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Recent Progress on Tissue-Resident Adult Stem Cell Biology and Their Therapeutic Implications

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Abstract

Recent progress in the field of the stem cell research has given new hopes to treat and even cure diverse degenerative disorders and incurable diseases in human. Particularly, the identification of a rare population of adult stem cells in the most tissues/organs in human has emerged as an attractive source of multipotent stem/progenitor cells for cell replacement-based therapies and tissue engineering in regenerative medicine. The tissue-resident adult stem/progenitor cells offer the possibility to stimulate their *in vivo* differentiation or to use their *ex vivo* expanded progenies for cell replacement-based therapies with multiple applications in human. Among the human diseases that could be treated by the stem cell-based therapies, there are hematopoietic and immune disorders, multiple degenerative disorders, such as Parkinson's and Alzeimeher's diseases, type 1 or 2 diabetes mellitus as well as eye, liver, lung, skin and cardiovascular disorders and aggressive and metastatic cancers. In addition, the genetically-modified adult stem/progenitor cells could also be used as delivery system for expressing the therapeutic molecules in specific damaged areas of different tissues. Recent advances in cancer stem/progenitor cell research also offer the possibility to targeting these undifferentiated and malignant cells that provide critical functions in cancer initiation and progression and disease relapse for treating the patients diagnosed with the advanced and metastatic cancers which remain incurable in the clinics with the current therapies.

Keywords

Adult stem/progenitor cells; Regenerative medicine; Cancer stem/progenitor cells; Targeted therapies; Gene therapy

Introduction

Recent progress in the stem cell research, especially on the tissue-resident adult stem cell biology, has suspired great optimism and given new hopes in offering the possibility to use

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these undifferentiated cells or their further differentiated progenies for cell replacement in regenerative medicine and cancer therapy in human [1–16]. All of multipotent adult stem/progenitor cells are characterized by an unlimited self-renewal capacity and are able to give rise to the mature cell lineages in tissue from which they originate along the lifespan of an individual [2–9,11–14,16–25]. Moreover, certain adult stem/progenitor cell types, and more particularly, bone marrow (BM)-derived stem/progenitor cells may also be attracted at distant extramedullary peripheral sites after intense injuries and participate to the tissue repair through remodeling and regeneration process of damaged areas [2, 8, 11, 16, 26–30]. These unique features of adult stem/progenitor cells make them a relevant and suitable source of immature cells for the repair of damaged tissues after severe injuries based on the body's own regenerative potential. The *in vivo* stimulation of tissue-resident adult stem cells or use of their *ex vivo* expanded and differentiated progenies is emerging as a promising approach with multiple important clinical applications for cell replacement-based therapies and tissue engineering [1, 2, 4–9, 11–15, 23, 31–35]. Among the human inherited and degenerative disorders that could be treated by stem cell-based therapies, there are age-related functional defects, hematopoietic and immune disorders, type 1 or 2 diabetes mellitus, lung, liver and cardiovascular diseases, neurodegenerative and eye disorders and aggressive and recurrent cancers [8, 9, 11, 13, 15, 16, 18, 20, 28–30, 36–60].

Numerous recent investigations revealed that the accumulation of genetic and/or epigenic alterations occurring in stem/progenitor cells during aging and severe injuries including chronic inflammatory atrophy could trigger their malignant transformation into cancer stem/progenitor cells [11, 16, 23–25, 31, 32, 34, 36, 61–67]. Thus, the targeting of the deregulated signaling pathways in the cancer stem/progenitor cells, which may contribute to their sustained growth, survival, invasion, metastasis and/or treatment resistance during cancer progression, is also of particular therapeutic interest for eradicating these cancer-initiating cells [11, 16, 23–25, 36, 67, 68]. The elimination of cancer stem/progenitor cells should permit to counteract the cancer progression and disease recurrence. Thereby, the targeting of cancer stem/progenitor cells and their local microenvironment should lead to a complete remission of patients diagnosed with advanced and metastatic cancers which remain lethal in the clinics with the current surgical, hormonal, radiation and/or chemotherapeutic treatments. We describe here the anatomic localization, known specific biomarkers and functional characteristics of diverse human tissue-resident adult stem/progenitor cell types. The emphasis is on the recent research on adult stem/progenitor cells and their niches in term of their functions in the tissue regeneration in physiological and pathophysiological conditions. We also summarize and discuss the therapeutic potentials of adult stem/progenitor cells to give rise to particular cell lineages in the well-defined culture conditions *ex vivo* as well as in animal models *in vivo* and clinical settings. The provided information should help to develop novel therapeutic strategies that could be translated into clinical applications for treating and curing the patients with diverse degenerative disorders and lethal diseases including the metastatic and recurrent cancers.

Tissue-Resident Adult Stem Cell Types and Their Therapeutic Implications

Diverse poorly-differentiated adult stem/progenitor cell types, which have generally small size relative to the terminally differentiated cells and express specific stemness markers, such as CD133, CD44, nestin and/or ABCG2, have recently been identified in the most mammalian tissues/organs [11, 16, 36]. The adult stem cells have notably been isolated by fluorescence-activated cell sorting (FACS) with the specific antibodies directed against specific stem cell markers as well as by side population (SP) technique based on their ability to efflux Hoechst 33342 dye due to their high expression of ATP-binding cassette (ABC) transporters such as ABCG2 [11, 16, 36, 69–71]. Among the tissues and organs harboring a very small number of specific multipotent and undifferentiated adult stem/progenitor cells,

there are BM, vascular walls, adipose tissues, skeletal muscles, heart and brain as well as epithelium of lung, liver, pancreas, digestive tract, skin, limbus, retina, breast, ovaries, prostate and testis [2–9, 11–14, 16–25, 69–71]. Several efforts have permitted to establish the unique features of each tissue-resident adult stem/progenitor cell type and their specialized local microenvironment as well as their critical functions in homeostatic state maintenance and tissue regeneration [1, 5, 7, 11, 15, 16, 72–75]. In general, the adult stem/progenitor cells are localized within a specialized microenvironment designated as niche consisting of the neighboring cells such as fibroblasts, endothelial cells and/or stromal components that tightly regulate their functions through the direct interactions and release of specific soluble factors [1, 5, 7, 11, 15, 16, 24, 25, 72–74]. All of the multipotent or bipotent adult stem/progenitor cell types display a long-term self-renewing capacity and can give rise in appropriate conditions including after intense injury to all of mature and specialized cell types of distinct lineages in the tissues/organs from which they originate or in certain cases to cell lineages at distant sites [1, 2, 4–9, 11–16, 23–25, 31, 32, 34, 61]. Despite certain adult stem/progenitor cells found in BM, skin and gastrointestinal tract usually show a rapid turnover to replenish the cell loss along lifespan, other adult stem/progenitor cell types remain under a quiescent state and rarely divide in normal conditions, and undergo only a sustained proliferation after intense tissue injuries [2, 3, 11, 16, 73]. The expansion of adult stem/progenitor cell pool within niche is accomplished through a symmetric cell division that gives rise to two identical stem cell daughters. The generation of differentiated cell lineages rather generally implicates an asymmetric division of a stem cell that gives rise to one stem cell daughter and one cell termed early transit-amplifying (TA)/intermediate cell [2, 11, 16, 21, 24, 25, 72, 73]. The early TA/intermediate cells, which possess a high proliferative potential and migratory ability, may exit the stem cell niche and give rise to late TA cells. The changes in the local environment of early and late TA/intermediate cells during amplification process and their migration at distant sites from niche may also influence the phenotype of their further and terminally differentiated progenies, and thereby contribute to the populational asymmetry and cellular diversity characterizing each tissue and organ [11, 16, 76]. The tissue regeneration mediated *via* adult stem/progenitor cells is usually accompanied by environmental changes in the niche and orchestrated by several growth factor and cytokine initiated cascades. Among them, there are epidermal growth factor (EGF)-epidermal growth factor receptor (EGFR), sonic hedgehog (SHH)-patched receptor (PTCH)/Gli, wingless ligand (Wnt)/β-catenin, Notch, bone morphogenic proteins (BMPs), and stromal cell-derived factor-1 (SDF-1)-CXC chemokine receptor 4 (CXCR4) signaling pathways [11, 16, 25]. These soluble factors may be released by tissue-resident activated stem/progenitor cells and stromal cells including the myofibroblasts, endothelial cells and immune cells such as macrophages attracted at the injured areas. BM-derived stem/progenitor cells may also contribute to the tissue repair by the release of diverse factors and/or to transdifferentiate into specific cell types within the host tissue. Hence, the tissue-resident adult stem/progenitor cells are unique as compared with other embryonic, umbilical cord, fetal and placenta-derived stem cell sources, in being enriched in an anatomic location that may be easy to access. Thus, in this way the adult stem cells may be stimulated *in vivo* in their respective environment by the exogenous application of specific growth factors and cytokines in the damaged areas that restores the endogenous tissue regeneration program.

Certain aberrant molecular pathways and deregulated interactions with the niche components resulting to a dysfunctional behavior of adult stem cells have been identified and associated with the occurrence of particular human degenerative disorders and aggressive cancers [7, 11, 16, 31, 72, 73]. Hence, the supply of new functional adult stem cells or their further differentiated progenies offers great therapeutic potentials for regenerating damaged tissues as well as gene delivery vehicle for treating and even curing diverse degenerative diseases and recurrent cancers. We describe here in more detailed manner, the specific biomarkers and functional properties of tissue-resident adult stem cells

and their niches, with a particular emphasis on the adult stem/progenitor cells localized in BM, adipose tissues, muscles, heart, brain, gastrointestinal tract, liver and pancreas as well as their potential therapeutic applications in cell replacement-based therapies for treating diverse degenerative disorders and diseases in human.

BM-Derived Stem/Progenitor Cells

Hematopoietic Stem Cells—The BM-derived hematopoietic stem cells (HSCs) provide a critical role by continually renewing all of the new mature and differentiated hematopoietic cell lineages in peripheral circulation including leucocytes, erythrocytes and thrombocytes along lifespan of an individual [11, 16, 72]. The most immature and quiescent multipotent HSCs, which are characterized by the expression of specific biomarkers including $CD34^-$ or $CD34^+/CD38^{-/low}/Thy1^+/CD90^+/C\text{-}kit^{-/lo}/Lin^-/CD133^+$/vascular endothelial growth factor receptor 2 ($VEGFR2^+$) are co-localized with the osteoblasts in a specialized niche within a BM region designated as endosteum (Fig. 1) [11, 16, 72, 73, 77]. Moreover, another subpopulation of HSCs, which is found in a BM microvasculature-sinusoidal endothelium niche, appears to represent the stem cells that may rapidly supply new mature blood cell lineages which have a short live into peripheral circulation (Fig. 1) [16, 72, 74, 77].

Mesenchymal Stem Cells and Endothelial Progenitor Cells—The BM stroma as well as the walls of large and small blood vessels in most tissues/organs including brain, spleen, liver, kidney, lung, muscle, thymus and pancreas also contain the multipotent mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs) [11, 16, 29, 30, 78–82]. Much of the work conducted on adult stem/progenitor cells has focused on MSCs found within the BM stroma. More particularly, the MSCs expressing CD49a and CD133 markers are localized in a perivascular niche in BM, and may give rise to the osteoblasts that are co-localized with HSCs, and which may support the hematopoieisis by producing the growth factors and cytokines that promote the expansion and/or differentiation of HSCs (Fig. 1) [11, 16, 83, 84]. The BM-derived or tissue-resident MSCs can generate diverse mesodermal cell lineages involved in osteogenesis, adipogenesis, cartilage and muscle formation including the osteoblasts, osteocytes, adipocytes, chondrocytes, myoblasts and myocytes under appropriate culturing conditions *ex vivo* and *in vivo.* Moreover, MSCs may also be induced to differentiate into fibroblasts, neuronal cells, pulmonary cells, pancreatic islet β cells, corneal epithelial cells and cardiomyocytes *ex vivo* and/or *in vivo* using specific growth factors and cytokines [11, 16, 21, 85–91]. In the case of EPCs, which are derived like HSCs from the embryonic hemangioblasts, they may be distinguished by the expression of different biomarkers, including $CD34^+$ or $CD34^-$, CD133, vascular endothelial growth factor receptor- 2 (VEGFR-2), also designated as Flk-1 (fetal liver kinase-1), stem cell factor (SCF) receptor KIT and CXCR4 [24]. EPCs may contribute in a significant manner to give rise to mature endothelial cells that form new vascular walls of vessels after intense injury and vascular diseases (Fig. 1) [11, 16, 29, 30, 79, 81, 92]. The critical role of circulating EPCs in endothelial cell maintenance after tissue injury is notably supporting by the observation that their number and function is inversely associated with the progression of atherosclerosis and an enhanced risk of cardiovascular diseases. Hence, all of the above functional properties of BM-resident stem cells made them the promising sources of immature cells for treating numerous degenerative and vascular disorders in human.

Therapeutic Applications of BM-Derived Stem/Progenitor Cells

The autologous or allogeneic transplantation of BM or peripheral blood (PB) can lead to the homing and engraftment of functional HSCs, MSCs and EPCs and/or their differentiated progenies at BM and distant damaged tissues. Thus, this supports the feasibility of this strategy for improving the tissue remodeling and healing processes after severe injury (Fig.

1) [11, 16, 79, 81, 87, 88, 90]. More specifically, HSC transplants, alone or in combination therapy, may be used for the treatment of patients with autoimmune diseases, refractory and severe aplastic anemias, congenital thrombocytopenia, osteoporosis, cardiovascular disorders, chronic inflammatory Bowel disorders (IBD) including Crohn's disease and ulcerative colitis, diabetes mellitus, leukemias, multiple myelanomas and Hodgkin's and non-Hodgkin's lymphomas and aggressive tumors [1, 2, 11, 16, 57–60, 93–97]. It has also been reported that MSCs, EPCs and their progenies can contribute to the regenerative process of several tissues including bone, cartilage, tendon, muscle, adipose, brain, lung, heart, pancreas, kidney and eye [98, 99]. Thus, these immature cells may constitute a cellular source for the treatment of diverse human disorders including osteogenesis imperfecta, atherosclerotic lesions, ischemic cardiovascular and muscular diseases (Fig. 1) [11, 16, 79, 81, 87, 88, 90, 100]. Importantly, adult BM-derived and tissue-resident MSCs are little immunogenic and display immunomodulatory and anti-inflammatory effects in host *in vivo* [96, 99, 101]. Therefore, these therapeutic properties of MSCs also support their possible clinical applications to prevent the tissue/organ allograft rejection and severe acute graft-versus-host diseases as well as to treat the autoimmune disorders such as inflammatory bowel disease and inflammation of the heart muscle walls associated with autoimmune myocarditis in which immunomodulation and tissue repair are required [96, 99, 102]. Indeed, MSCs can prolong skin allograft survival and reverse severe acute graft-versus-host disease *in vivo* supporting their use in treating skin diseases as well as in the maxillofacial surgery [99, 103].

In counterpart, the migration and proliferation of vascular smooth-muscle cells (SMCs) derived from BM cells including HSCs and MSCs in vascular injured area leading to an excessive cell accumulation may however contribute to the development of vascular pathologies such as intimal hyperplasia and atherosclerotic lesions (Fig. 1) [104, 105]. The recruited SMCs may mediate their detrimental effects through the synthesis of the extracellular matrix components such as collagen and fibronectin that accumulate on the luminal side of the damaged vessel walls, and thereby induce an occlusive vascular remodeling that may result in an ischemic heart attack or restenosis (Fig. 1) [104]. Therefore, future studies to optimize the BM-derived cell transplantation strategies and establish the specific mechanism(s) of action and physiological effects of HSCs, MSCs and EPCs at long term is essential in order to improve their therapeutic and curative benefits and prevent their detrimental clinical effects in treated patients.

Adipose Tissue-Derived Stem Cells and Their Therapeutic Applications

Adipose tissue is a highly specialized, complex and active metabolic and endocrine structure that contributes to the energy storage under form of fat. In mammals, the adipose-tissues are found in diverse anatomic compartments and designed as subcutaneous adipose tissue, internal organ-surrounding adipose tissue and interstitial adipose tissue [106]. Adipose tissue, like BM, is derived from the embryonic mesenchyme and contains a stroma-vascular fraction. More specifically, adipose tissue is mainly constituted of mature adipocytes, loose connective tissue matrix, nerve tissue and stromal host cells including immature MSC-like cells, fibroblasts, vascular smooth muscle cells, endothelial cells, and immune cells such as the resident hematopoietic progenitor cells and macrophages [107]. Recent studies have permitted to identify a putative adult stem/progenitor cell population termed as processed lipoaspirate (PLA) cells or adipose tissue-derived stem cells (ADSC), within the human adipose compartment [13, 107–111]. The stromal immature cell population, termed processed lipoaspirate (PLA) cells can be easily isolated from human lipoaspirates and, like BM-derived human MSCs express the CD29, CD44, CD71, CD90, CD105/SH2 and SH3 [108]. Importantly, it has also been noticed that the PLA cells could be distinguished from BM-derived stromal human MSCs by its unique expression of antigen CD49d (a4-integrin)

and CD106 (VCAM) while they did not express MSC marker, CD106 [108]. Moreover, it has been shown that the ADSCs may be differentiated into functional cells expressing the specific markers of mesodermal (adipocytes, chondrocytes, osteocytes, myocytes, cardiomyocytes and endothelial/vascular cells, endodermal (hepatocytes and endocrine pancreatic cells) or ectodermal (neurons) tissue origin *in vitro* and/or *in vivo* under well definite culture containing specific differentiation factors [13, 52–54, 107–111]. Since human adipose tissue containing ADSCs can be easily obtained by surgical resection, tumescent lipoaspiration, or ultrasound-assisted lipoaspiration, it constitutes another promising source enriched in immature cells for cellular therapy for diverse human diseases. Among them, there are the clinical management of diverse bone, cartilage and musculoskeletal disorders, muscular dystrophies, cardiovascular and liver disorders, neuronal diseases and diabetes mellitus as well as the bioengineering of fat and musculoskeletal tissue reconstitution (Fig. 1; Table 1) [13, 52–54, 109, 112, 113].

Muscle-Derived Stem Cells and Their Therapeutic Applications

Adult skeletal muscles contain two distinct stem/progenitor cells, the muscle-derived stem cells (MDSCs) and satellite cell population that may actively participate to myofiber regenerative process and repair of injured or diseased musculoskeletal tissues [20, 114]. Muscle-committed satellite cells expressing the markers such as M-cadherin, myogenic factor 5 (MYF5) and paired box gene 7 (PAX7) transcription factors, and neural cell adhesion molecule-1, are quiescent progenitor cells located at the periphery of skeletal myofibers under homeostatic conditions [20, 115]. The satellite cells endowed with self-renewal ability may be activated and to trigger a migration and differentiation into myogenic cells *in vitro* and after muscle injury *in vivo* [20, 115]. In addition, the multipotent MDSCs, which may correspond to the more immature progenitor cells relative to satellite cells, can give rise to satellite cells and more committed progenies such as musculoskeletal, osteogenic, chondrogenic, vascular, cardiac and peripheral nerve (Schwann cells and perineurium) cell lineages *in vitro* under specific conditions and induce new myofiber formation in animal models *in vivo* [19, 20, 51, 114, 116, 117]. Muscle stem/progenitor cell-based regenerative therapy and orthopaedic tissue engineering using *ex vivo* gene therapy, are promising approaches for the treatment of muscle atrophy with aging, muscle wasting (cachexia) and various musculoskeletal and neuromuscular degenerative disorders such as muscular Duchenne and Becker dystrophies and amyotrophic lateral sclerosis as well as the urological degenerative disorders and cardiovascular disorders (Fig. 1; Table 1) [20, 114, 118]. More specifically, Duchenne muscular dystrophy (DMS) is a severe X-linked recessive muscle disease occurring majoritly in boys, which is associated with a defect on the gene encoding protein dystrophin on the sarcolemma of muscle fiber, and that results in a rapidly progressive weakness of the body's muscles [113, 119]. At present time, no curative treatment for DMS exists and the current therapies principally consist to delay its progression and provide palliative cares that will result to the death of young patients. Importantly, the results from a phase I trial have revealed that the autologous transplantation of $CD133^+$ MDSCs was safe, without systemic secondary effects and improved the symptoms of DMS in treated patients [119]. Recently, MDSC or ADSC injection based-therapies have also emerging as a potent alternative therapeutic option for the remedial treatment of deficient urethral functions such as the repair of the damaged urethral sphincter associated with the stress urinary incontinence [118].

The genetic and/or epigenic alterations and changes in the microenvironment "niche" of adult MDSCs and/or satellite cells or the embryonicmuscle precursorsmay however lead to defective skeletal muscle differentiation and rhabdomyosarcoma development [120–123]. The metastatic forms of embryonal, alveolar and pleomorphic rhabdomyosarcomas have a poor clinical management and prognosis. Thus, among the possible therapeutic approaches

to treat the rhabdomyosarcomas, the targeted therapies consisting to the toxic gene product delivery in satellite tumor cells by the carriers such as MSCs may represent a promising strategy [120]. In addition, it has also been observed that the injection of MDSCs or MDSC engineered to overexpress vascular endothelial growth factor (VEGF) into an animal model of acute myocardial infraction induced angiogenesis and improved cardiac function suggesting that the MDSCs could constitute an adjuvant therapy for treating the cardiovascular disorders (Fig. 1) [124].

Cardiac Stem/Progenitor Cells and Their Therapeutic Applications

The heart is a vital muscular organ that by its repeated and rhythmic contractions is responsible for pumping the blood through the circulatory system and delivering the oxygenated blood *via* the systemic circulation to all parts of the body. The heart muscle is constituted by the cardiac involuntary striated muscle cells also called cardiomyocytes or cardiac myocytes. Importantly, the cell renewal in the adult myocardium may be accomplished along lifespan *via* the activation of cardiac stem/progenitor cells (CSCs) found within the specialized niches localized at the apex and atria of the heart (Fig. 1) [9, 11, 16–18, 125, 126]. CSCs are able to give rise to three major cell types constituting the myocardium including cardiomyocytes, smooth muscles and vascular endothelial cells in physiological and pathological conditions. With this regard, in infracted myocardium of patients with heart failure or animal models, the regenerative process appears notably to occur through the differentiation of resident small interstitial cells expressing nestin, KIT, Sca-1 and efflux transporters, P-glycoprotein and ABCG2 into cardiomyocytes, endothelial cells, smooth muscle cells, neuronal cells and fibroblasts [127]. Therefore, the *in vivo* stimulation of these endogenous CSCs or the intravascular, intramyocardial or catheter-based delivery of *ex vivo* expanded CSCs or their further differentiated progenies may constitute the therapeutic strategies for the cardiac cell replacement-based therapies (Fig. 1; Table 1) [9, 11, 16–18, 128–131]. Particularly, the CSC-based therapies could be used to replace the aged, dysfunctional or lost CSCs by new functional cardiomyocytes and regenerate coronary vessels after cardiac injury. The transplantation of genetically modified cells also offers great promise by permitting to delivery a specific therapeutic gene product such as angiogenic factors or survival agents of endogenous cardiomyocytes in the ischemic or non-ischemic heart diseased areas (Fig. 1). For instance, it has been observed that the transplantation of tumor necrosis factor receptor (TNFR) gene-modified MSCs induced an anti-inflammatory effect and inhibited the apoptotic death of resident cardiomyocytes, and thereby improved the left ventricular function in rat with acute myocardial infraction [132]. Similarly, the transplantation of adenovirus carrying human vascular endothelial growth factor 165 (Ad-hVEGF165) gene-transfected MSCs into rats with ischemic heart disease significantly promoted the host-derived angiogenesis and produced effective myogenesis as compared to MSCs transplant [133]. The transplantation of angiogenin-overexpressing human MSCs obtained after infection with adenovirus containing angiogenin gene (AdAng) also improved the heart perfusion and function in a porcine model of chronic ischemia as compared to MSC (AdNull) [134]. These treatment types, alone or in conjunction with the conventional medical therapies by using pharmaceutical agents such as angiotensin-converting enzyme (ACE) inhibitors, β-adrenergic blockers, and nitroglycerin, should permit to improving the myocardiac regeneration and long-term outcome of patients diagnosed with heart failures resulting from ischemic heart disease, hypertension and myocardial infarction [9, 11, 16–18, 37, 128–131, 135].

In addition, several lines of evidence have also revealed that the functional and contractile cardiomyocytes and/or vascular endothelial cells could be derived from other stem/progenitor cell sources including embryonic stem cells (ESCs), umbilical cord blood (UCB)-derived stem cells ($CD133^+$ cells, HSCs or MSCs), amniotic epithelial stem cells (AECs),

BM-derived stem cells ($CD133^+$ cells, HSCs, MSCs or EPCs), ADSCs, MDSCs, pancreatic stem cells (PSCs) and adult testicular stem cells or their progenies *in vitro* and/or *in vivo* under specific differentiation conditions [9, 11, 13, 16, 18, 37, 38, 87, 88, 110, 125, 130, 136–139]. Interestingly, it has been observed that the co-culture of adult rat liver stem cells or human PSCs in a cardiomyocyte microenvironment consisting to the rat neonatal cardiac cells or human myocardial biopsies, respectively promoted their differentiation into autonomously contracting cardiomyocyte- like cells *in vitro* [140]. Hence, these stem/progenitor cell types or their further differentiated progenies could be used for improving the myocardial and vascular regeneration and cardiac function. In support with this, the results from some investigations have revealed the potential benefit to use these stem cell types or their further differentiated progenies with the cardiomyogenic properties to repair the damaged myocardium in animal injury models *in vivo* [13, 16, 17, 37, 38, 87, 88, 110, 128–130, 138, 139]. For instance, it has been observed that the transplantation of *ex vivo* differentiated cardiomyocytes derived from human ESCs resulted in a stable cardiomyocyte engraftment and improvement of myocardial performance in rat with extensive myocardial infraction [141]. The data from small clinical trials have also revealed that the transplantation of human BM-derived stem cells, mobilized PB cells or purified $CD133^+$ BM-derived stem cells into patients with advanced ischemic heart diseases generally improved the vascularization process and/or myocardial function [37, 131, 136, 142, 143]. More specifically, the BM-derived cells, ADSCs and MDSCs may contribute to the repair of the injured cardiovascular system *via* multiple molecular mechanisms. Among them, there are the transdifferentiation of these adult stem cells into new cardiomyocytes, smooth muscle cells and/or endothelial cells as well as their release of diverse paracrine factors such as hepatocyte growth factor (HGF), insulin-like growth factor (IGF-I) and VEGF that may in turn stimulates the angiogenesis and endogenous CSCs and inhibit their apoptotic/necrotic cell death (Fig. 1) [92, 124, 144–146]. More specifically, BM-derived MSCs recruited to the infracted heart in animal model *in vivo* seem principally to mediate their therapeutic cardioprotective effects through the releasing of paracrine growth factors and cytokines including HGF that promotes the repair of cardiac lesion by inducing re-vascularization of diseased vessels and stimulating resident CSCs that contribute to repair of damaged cardiac lesion [102, 144, 147].

Unfortunately, in certain cases, MSCs may also differentiate into aortic smooth muscle cells and contribute to intimal hyperplasia development after coronary vascular injurywhose pathological effect may be attenuated by co-culture with late-outgrowth endothelial cells (Fig. 1) [105]. Moreover, it has also been observed that MSCs may display cytogenic instability and may differentiate toward progenies endowed with unwanted phenotype *in vivo* such as osteocytes and adipocytes that are undesirable for their therapeutic application in the cardiac repair [148]. All of these above detrimental effects of MSCs must be considered before their use to treat cardiovascular diseases in clinical setting.

There are great therapeutic potential and clinical interests of using these diverse stem/progenitor cell types for curing cardiovascular diseases in humans, and more particularly for treating late-stage heart failure patients that have little hope of survival without an opportunity of heart transplantation due to a massive loss of functional cardiomyocyte mass. In counterbalance, additional work appears however necessary for establish more precisely the specific biomarkers and anatomic localization, niche of endogeneous CSCs within heart and the intrinsic and extrinsic factors that regulate their self-renewal and differentiation ability. Moreover, the functional properties of transplanted stem/progenitor cells and the progenies, their cytogenetic stability at long-term, and the molecular mechanisms at the basis of observed effects in the animal models *in vivo* and clinical setting also require additional studies. Particularly, it will be important to ascertain the therapeutic effects on cardiac function associated with each stem/progenitor cell type found in BM-derived

transplants. An optimization of cell delivery methods and number of cell injected as well as the establishment of possible interactions between the cardiac cell-replacement therapies and conventional pharmacotherapies currently used to treat the ischemic and non-ischemic heart diseases in the clinics and their specific therapeutic potential after long-term treatment also merit further investigations. These future works are necessary for minimizing the potential clinical risks associated with cell replacement therapy before their possible applications as effective cellular or gene therapies of cardiovascular diseases in the safe conditions in humans.

Neural Stem/Progenitor Cells and Their Therapeutic Applications

Although the mammalian adult central and peripheral nervous systems have been considered during long time as non-renewal tissues, accumulating body of evidence over the past few years to reverse this dogma by showing that the neurogenesis may occur in adult life through self-renewal and multipotent adult neural stem/progenitor cells present in central and peripheral nervous tissues. More specifically, neural stem cells (NSCs) found in the adult human brain are localized within two specific neurogenic regions designated as the lateral subventricular zone of lateral ventricle in the forebrain and dentate gyrus in hippocampus (Fig. 2) [5, 11, 15, 16, 149]. Multipotent $CD133^{+}$/nestin NSCs with an astroglia-like cell phenotype are endowed with a self-renewal potential and capable to give rise to the progenitors that can proliferate and migrate at distant damaged areas of brain where they can generate further differentiated and functional progenies [5, 11, 15, 16, 149, 150]. More particularly, NSCs found in the subraventricular zone, can give rise to three principal neural cell lineages, including mature neurons and glial cells, astrocytes and oligodentrocytes while them localized in the subgranular cell layer of hippocampus may generate the granule cell projection neurons [5, 11, 15, 16, 149]. Hence, NSCs and their progenitors can participate to regenerate and repair the injured tissues after neurological damages and trauma in human. NSCs may notably give rise to diverse neural and glial cell lineages in appropriate conditions *ex vivo* and *in* vivo [11, 16, 39, 149, 151, 152]. Numerous developmental signaling cascades [EGF-EGFR, SHH-PTCH/GLI, Wnt/β-catenin, Notch, basic fibroblast growth factor (bFGF), nerve growth factor (NGF), neuregulins, BMPs, platelet-derived growth factors (PDGFs), ciliary neutrophic factor, VEGF, thyroid hormone T3, dopamine, TGF-β, integrins, Ephrins/Ephs, leukemia inhibitory factor (LIF) and/or RNA-binding proteins, Musashi (Msi-1 and Msi-2)] may contribute to the stringent regulation of the proliferation and cell fate decision of NSCs and astroglial progenitor cells in developing and adult CNS [5, 16]. In regard with this, the sustained activation of these mitotic cascades including EGF-EGFR and SHH-PTCH pathways in NSCs may also result in their malignant transformation and brain tumor formation [16, 24, 25, 31, 34, 36, 67]. The local microenvironment of NSCs also may influence their behavior. The changes in the niche components including neighboring endothelial cells co-localized with NSCs in the subraventricular zone may assume a critical function during regeneration process as well as during the progression of several neuropathologic diseases including the brain cancers which may arise from the alterations occurring in NSCs and their microenvironments [5, 11, 15, 16, 149]. More recently, the adult stem/progenitor cells derived from neural crest-derived stem cells have also been identified in peripheral nervous system within a germinal center designated carotid body (CB) [153]. Multipotent CB-resident adult stem cells, which represent the glia-like sustentacular cells expressing the glial markers can give rise to the dopaminergic glomus cells that produce the glial cell line-derived neurotrophic factor [153].

The identification of NSCs has important therapeutic repercussions by offering the possibilities to stimulate them *in vivo* or replace these immature cells by new one for treating diverse CNS degenerative disorders including Parkinson’s, Alzheihmer’s, Lou Gehrig’s and Huntington’s diseases, temporal lobe epilepsy, stroke, multiple sclerosis and

amyotrophic lateral sclerosis (Table 1) [11, 15, 16, 39–42, 149, 154–159]. Several lines of evidence revealed that the *ex vivo* expanded NSCs or their progenies may be transplanted in damaged areas of brain where they can proliferate, survive, migrate, and differentiate into functional neural and glial cell *in* vivo [11, 16, 157–160]. For instance, it has been reported that the transplantation of adult neural precursor cells (aNPCs) from the brain of adult transgenic mice into the spinal cords of adult Shiverer (shi/shi) mice with congenitally dysmyelinated adult CNS axons, give rise to the cells expressing the oligodendrocyte markers and resulted in formation of nodes of Ranvier and improved axonal conduction [157]. Importantly, it has also been reported that the transplanted dopaminergic neurons derived from mouse ESCs survived for more than 32 weeks and displayed the functional properties into an animal model of Parkinson's disease [159]. In regard with this, the intrastriatal transplantation of CB-stem/progenitor cells or their progenies also offers great promise as antiparkinsonian therapy [153]. Additionally, ESCs, fetal stem/progenitor cells, UC-derived stem cells, AECs, BMSCs including MSCs, ADSCs, and pluripotent epidermal neural crest stem cells (eNCSCs) found in bulge areas within the hair follicle of the skin may also be induced to differentiate or transdifferentiate into functional neurons (tubulin-β and Tuj1), astrocytes (glial fibrillary acidic protein, GFAP) or oligodendrocytes (O4) *in vitro* and/or *in vivo* [11, 13, 16, 39, 161–163]. These observations support the feasibility to use these immature cells or their further differentiated progenies for treating diverse incurable neurodegenerative diseases. Nevertheless, before the clinical applications of NSCs, CB-resident stem/progenitor cells and other stem/progenitor cell sources for neurorestoration therapies, future investigations are required in order to more precisely establish the extrinsic and intrinsic factors that control their behavior within the niche *in vivo* as well as their therapeutic advantages at long term after treatment initiation.

Ocular Stem Cells

Corneal and Conjunctival Epithelial Stem Cells—The human ocular surface is covered by the corneal, limbal, and conjunctival epitheliums. These stratified and squamous epitheliums, which consist from a basement membrane cover up by the epithelial cell layers, are connected *via* a connective tissue, the stroma (Fig. 3). Functionally, all of these three epithelial regions of the ocular surface may protect against fluid loss and pathogen entrance while the connective tissue and stromal cells may act for providing the oxygen and nutrients. More particularly, the cornea is avascular under the normal physiological conditions and constitutes the transparent front part of the eye that provides critical functions in permitting at the light to reach the retina and protecting against insults from external environment. Several lines of evidence have revealed that the renewal of the mature corneal epithelial cells may be accomplished *via* the activation of a small population of corneal epithelial stem cells (CESCs) found within a distant compartment know as the limbus situated at the junctional zone between the cornea and conjunctiva [4, 11, 16, 69, 164, 165]. CESCs also designated as limbal stem cells, appear notably to be concentrated within the basal cell layer of limbal epithelial crypts in a definite structure termed as Palisades of Vogh (Fig. 3). The limbal CESCs, which express several markers [p63, ABCG2, α9- and β1-integrins, EGFR, cytokeratin 19 (K19), α-enolase, CD71, CCAAT enhancer binding protein δ (C/EBPδ), Bmi-1 polycomb ring finger oncogene and Msi-1] but do not form gap junctions, possess the ability to reconstitute an intact and functional corneal epithelium *in vivo* [4, 69–71, 164–166]. In fact, despite CESCs are generally maintained under a mitotically quiescent state in homeostatic conditions prevalent in their specialized local microenvironment "niche", the changes in their local microenvironment, and more particularly after corneal epithelium injury, may result in their activation [71, 167, 168]. The extrinsic signals provided by activated limbal stromal cells including melanocytes, myofibroblasts and endothelial cells as well as resident MSCs and BM-derived cells attracted at limbus may contribute to the stimulation of CESCs and generation of further differentiated progenies. For instance, after

ocular injury, the limbal CESCs are activated by a complex network of growth factors such as EGF, FGF, TGF and PDGF and inflammatory cytokines and can produce by asymmetric division the stem cell daughters that remain undifferentiated and replenish the limbal CESC pool and the early TA/intermediate cells (Fig. 3) [169]. Early TA/intermediate cells in turn may proliferate and give rise to late TA/intermediate cells that migrate to the corneal surface epithelium where they undergo a differentiation into corneal epithelial cell precursors (Fig. 3). The corneal epithelial cell precursors display a rate of proliferation inferior to that of CESCs *in vitro* and correspond to a basal cell population that are involved in the replenishment of the corneal epithelium cells, which have a limited lifespan of less than 1 year in homeostatic conditions [4]. Hence, a transient renewal of the corneal epithelial cell precursors located in basal cell layer derived from limbal CESCs, may contribute to replace unfunctional or lost corneal epithelial cells after wounding, and thereby repair the damaged areas of corneal surface. On the other hand, the limbal CESCs in the adult cornea are also able to transdifferentiate into neurons and glia-like cells *ex vitro* in the presence of BMP and under heterotopic transplantation.

Retinal Stem Cells—The retina is a multi-layered sensory tissue constituted from neural cells that lines the back of the eye. During mammalian eye development, the neural crest-derived optic vesicle under the influence of the mesenchyme gives rise to the neural and non-neural tissues including the neural retina, the pigmented epithelium, the iris, the ciliary epithelium of the ciliary body and the optic stalk [170]. Importantly, the retina may also continue to grow after birth and new cells may be generated during lifespan after injury due to the presence of retinal stem cell (RSCs) resident in a region adjacent to the retina, the ciliary epithelium (CE) located in the pigmented ciliary bodies of the adult mammalian eye (Fig. 3) [11, 16, 170–173]. These multipotent RSCs located in the pigmented ciliary bodies, also designated CE stem cells, express several stem cell markers, including telomerase, neural markers such as nestin, and retinal progenitor markers such as Pax 6 [170–172]. The stringent regulation of the proliferation *versus* differentiation of RSCs in CE is accomplished through the activation of distinct mitogenic and differentiation signaling cascades such as FGF2, EGF, hedgehog, KIT, and Notch pathways, which are also known to be important regulators of neurogenesis [11, 170, 171]. The activated RSCs in CE can give rise to neural spheres containing the cell types that in turn can differentiate *in vitro* into distinct adult retinal progenitor populations, including retinal ganglion cells, as well as rod photoreceptors, bipolar cells, and Müller glia, which are derived from early and late stages of retinal histogenesis, respectively [171, 172]. In spite of this advance, future works are required to establish the functional properties of RSCs and the niche components as well as their possible implication in the replenishment of the functional retinal cell types in normal and pathological conditions *in vivo*.

Other Ocular Stem Cell Types—In addition to CESCs and RSCs, another putative stem cell population, which appears to be sequestered in a niche localized at the region between the corneal endothelium and the trabecular meshwork, may also give rise to both the mature cells that constitute the corneal endothelium and trabeculae [174]. Moreover, the conjunctival epithelial stem cells enriched in the bulbar and forniceal conjunctiva, may contribute to the conjunctival epithelium regeneration [175]. Importantly, multipotent MSC-like cells expressing octamer-binding protein/Nanog/Rex/CD29/CD44/CD166/CD13/SH2/SH3 have also been isolated from the stroma in human eye conjunctiva biopsies. These immature cells can differentiate toward the osteogenic, adipogenic, chondrogenic and neurogenic lineages *in vitro* [176]. Hence, all these above adult stem/progenitor cell types found in different ocular compartments in adult eye may contribute to the maintenance of the eye homeostasis and visual acuity along lifespan. Future research on the regulatory mechanisms of self-renewal and fate decision of ocular stem cells, and more particularly on

the specific signals from their local microenvironment should permit to establish more precisely the influence of the stromal cells and/or extracellular components on their behavior. These additional investigations should lead to more successfully surgical engraftment procedures of the ocular stem cells. In regard with this, we reviewed here the recent advances in the development of novel ocular stem cell-based transplantation strategies for treating the diseased eyes.

Eye Diseases and Stem Cell-Based Treatments

The development of novel stem cell-based transplantation strategies has improved considerably the efficacy of treatments for corneal and retinal diseases, and thereby lead to the new surgical methods to preserve or restore the vision [177, 178]. The current surgical approaches in ophthalmic practice to manage severe ocular surface disease consist to the epithelial tissue transplantation with or without the use of bio-engineering support into the diseased eye. Among these procedures which aim at replacing unfunctional or loss conjunctival and/or limbal stem cells, there are limbal autograft, conjunctival autograft, conjunctival limbal autograft, living related conjunctival allograft, keratolimbal allograft, with the biological supports such as amniotic membrane. Moreover, the *in vivo* stimulation of immature limbal CESCs, conjunctival stem cells and RSCs in CE in human adult eye, which possess the capacity to give rise to the epithelial and neural cell lineages, also offers the possibility to stimulate these adult stem cell types for the repair of damaged corneal and conjunctival epithelia and retina after severe injuries.

The occurrence of limbal and cunjunctival epithelium damages may cause a partial or complete loss of limbal CESCs and/or conjunctival stem cells, and thereby this deficiency in turn may lead to an interruption of supply of the essential corneal epithelial cell precursors arising from the TA/intermediate cells and result in a partially or completely defective cornea regeneration process (Fig. 3). In the case of a major corneal epithelium degeneration that affects whole ocular surface due to a partial or total limbal stem/progenitor cell deficiency, the cornea does not maintain its natural functions, and thereby the corneal wound healing may result in the persistence of recurrent epithelial defects. Numerous growth factors and inflammatory cytokines released by corneal epithelial cells, keratocytes, endothelial cells and recruited immune cells may act in cooperation to promote the corneal wound healing [169]. Moreover, in certain pathologies, the corneal remodeling may be accompanied by a neovascularization of corneal stroma, ulceration, chronic inflammation, opacification, and scarring associated with the invasion of the corneal surface by the conjunctival epithelial cells “conjunctivalization”, and ultimately may lead to blindness and a partial or complete loss of vision [169, 179]. The available treatments for severely injured ocular surface may consist to stimulate the residual limbal CESCs in patient’s limbus *in vivo* by using appropriate growth factors or alternatively to perform an autologous or allogenic graft transplant of the new exogenous and functional limbal CESCs from patient’s or host donor’s limbus onto damaged ocular surface of diseased eye. The limbal CESCs explants may be cultured and expanded *ex vivo* on appropriate extracellular carrier/matrix consisting to human amniotic membrane, anterior lens capsule, human AECs used as feeder layers or fibrin based substrates which can help maintain and support their expansion and survival in acting as the microenvironmental components within the niche [11, 16, 180]. A new effective strategy of treating limbal CESCs deficiency-derived eye disorders in clinic is to transplant a bio-engineered graft by expanding limbal and/or cunjunctival epithelial stem cells *ex vivo* on amniotic membrane [4, 11, 16, 180]. The amniotic membrane covered by host epithelium constitutes an ideal extracellular matrix for eye surgery because it displays the biological and physical properties that are very similar to the ocular surface tissue of eye. Particularly, the amniotic membrane does not contain blood vessels, has a similar thickness and is relatively transparent like the cornea surface. Hence, the amniotic membrane exhibits

important clinical beneficial effects since it may promote the ocular surface healing by supporting epithelial cell attachment, growth and differentiation of CESCs into functional corneal epithelial cells and providing anti-scarring, anti-angiogenic, and anti-inflammatory properties [4, 11, 16, 180]. The amniotic membrane transplant, especially when performed with limbal and/or conjunctival stem cell autograft, is now being used extensively in ophthalmic practice. The surgically transplantation of resultant bioengineered composite as autologous or allogenic graft tissues onto the damaged corneal surface of eye may represent an effective strategy for ocular surface reconstruction. This therapeutic treatment may be used for treat the patients with partial or total limbal and/or conjunctival stem cell deficiency, persistent epithelial defects due to chemical or thermal burns of the ocular surface, bullous keratopathy, glaucoma, oculoplastic and refractive surgery and primary pterygium [11, 16, 181, 182]. Additionally, the results from recent investigations in animal models have also revealed the possibility to use BM-derived human mesenchymal cell transplants, which can engraft at injured cornea and act in synergy with HSCs, to promote cornea wound healing after alkaline or chemical burn [167, 183]. Moreover, it has been reported that the differentiation of human ESCs into corneal epithelial-like cells may be performed *in vitro* using limbal fibroblasts' conditioned medium which may provide the collagen IV acting as CESC's niche component [184]. Similarly, the ESC-derived neural progenitors which express the regulatory factors that are implicated in retinal differentiation also may differentiate along photoreceptor lineage in response to epigenetic cues suggesting their potential application for treating certain retinal diseases [185].

The ocular stem cell-based therapies might then offer an alternative to patients with ocular lesions and a unique therapeutic chance for restoring the vision of patients with severe or complete corneal-limbal epithelial and retinal defects. Future research on the identification of specific biomarkers and potent growth factors, cytokines and immunoregulatory molecules that may influence the self-renewal capacity and differentiating rate of limbal and retinal stem/progenitor cells in normal and pathological conditions is however necessary for the optimization of their *in vivo* or *ex vivo* expansion and use in the optimal and safe conditions as therapeutic treatment to care the diseased eye and recovery of the functional vision. This should improve the *ex-vivo* expansion techniques of ocular stem cells, reduce the risk of graft rejection which represents yet one of the major cause of stem cell-based treatment failure, and thereby result in a high success rate of ocular surface transplantation in clinical opthamologic practice.

Gastrointestinal Stem/Progenitor Cells and Their Therapeutic Applications

The mucosal surface of the gastrointestinal tract is lined by a simple columnar epithelium that is organized under form of invaginations, designated as the crypt-villus structures, which are surrounded by the connective tissue (Fig. 4). More specifically, the intestinal epithelium acts as a physical barrier which protects against the aggressions from external environment including the microbial infection. The gastrointestinal epithelium is a complex tissue with high rate of cell turnover where the cells that reach the villus tip are shed from intestinal and gastric epithelium and constantly replaced by new specialized epithelial cells. In regard with this, several accumulating lines of evidence indicated that the regeneration of intestinal epithelial cells in villi is provided through the precursor cells arising from a multipotent intestinal stem cells located at the base of each crypt of Lieberkühn (Fig. 4). More specifically, the small intestinal epithelial stem cells expressing markers such as Msi-1, CD24, KIT and leucine-rich-repeat-containing G-protein-coupled receptor 5 (Lgr5) appear to reside up at the crypt base within a protective niche containing the surrounding mesenchymal cells [11, 16, 186–188]. These stem cells can give rise to all cell types within each crypt including the Paneth cells that migrate down at the base of crypt as well as the highly proliferative precursor cells that migrate up at the bottom the crypt where they

differentiate into absorptive enterocytes, mucus-secreting globlet cells and peptide hormone-secreting enteroendocrine cells that form villus epithelium (Fig. 4) [3, 11, 186, 188]. Similarly, the stem/progenitor cells in the colon, which are localized at the crypt base (due to the absence of Paneth cells), may also give rise to the proliferative progenitors that differentiate toward all lineages during epithelium regeneration [186–188]. Moreover, the millions of glands constituting the stomach also appear to arise from gastric stem/progenitor cells residing in a niche localized in the isthmus region within each gastric gland [2, 189]. The gastric stem/progenitor cells can give rise to the progenitors that may undergo a bipolar migration and differentiate into all the different types of specialized cell lineages including parietal, zymogenic and pit cells that form the functional gastric glands lining the basis of the stomach. Each gastric gland is also constituted of mesenchymal cells and extracellular matrix components that regulate the functions of gastric stem/progenitor cells through mesenchymal-epithelial interactions [2, 31, 189, 190].

The self-renewal of gastrointestinal stem/progenitor cells and differentiation of their progenies localized along crypt-villi axis is tightly regulated through the interplay of different developmental growth factor signaling including EGF, FGFs, IGF, hedgehog, Wnt/β-catenin, Notch, BNP and/or TGF-β signaling cascades [2, 31, 186, 188, 189]. Moreover, the BM-derived and gastrointestinal tract-resident mesenchymal progenitor cells may also contribute to the gastrointestinal tissue regeneration by providing new endothelial cells and pericryptal myofibroblasts that may improve the vasculogenesis, and thereby promote the epithelial repair after injury [188, 191]. The genetic and/or epigenic alterations in the gastrointestinal stem/progenitor cells or changes in their local microenvironment “niche” including the host stromal cells, resident and BM-derived myofibroblasts and immune cells, may lead to different disorders including chronic inflammatory bowel diseases such as Crohn’s autoimmune disease, intestinal and gastric ulcers and cancers [2, 3, 31, 47, 97, 189, 190, 192, 193]. Therefore, the gastrointestinal stem/progenitor cell- or BM-derived stem cell-based therapies may constitute a promising approach for improving the repair of the damaged areas of intestinal and gastric epithelium after severe injury and in gastrointestinal diseases as well as to develop new gastrointestinal tissue engineering strategies. The molecular targeting of gastrointestinal cancer stem/progenitor cells also may represent a potential therapy for treating the aggressive cancer forms as described below in more detailed manner.

Hepatic Oval Cells and Their Therapeutic Applications

Mammalian adult liver constitutes the largest glandular organ of the body and provides multiple important physiological functions related to metabolism, glycogen storage and detoxication of harmful substances from the blood. Therefore, the liver possesses unique and high capacity of tissue repair for triggering a rapid regenerative response after hepatic tissue injury, and thereby providing a constant renewal of mature liver cell mass [194–196]. In pathophysiological conditions, mature hepatocytes in fetal and adult livers can undergo several cell division cycles and are responsible for continuous hepatic cell replacement during liver injury [194, 195]. In addition, a small population of postnatal hepatic stem/progenitor cells, also designated as hepatic oval cells (HOCs), may also be activated following chronic or extensive damages of the liver, and more particularly in an environment inhibiting the hepatocyte replication [8, 11, 16, 194–197]. The HOCs appear to reside in the smallest units of the intrahepatic bile ducts within the periportal region of adult liver, termed the canals of Hering and terminal bile ductules and/or periductular region, from where they can migrate into the liver parenchyma (Fig. 4) [8, 11, 16, 195, 197]. The HOCs with an oval nuclei and limited cytoplasm as well as their early progenies may express several phenotypic markers of hepatic cells [α-fetoprotein (AFP) and albumin], biliary cells [γ-glutamyl-transferase, CK7 and 19, OV-6 (an anticytokeratin 19 antibody), OC2 (anti-

myeloperoxidase)] as well as HSCs [CD34, Thy-1, Flt3-receptor and KIT]. More recently, the analyses of the cell surface markers in adult rat progenitor cells of injury rat liver have also revealed that they expressed CD133, claudin-7, cadherin 22, mucin-1, ros-1 and Gabrp [198]. The HOCs display a bipotent ability and can give rise to a heterogeneous population of TA/intermediate cells that in turn may mature into both parenchymal cells, hepatocytes and epithelial cells of the biliary duct, cholangiocytes, and thereby contribute to liver repair [8, 195, 199, 200]. In particular, the activation of a complex signaling network involving numerous growth factor and cytokine pathways [Wnt/β-catenin, HGF/tyrosine kinase receptors for HGF (c-met), EGF/TGF-α/EGFR, tumor necrosis factor (TNF), VEGF, SCF and SDF-1] appears to play a critical role in the regulation of the proliferation, survival and differentiation of HOCs into mature hepatocytes and cholangiocytes during hepatic tissue regeneration [8, 11, 16, 31, 195, 196].

Numerous studies have revealed the beneficial effect to transplant *ex vivo* expanded fetal or adult HOCs or to activate the pool of endogenous HOCs for inducing the liver regeneration after acute liver failure and chronic liver diseases including in the late-stage cirrhoses that are associated with an important hepatocyte necrosis and loss [195, 196]. For instance, it has been observed that the transplantation of wild-type (dipeptidyl peptidase IV [DPPIV(+)]) rat fetal liver stem/progenitor cells may lead to their liver incorporation into DPPIV(−) mutant F344 rats and differentiation into mature hepatocytes and bile duct cells [201]. The transplanted progenitor cells, which repopulated about 23.5% of the total hepatic cell mass and exhibited a greater proliferative activity and a lower rate of apoptotic death relative to host hepatocytes, shown a longterm liver replacement at 6 months after cell transplantation [201]. In regard with this, it has also been noticed that the Thy-1^- stem/progenitor cells expressing α-fetoprotein, albumin, CK19, E-cadherin and CXCR4 isolated from embryonic day 14 rat fetal liver substantially repopulated normal adult rat liver and totally repopulated retrorsine-treated rat liver while the Thy-1^+/$CD45^+$/$CXCR4^+$ subpopulation was only incorporated after severe hepatic injury [202]. This suggests then that fetal Thy-1^- liver progenitor cells may represent a most immature progenitor cell population than Thy-1^+ counterpart with distinct regenerative properties [202]. In support with this, a recent study has revealed that Thy-1 expression was induced during transit-amplification process of the oval cell population while Thy-1 mRNA was undetectable in the α-fetoprotein-expressing oval cells during liver regeneration after tissue injury in animal models and patients with liver failure [203]. More recently, it has also been reported that a population of human liver stem cells (HLSCs) expressing nestin, vimentin, albumin, α-fetoprotein and several mesenchymal stem cell markers such as CD29, CD73, CD44, and CD90 could also contribute to the regeneration of the liver parenchyma in severe-combined immunodeficient mice *in vivo* [204].

In addition, the hepatocyte-like cells can also be derived from ESCs, UCB, BM and pancreatic stem/progenitor cells under specific culture conditions *in vitro* and/or *in vivo*, and thereby these cells could then constitute the alternative extrahepatic sources for liver regeneration in pathological conditions [8, 26, 151, 205]. As a matter of fact, the transplantation of BM-derived cells or enriched HSCs in the animal models *in vivo* has been observed to restore the HOCs and their progenitors and improve the liver regeneration after injury [11, 16, 26, 28]. However, despite the beneficial effects associated with the BM-derived cells, numerous studies have also indicated that the transdifferentiation of BM-derived cells into hepatocytes did not occur or only occur at a low frequency under certain physiological and pathological conditions [8, 11, 205, 206]. Thus, other molecular mechanisms including the vascular regeneration mediated by BM-derived cells may also be responsible at least in part for the improvement of liver repair after specific damages. In addition, among the most important risk factors associated with the liver cancer development there are chronic viral and alcoholic hepatitis (also known as chronic liver

inflammation) and chronic liver diseases leading to cirrhosis. In certain cases of the chronic liver diseases as well as the hepatocellular carcinoma (HCC), bile duct cancers such as intrahepatic cholangiocarcinomas and hepatoblastoma, the dysplastic foci of activated hepatic progenitor cells may be detected in diseased area suggesting that them could constitute a potent cellular target for treatment of these hyperproliferative liver disease and cancer types [11, 16, 197, 207–209].

Additional works appear to be essential for establishing more precisely the factors that control the incorporation, homing, expansion, migration and differentiation of HOCs and extrahepatic stem/progenitor cells in the liver under specific normal and pathological conditions *in vivo* as well as their specific functions in liver carcinogenesis. The differences between human and rat liver anatomy also underline the necessity to consider the species differences before to extrapolate the data obtained from animal models into human applications. Since hepatic progenitor cells can be easily expanded, genetically manipulated and potentially used in transplantation for a long-term replacement of hepatic cells, they constitute a promising strategy that could lead to development of new cell-based therapies for chronic liver diseases in human.

Pancreatic Stem/Progenitor Cells and Their Therapeutic Applications

The pancreas is a glandular organ constituted by an exocrine compartment, comprising the ductal epithelium and acinar cells that produce digestive enzymes, and the endocrine islets of Langerhans containing four different types of cells: insulin-producing β cells, glucagon-releasing α cells, somatostatin-producing δ cells and pancreatic polypeptide-containing cells (Fig. 4) [11, 210]. The pancreatic β cells, which represent the major type of endocrine cells, are co-localized near at a vascular basement membrane and produce the insulin that is released into bloodstream, and which in turn controls the level of blood glucose in the peripheral circulation [211]. Recent lines of evidence have revealed that the human and rodent mature insulin-producing islet β cells could arise from adult pancreatic stem/progenitor cells (PSCs) expressing ductal epithelial cell markers, cytokeratin 19 ($CK19^{high}$), neural (nestin) and endocrine nuclear pancreatic and duodenal homeobox factor-1 (PDX-1) markers and/or more committed $nestin^{+}/PDX\text{-}1^{+}/CD19^{low}$ islet precursors localized in the ductal regions and/or within islet compartment (Fig. 4) [10–12, 16, 210, 212–215]. Therefore, these poorly differentiated adult putative PSCs or their early progenies within the adult pancreas could represent a potential source of β cells for cell replacement or gene therapy for treating the type 1 or 2 diabetes mellitus. More particularly, the *in vivo* stimulation of putative PSCs or transplantation of *ex vivo* expanded pancreatic β cells in the host diseased recipient may constitute a therapeutic strategy for restoring the β cell mass and treating the type 1 or 2 diabetes mellitus [10, 11, 13, 16, 48–50, 216, 217]. In addition, the use of functional pancreatic insulin-producing β cell-like progenitors derived from other stem cell types [embryonic, fetal and UCB stem/progenitor cells, human amniotic epithelial cells (hAECs), placental-derived multipotent stem cells (PDMSCs), and adult stem cells including HSCs, MSCs, HOCs, NSCs, hAECs, ADSCs] also may represent an alternative therapeutic strategy for the treatment of type 1 or 2 diabetes mellitus (Table 1) [10, 11, 13, 16, 50, 82, 91, 137, 151, 216, 218–221].

Additional *in vivo* studies appear however to be necessary for establishing the beneficial effects to use these stem cell types and their further differentiated progenies for treating patients suffering from type 1 or 2 diabetes mellitus or other human pancreatic diseases in the clinics. Particularly, it will be essential to establish the effects of insulin-producing progenitors on the restoration and normalization of blood sugar levels after long-term treatment. On the other hand, the targeting of the malignant counterparts of PSCs including pancreatic cancer stem/progenitor cells and their local microenviroment involved in the development of autoimmune or chronic pancreatitis and ductal pancreatic adenocarcinomas

also offer great promises for the development of new therapeutic approaches for treating these pancreatic disorders [24, 65, 222, 223].

Cancer Stem/Progenitor Cells and Novel Targeting Therapy

Recent progress in stem cell field has also revealed the critical implications of leukemic and tumorigenic cancer stem/progenitor cells in the initiation and progression of the most the aggressive and recurrent cancers and treatment resistance [11, 16, 24, 25, 32, 36, 62–65, 67, 224]. Furthermore, further differentiated tumor cells and activated stromal cells including myofibroblasts as well as BM-derived cells including immune cells, macrophages, HSCs and EPCs attracted at the tumoral sites, also may actively collaborate during each step of the tumor formation at primary and secondary sites [16, 24, 25, 36, 67, 225–228]. Therefore, the targeting of the cancer stem/progenitor cells and their local microenviroment involved in the cancer development offers great promises for the development of new therapeutic approaches for treating the aggressive, metastatic and recurrent cancers in the clinics [16, 24, 25, 36, 65, 67]. More specifically, the molecular targeting of the oncogenic cascades such as EGFR, hedgehog and/or Wnt/β-catenin, oncogenic signaling elements [telomerase, Scr, Bcl-2, nuclear factor-kappa beta (NF-kB), phosphoinositide- 3 kinase (PI_3K)/AKT, cyclooxygenase-2 (COX-2)] and ABC multidrug efflux pumps that assume a critical function in regulating the stem cell self-renewal, differentiation, survival and/or drug resistance of cancer stem/progenitor cells, in certain leukemia subtypes, multiple myeloma and numerous solid cancers is of particular therapeutic interest for eradicating the cancer-initiating cells [11, 16, 24, 25, 31, 35, 36, 67, 68, 229]. The targeting of the microenvironment of cancer stem/progenitor cells including the host cells such as myofibroblasts that support their malignant transformation as well as the use of anti-angiogenic agents also may constitute an adjuvant treatment for counteracting the cancer progression to metastatic and lethal disease states [16, 24, 25, 36, 67]. For instance, it has been observed that the treatment of the mice bearing orthotopic U87 glioma cell xenografts with anti-VEGF monoclonal antibody, bevacizumab markedly reduced the microvasculature density and tumor growth and this anti-angiogenic effect was also accompanied by a decrease of the number of vessel-associated self-renewing $CD133^+$/$nestin^+$ brain tumor stem cells (BTSCs) (Fig. 2) [230]. Moreover, the gene therapies by using genetically-modified stem cells as carriers for the delivery of anti-angiogenic or cytotoxic agents at specific tumoral sites may also represent other therapeutic strategies for treating numerous aggressive and metastatic cancers (Fig. 2) [11, 100, 231–233]. For instance, it has been observed that genetically-modified migrating NSCs, which are able to migrate through the CNS and reach the extracranial neoplastic sites, may be transplanted in the animal models *in vivo* and specifically attracted to tumoral sites due to the release of chemotactic signals such as VEGF and SDF-1 [231, 233, 234]. Importantly, the combined treatment with 5-fluorocytosine plus engineered NSCs expressing cytosine deaminase, which acts as a pro-drug activating enzyme, resulted in significant cytotoxic effects on melanoma cells as well as a reduction in tumor border in animal models with established melanoma brain metastasis *in vivo* [234].

Conclusion and Future Research

Recent progress revealed the major implications of adult stem/progenitor cells in tissue homeostasis and regeneration after severe injuries as well as their malignant counterparts in diverse human pathologies including aggressive cancers. A better understanding of specific features of each tissue-resident adult stem/progenitor cell is however essential for the successful formulation of therapeutic approaches to treat particular degenerative disorders and diseases by cell replacement therapy. Further research is required to establish the gene expression patterns of normal and malignant adult stem/progenitor cells *versus* their

differentiated progenies in order to identify their specific biomarkers. Furthermore, the identification of the intrinsic and extrinsic factors that govern the decision between the self-renewal *versus* differentiation of tissue-resident adult stem cells as well as the influence of the extracelllular signals from their local microenvironment "niche" on their behavior *in vivo* is also of immense interest for the design of new therapeutic strategies. The characterization of the biological properties of *ex vivo* expanded adult stem/progenitor cells and their further differentiated progenies in diverse animal models *in vivo* after long-term treatment also merits future investigations. These additional studies on the adult stem/progenitor cells and their progenies should ultimately lead to the development of new effective therapies for treating and even curing numerous degenerative disorders which remain incurable with the current therapeutic treatments in the clinics.

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Abbreviations

ABC	ATP-binding cassette
ADSCs	adipose tissue-derived stem cells
ATP	adenosine triphosphate
BM	bone marrow
BMP	bone morphogenic protein
CB	carotid body
CESCs	corneal epithelial stem cells
CE	ciliary epithelium
CNS	central nervous system
CSCs	cardiac stem/progenitor cells
CXCR4	CXC chemokine receptor-4
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EPCs	endothelial progenitor cells
ESCs	embryonic stem cells
FGF	fibroblast growth factor
hAECs	human amniotic epithelial cells
HGF	hepatocyte growth factor
HOV	hepatic oval cells
HSCs	hematopoietic stem cells
IGF	insulin-like growth factor
MDSCs	muscle-derived stem cells
MSCs	mesenchymal stem cells

NCSCs	neural crest stem cells
NSCs	neural stem cells
Oct-3/4	octamer-binding protein
PTCH	patched receptor
SDF-1	stromal cell-derived factor-1
TA	transit-amplifying
UC	umbilical cord
SHH	sonic hedgehog ligand
UCB	umbilical cord blood
PSCs	pancreatic stem cells
RSCs	retinal stem cells
SMCs	smooth-muscle cells
VEGF	vascular endothelial growth factor
Wnt	Wingless ligand

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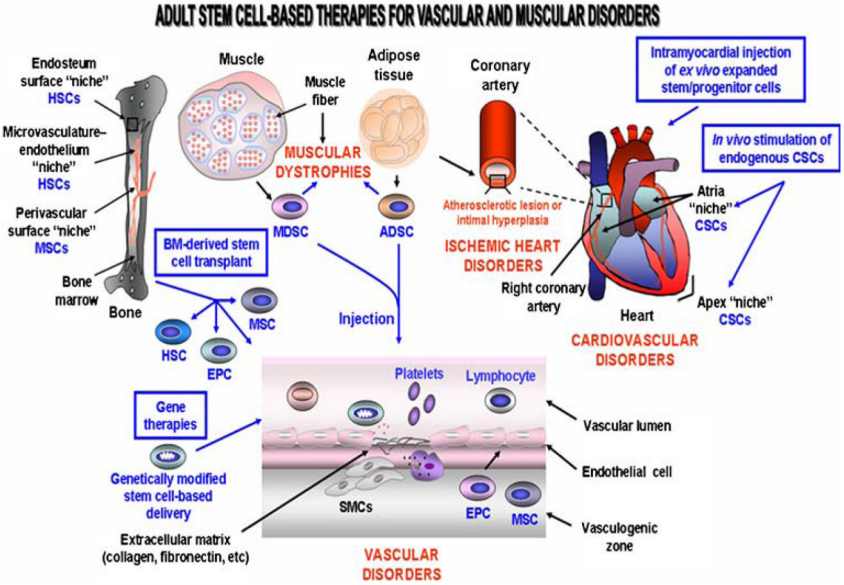

Fig. 1.

Scheme showing the possible molecular events and cellular changes associated with the development of vascular disorders and the potent cellular and gene therapies for restoring the damaged walls of blood vessels. The recruitment of smooth muscle cells (*SMCs*) which may participate to the vascular disorder formation by the release of extracellular matrix components such as collagen and fibronectin and immune cells including macrophage in injury area is shown. The stem cell-based therapy using genetically-modified stem/progenitor cells or BM-derived stem/progenitor cell transplant is also illustrated. *ADSCs*, adipose tissue-derived stem cells; *CSCs*, cardiac stem cells; *EPCs*, endothelial progenitor cells; *HSCs*, hematopoietic stem cells; *MDSCs*, muscle-derived stem cells; *MSCs*, mesenchymal stem cells

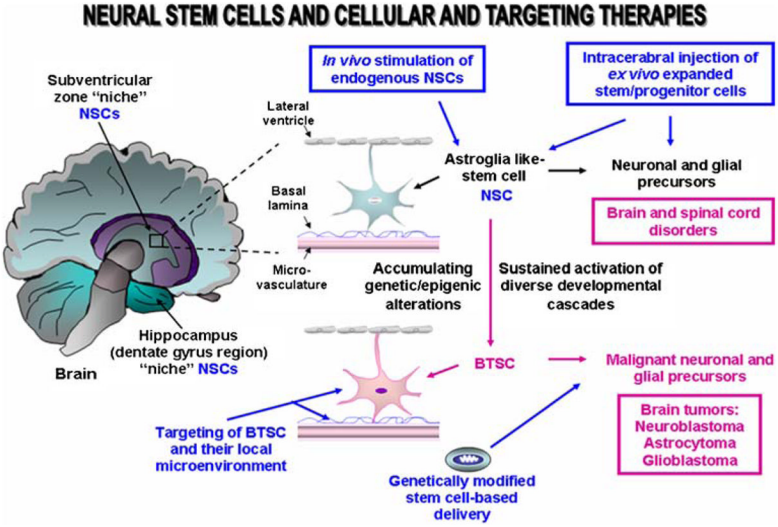

Fig. 2.

Scheme showing the anatomic localization of the neural stem/progenitor cells and their putative niches in human adult brain as well as their malignant transformation into brain tumor stem/progenitor cells. The disorders that could be treated by stem cell-based and targeting therapies are indicated. *BTSCs*, brain tumor stem cells; *NSCs*, neural stem/progenitor cells

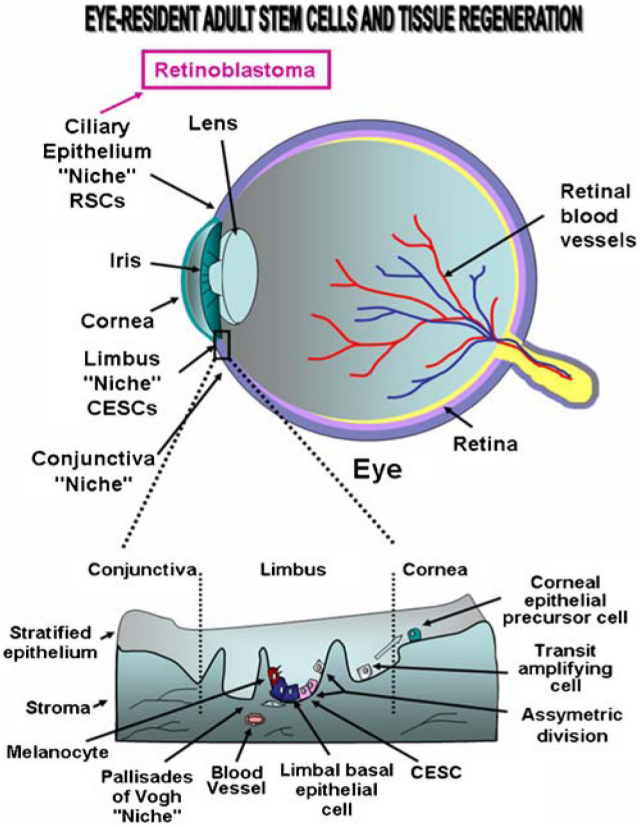

Fig. 3.

Schematic structure of human eye showing the stem/progenitor cell localization in conjunctival, limbal and corneal epitheliums and retina as well as the disorders that could be treated by stem cell-based therapies. The corneal epithelial stem cells (*CESCs*) located in basal layer of the limbal epithelium and the migration of early and late transit-amplifying (TA) cells from limbus to the corneal basal cell layer during corneal epithelium regeneration is also illustrated. *RSCs*, retinal stem cells

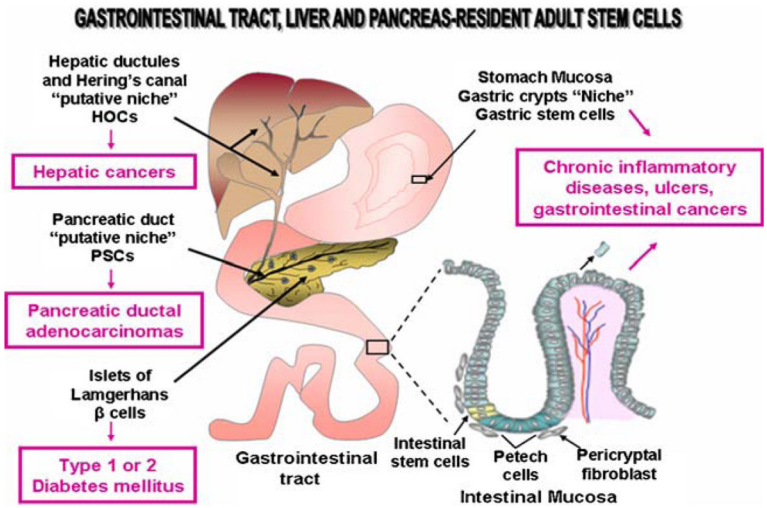

Fig. 4.

Scheme showing the anatomic localization of the adult stem/progenitor cells and their putative niches in epithelium lining the gastrointestinal tract, hepatic ductules and Hering's canal and pancreatic duct epithelium. The disorders that could be treated by stem cell-based therapies are indicated. *HOCs*, hepatic oval cells; *PSCs*, pancreatic stem/progenitor cells

Table 1

Tissue-resident adult stem/progenitor cells and their therapeutic applications in disease treatment

Adult stem cell/progenitor cell source and type	Differentiated cells	Treated degenerative disorders and diseases
BM and vascular walls		
HSCs	Myeloid and lymphoid cells, platelets	Autoimmune diseases, anemias, thrombocytopenia, leukemias, aggressive solid tumors
MSCs	Osteoblasts	Osteoporosis, Osteogenesis imperfecta
	Chondrocytes	Cartilage disorders, osteoarthritis
	Muscular cells	Muscular disorders
HSCs, MSCs	Neural cells	Nervous system disorders
	Cardiomyocytes	Heart disorders
	Insulin-producing β cells	Type 1 or 2 diabetes mellitus
	Hepatocytes	Liver disorders
EPCs	Endothelial cells	Vascular disorders
Adipose tissue/skeletal muscle		
ADSCs and MDSCs	Muscle cells	Muscular disorders (muscular Duchenne and Becker dystrophies, neuromuscular disorders)
	Osteoblasts	Osteoporosis, Osteogenesis imperfecta
	Chondrocytes	Cartilage disorders, osteoarthritis
	Endothelial cells	Vascular disorders
	Cardiomyocytes	Heart disorders
	Neural cells	Nervous system disorders
ADSCs	Insulin-producing βcells	Type 1 or 2 diabetes mellitus
	Hepatocytes	Liver disorders
Heart		
CSCs	Cardiomyocytes	Heart disorders
Brain		
NSCs	Neurons, Astrocytes	Nervous system disorders
	Oligodentrocytes	Myelin disorders
	Insulin-producing βcells	Type 1 or 2 diabetes mellitus
Eye		
CESCs	Corneal epithelial cells	Corneal disorders
Conjunctival SCs	Conjunctival epithelial cells	Conjunctival epithelial injury
CE-RSCs	Retinal progenitor cells	Retinal disorders
Skin		
KSCs, bESCs and eNCSCs	Skin cells	Skin and hair disorders
Gastroinestinal tract		
ISCs and GSCs	Intestinal and stomach cells	Chronic inflammatory bowel diseases, ulcers
Pancreas		
PSCs	Insulin-producing βcells	Type 1 or 2 diabetes mellitus
	Hepatocytes	Liver disorders
Liver		
HOCs	Hepatocytes, cholangiocytes	Hepatitis, acute liver failure, cirrhosis

Adult stem cell/progenitor cell source and type	Differentiated cells	Treated degenerative disorders and diseases
	Cardiomyocytes	Heart failures
Lung		
BASCs	Lung cells (Bronchiolar Clara Cells and alveolar cells	Interstitial lung diseases, cystic fibrosis, asthma, chronic bronchitis, emphysema

BASCs = bronchioalveolar stem cells, bESCs = bulge epithelial stem cells, CE-RSCs = ciliary epithelium-retinal stem cells, CESCs = corneal epithelial stem cells, CSCs = cardiac stem cells, EPCs = endothelial progenitor cells, eNCSCs = epidermal neural crest stem cells, GSCs = gastric stem cells, HOCs = hepatic oval cells, HSCs = hematopoietic stem cells, ISCs = intestinal stem cells, KSCs = keratinocyte stem cells, MDSCs = muscle-derived stem cells, MSCs = mesenchymal stem cells, NSCs = neural stem cells, PSCs = pancreatic stem cells, SCs = stem cells