the case of fusion, the plasticity is trigged by endogenous factors upon mixing of the cytoplasm and joining of the nuclei. It must also be noted that the fused cells are aneuploid and potentially unstable[15]. Consequently, the possibility of cell fusion and the risk of malignant transformation of the transplanted cells, especially those pre-expanded *in vitro* before reinfusion, cannot be excluded and impose a need for careful evaluation and longer follow-up periods for assessing the safety and efficacy of these SC-based treatments[24].

STEM CELL ORIGIN OF CANCER AND CANCER STEM CELLS

In the nineteenth century, Virchow and Cohnheim proposed that some tumors, such as teratocarcinomas, exhibiting features of a whole range of different organs and therefore mimicking fetal development, could originate from embryonic rests[10,65-67]. Over 150 years later, the hypothesis of a SC origin of cancer lends itself to a modern-day interpretation of this theory: in a given tissue, somatic tumors could originate from the malignant transformation of a SC or its progeny during the determination process, a phenomenon called maturation arrest[10]. It is well accepted that carcinogenesis is a multistep process, involving accumulation of genetic mutations leading to the transformation of normal cells into tumorigenic cells. Every proliferating cell within a tissue may be targeted by carcinogenetic stimuli and undergo the process of transformation. Because of the specific characteristics of SCs, mutations within the SC compartment may result in cancer transformation[15]. Similarly, tumors might also arise from mutated progenitor cells which have regained the property of self-renewal, thereby dedifferentiating towards a SC phenotype[68-72]. Presumably, fewer mutagenic changes are required to transform a SC, in which the machinery to specify and

regulate self-renewal is already active, as compared to more committed progenitor cells, in which self-renewal must be activated ectopically[70]. Another potential source of tumorigenic cells may be represented by circulating pluripotent cells, originating from the BM and able to migrate into non-hematopoietic sites. The existence of such a population of SCs, whose properties are reminiscent of ESCs, has been suggested in humans and experimental animal models[73]. Once recruited, these cells may behave as normal SCs, and, therefore may accumulate mutations over time and initiate malignancies. Indeed, a recent report described a mouse model of gastric cancer induced by *H Pylori* infection, in which BM-derived cells were able to contribute to cancer development[74]. The hypothesis of a SC origin of tumors imposes caution when proposing SC-based therapies to treat human diseases. It is well known that ESCs may give rise to tumors, while cancers derived from ASC-therapies have never been reported. Nonetheless, the long-term safety of ASC infusion has not been adequately tested: preclinical studies and clinical trials with longer follow-up periods should be recommended prior to large-scale clinical applications of such cell-based therapies.

Along with the possible role of SCs in the cellular origin of tumors, mounting evidence suggests that cancer might be considered as a SC disease. Over the past 30 years, several studies have demonstrated that most cancers possess a hierarchic organization: the great majority of cancer cells cannot sustain the tumor mass, nor establish secondary lesions elsewhere in the body. Only a minority of cancer cells appear to be tumor-initiating and possess the metastatic phenotype. These cells have the property of self-renewal, can differentiate into any cell within the tumor population, and can migrate, establishing metastases. Given the similarities between normal SCs and tumor-initiating cells, the latter have been termed cancer SCs (CSCs)[75]. Studies on acute myelogenous leukemia (AML) firstly showed that only a small subset of cancer cells was capable of extensive proliferation both *in vitro* and *in vivo*. Two models have been proposed to explain this phenomenon: the stochastic theory and the cancer SC theory[76]. In the first model, processes of self-renewal versus differentiation occur randomly, so that every cancer cell has an equal probability of retaining self-renewal capacity. Conversely, the cancer SC theory postulates a hierarchical organization of functionally distinct cell subpopulations, at the apex of which resides a small population of tumor-initiating cells, responsible for cancer growth and progression. Such a hierarchical organization was first documented in hematological malignancies by Dick *et al*, who showed that only AML-initiating cells could induce AML when transplanted into SCID mice[77,78]. These results represented both the first direct demonstration of the existence of CSCs, and a proof of principle extendible to solid tumors. Currently, distinct populations of CSCs have been identified within the hematopoietic system[77,79], breast[80], brain[81], prostate[82,83], lung[84], skin, bone, kidney, ovary, head and neck cancers, and also gastrointestinal and liver tumors[85-90].

Tumor-initiating cells mimic SC properties to sustain the growth and spread of the tumor, while eluding the intrinsic and extrinsic controls that regulate homeostasis within SC populations. The unique properties of CSCs explain the failure of traditional chemotherapic strategies aimed at reduction of tumor mass by targeting proliferating cells: CSCs are usually quiescent and thus refractory to these treatments. The cancer SC hypothesis offers new insights for the development of therapeutic strategies in oncology, which will require a deep understanding of CSC molecular profile and biological behaviour[15,65]. Potential targets for CSC-based therapies in oncology might be found by comparing SC and CSC properties. i.e. it is well known that CSCs share molecular pathways involved in the maintenance of stemness (such as Wnt, Sonic Hedgehog, and Notch signalling) with SCs and that they are responsive to similar motomorphogens involved in both SC migration and cancer metastasis. The development of drugs antagonizing these signals may be helpful in inhibiting CSC proliferation and mobilization, therefore blocking cancer growth and metastasis[15,65]. Moreover, SCs and CSCs are able to secrete cytokines and angiopoietic factors which are critical for sustaining tumors, and that can be specifically targeted by anti-angiogenetic therapies[24]. However, an ideal CSC-based therapy would require targeting of CSCs, while sparing normal SCs. Indeed, despite similarities in terms of immunophenotype with their normal counterparts, some cell-surface markers and metabolic pathways must differs in CSCs compared with SCs, implying a biological uniqueness of CSCs. As a consequence, the identification of specific CSC-markers and pathways appears to be fundamental in order to develop novel therapeutic strategies in oncology. The quest for a surface marker which will enable isolation and further characterization of tumor-initiating cells within human cancers has already begun. Several studies have suggested that the CSC fraction within various tumors might be identified by the expression of CD133, a trans-membrane glycoprotein[91]. CD133 is expressed by progenitor cells belonging to neuronal, hematopoietic, epithelial and endothelial lineages and its expression has been reported in several tumor tissues, including melanomas, kidney, ovarian, colon and liver cancers[85-91]. In our opinion, CD133 might be useful to enrich the CSC fraction within some tumors, but it cannot be considered as a specific cancer SC-antigen. Indeed, CD133 is expressed by various normal SCs and also progenitor cells; moreover, upon a careful examination of the published studies, it seems that only a minority of CD133+ cancer cells is tumor-initiating[85-91].

STEMNESS AS A TWO-EDGED SWORD

A regenerative medicine based on SCs is no longer a future perspective, since SC research is already supporting an escalating industry, engaged in testing treatments for every sort of disease. Nonetheless, critical aspects need to be further addressed, including the long-term safety, tolerability, and efficacy of SC-based treatments, as well as their carcinogenic potential. Indeed, SCs represent the key to tissue genesis, regeneration and homeosta-

sis. However, for their specific characteristics, SCs may also represent a unique target for tumorigenic stimuli[16]. Stemness might be seen as a two-edged sword, its bright side being represented by normal SCs, its dark side by CSCs. This scenario leads to a reinterpretation of the previously mentioned Celsus' tumor classification, where ESCs represent the source of tumors secundum naturam; normal ASCs restore homeostasis following injuries, being responsible for tumors propter naturam; CSCs mimic normal ASCs in respect to self-renewal potential, but elude homeostatic regulation, resulting in tumors contra natura.

The CSC hypothesis imposes caution when proposing SC-based therapies, because infused SCs may degenerate into CSCs and give rise to neoplasms. This possibility should impose further preclinical studies prior to large-scale clinical applications of SC-based therapies. However, the CSC hypothesis also offers new insights for anti-cancer treatments, based upon the similarities and differences between SCs and CSCs. As a consequence, normal SC and CSC research must proceed side-by-side, because the identification of unique CSC targets requires a deep understanding of normal SC molecular profile and properties. The promise of regenerative medicine based on SCs imposes a better knowledge of SC and CSC biology, to help prevent and cure human pathologies and fight cancers from their roots.

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