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Targeting of cancer stem/progenitor cells plus stem cell-based therapies: the ultimate hope for treating and curing aggressive and recurrent cancers

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Abstract

The rapid progression from aggressive primary cancers into locally advanced and invasive and/or metastatic diseases remains a big obstacle for an early diagnosis and curative therapeutic intervention for cancer patients. The late-stage leukemias and disseminated and metastatic sarcomas, melanomas, brain tumors and epithelial cancers are the devastating diseases associated with a high rate of recurrence after treatment with the conventional clinical therapies including surgery, ionizing radiation, hormonal therapy and systemic chemotherapy, which generally lead to the death of patients. Therefore, the establishment of the molecular events underlying cancer initiation and progression into locally invasive and metastatic diseases is of major interest in basic cancer research as well as for the development of new effective clinical therapeutic options against the recurrent and lethal cancers. Recent advances have led to the identification of specific oncogenic products that are implicated in the malignant transformation of adult stem/progenitor cells into leukemic or tumorigenic and migrating cancer stem/progenitor cells during cancer progression. Of therapeutic interest, the molecular targeting of deregulated signaling elements in cancer stem/progenitor cells and their local microenvironment represents a new potential strategy for the development of more effective clinical treatments against aggressive cancers. Particularly, the combined use of chemotherapeutic drugs to eradicate cancer-initiating cells with hematopoietic stem cell or genetically-modified stem cell transplant is emerging as potential cancer treatments that hold great promise in the area of clinical cancer research. These targeting and stem cell-based therapies may offer the ultimate hope for treating and even curing the patients diagnosed with locally advanced cancers at high risk of recurrence, metastatic and/or relapsed cancers in the clinics.

Keywords

Adult stem cells; Neoplastic stem cells; Regenerative medicine; Gene therapy

Recent advancements in the early diagnostic and prognostic tests and therapeutic management of cancers by surgery, radiotherapy, hormonal therapy, and/or chemotherapy have led in last few years to a major improvement of clinical treatments and survival outcome for the patients diagnosed with diverse types of localized cancers.[1–15] Unfortunately, the progression from organ-confined cancers into the locally invasive and metastatic disease states frequently leads to resistance to the conventional treatments and disease recurrence, which is lethal for the patients.[8–19] This is due, in part, to the occurrence

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of some genetic abnormalities leading to an aberrant expression and/or activation of a complex network of oncogenic signaling elements (MYC, NF-κB, PI_3K/Akt, Bcl-2, survivin and/or fusion proteins resulting from chromosomal rearrangements) and down-regulation or inactivation of tumor suppressor gene products [p53, PTEN and/or Rb] in cancer cells (Figure 1).[8–18, 20–32] Particularly, the sustained activation of numerous tumorigenic signaling cascades initiated by hormones and/or distinct growth factors, cytokines and their cognate receptors in cancer stem/progenitor cells and/or their early progenies may contribute to their sustained growth, survival, invasion and/or metastatic spread during cancer progression, treatment resistance and disease relapse.[9–14, 20–22, 26–38] Hence, most patients who undergo potential curative treatments for locally advanced cancers and/or disseminated disease stages may subsequently relapse due to the persistence of cancer stem/progenitor cells and/or their early progenies in primary neoplasms and/or micrometastases at distant sites.[3, 10–15, 20, 22, 25, 26, 29–32, 39–48] Therefore, the development of novel therapeutic strategies to eradicate the total mass of cancer stem/progenitor cells and their further differentiated progenies is of great clinical therapeutic interest.

Numerous preclinical and clinical investigations have been undertaken to develop new therapeutic strategies for improving the efficacy of current chemotherapeutic regimens against locally advanced cancers at high risk of relapse as well as metastatic and recurrent cancers. Recent significant advances have been made on the development of novel combination therapies by targeting cancer stem/progenitor cells and their progenies for counteracting cancer progression and disease relapse.[3, 9–15, 20–22, 24, 26–32, 35, 36, 43, 45–47, 49–56] In general, it has been observed that the combinations of different classes of anticarcinogenic agents that target distinct oncogenic signaling elements, are generally more effective than individual drugs for eradicating the cancer-initiating cells at the primary neoplasms and distant metastatic sites.[10–14, 26, 29–32, 53–57] Unfortunately, the development of diverse resistance mechanisms by cancer stem/progenitor cells and their differentiated progenies to these chemotherapeutic regimens may still lead to the most aggressive cancer forms and disease relapse.[3, 4, 6, 9–15, 18, 20, 21, 25, 26, 29–32, 40, 45–48, 58–60] Of particular interest, the treatment consisting of molecular targeting therapy, high-dose chemotherapy, high-dose sequential chemotherapy or high-intensity ionizing radiation combined with a subsequent autologous or allogenic stem cell transplantation or genetically-modified stem cell-based therapy may constitute effective therapeutic strategies against the most of aggressive, metastatic and recurrent cancers.[8, 11–14, 26, 29, 32, 61–66] The stem cell transplant may remedy the systemic toxicity including the myeloablative effect often associated with the use of chemotherapeutic drugs at high doses. In addition, the gene therapies using genetically-modified stem cell transplant may constitute a potential approach for specifically delivering the anti-carcinogenic agents including anti-angiogenic factors or toxins in cancer stem/progenitor cells and their early progenies.[12–14, 26, 29, 32, 67–74] Among the cancer types that can be treated by these treatment types, there are relapsed/refractory leukemias, multiple myeloma and Hodgkin's and non-Hodgkin's lymphomas as well as locally advanced and/or metastatic solid tumors such as sarcomas, melanomas, neuroblastoma, medulloblastoma, lung, kidney, breast, ovarian, prostatic, pancreatic and colorectal cancers.[11–14, 26, 29, 32, 58, 65, 66, 75–89] The choice to use these stem cell-based therapeutic strategies for treating patients with aggressive cancers, and thereby counteract the recurrence of the disease, generally depends on factors such as the availability of appropriate transplant donors for the patients, age, overall health and specific oncogenic gene expression profiling of patients. In regard with this, we describe the molecular events that are often associated with cancer initiation and transition to invasive, metastatic and recurrent states. The emphasis is on the genetic and/or epigenic alterations occurring in leukemic or tumorigenic cancer stem/progenitor cells during cancer progression. Of particular interest, we also review recent advances on the development of therapeutic approaches consisting of the molecular targeting of cancer stem/

progenitor cells and their local microenvironment, cellular replacement and gene therapies that may be used for treating and even curing the aggressive and recurrent cancers.

New concepts on the implications of cancer stem/progenitor cells in cancer progression and disease relapse

Numerous recent lines of evidence have revealed that the accumulation of genetic and/or epigenetic alterations occurring in the tissue-resident adult stem cells and/or their early progenies may contribute to their malignant transformation into leukemic or tumorigenic and migrating cancer stem/progenitor cells during cancer initiation and progression (Figure 1).[10–14, 22, 26, 29–32, 34–37, 41, 44, 45, 47, 90, 91] More specifically, the highly leukemic or tumorigenic cancer stem/progenitor cells expressing the stem cell-like markers, such as CD133, CD44, Oct-3/4, c-KIT and/or ATP-binding cassette (ABC) multidrug transporters, have recently been isolated from leukemias and primary and/or secondary neoplasms from patients with skin, brain, gastrointestinal tract, pancreas, liver, breast, prostate and ovarian cancers as well as established cancer cell lines.[10–14, 26, 29–32, 34, 39, 48, 91–113] These multipotent and poorly differentiated cancer stem/progenitor cells also designated as cancer- or tumor-initiating cells were able to give rise to the total cancer cell mass *in vitro* and to reconstitute the patient's original leukemia or tumor in animal models *in vivo*.[39, 90–92, 94–103, 105, 114, 115] Importantly, certain experimental lines of evidence have also indicated that the cancer stem/progenitor cells, which express high levels of anti-apoptotic factors, ABC multidrug efflux pumps and enhanced DNA repair mechanisms could be more resistant than their differentiated progenies to radiation, hormonal and/or chemotherapeutic treatments.[10–15, 20–22, 25, 26, 29–32, 42–44] Hence, these immature cancer-initiating cells can then provide major functions in cancer progression to the aggressive and metastatic disease states, and resistance to current clinical treatments and disease relapse.[10–14, 20, 21, 25, 26, 29–32, 39, 40, 45–48, 59, 60] In this matter, the Authors are reporting the molecular events that are often associated with the early and late stages of cancer progression and treatment resistance by focusing on the critical implications of accumulating genetic abnormalities and the activation of diverse growth factors and cytokines in the malignant transformation of cancer stem/progenitor cells and/or their early progenies.

Cellular origin and clinical treatments of aggressive cancers

The precise establishment of the cellular origin and molecular events involved in cancer initiation and transition into locally aggressive, metastatic and recurrent disease stages is of major importance for the development of new effective diagnostic and prognostic methods and therapeutic interventions for cancer patients. Some recent studies revealed that the genetic and/or epigenic alterations leading to an aberrant activation of diverse developmental signaling cascades, which are involved in stringent control of the self-renewal and/or differentiation of tissue-resident adult stem cells, may occur with aging or during intense injuries such as inflammatory atrophies and fibrosis, and thereby promote leukemia or tumor initiation (Figure 1).[10–15, 20, 22, 25, 26, 29–32, 42, 116] Furthermore, the accumulation of different genetic and/or epigenic alterations in cancer stem/progenitor cells may also confer to them a more malignant behavior during cancer progression and may be associated with the occurrence of highly aggressive cancer subtypes.[10–15, 26, 29–32, 36, 46, 47, 59, 96, 97, 117] More specifically, the activation of diverse tumorigenic cascades initiated through distinct growth factors, cytokines and integrins such as epidermal growth factor (EGF)-EGFR system, hedgehog, Wnt/β-catenin, Notch, stem cell factor (SCF)/KIT, platelet-derived growth factor (PDGF)/PDGFR, stromal cell-derived factor-1 (SDF-1)-CXC chemokine receptor, transforming growth factor-β (TGF-β/TGF-βR) and/or integrin pathways in cancer stem/progenitor cells and their progenies may contribute to their sustained growth, survival, invasion and/or drug

resistance.[10–15, 26, 29–32, 36, 46, 47, 59, 96, 97, 117, 118] In addition, cancer progression is also accompanied by changes in the specialized microenvironment, niche of cancer stem/progenitors cells and stromal components, including host cells such as activated myofibroblasts, stellate cells and/or immune cells.[10–14, 26, 29–32, 119–123] The release of diverse soluble growth factors and cytokines by host stromal cells may notably contribute in a paracrine manner to the acquisition of a more malignant behavior by cancer stem/progenitors cells. In regard with this, we describe the recent observations indicating the critical functions of cancer stem/progenitors cells in cancer progression and disease relapse with a particular emphasis on the cellular origin of leukemias, sarcomas, cutaneous and non-cutaneous melanomas, brain tumors and diverse epithelial cancers as well as novel molecular targeting and stem cell-based therapeutic approaches for the treatment of aggressive and recurrent cancer subtypes.

Cellular origin and clinical treatments of leukemias

Leukemias are the types of hematological malignancies that arise from the genetic abnormalities occurring in the bone morrow (BM)-resident primitive immature hematopoietic stem cells (HSCs) or more committed lymphoid or myeloid precursors. The accumulation of genetic alterations may result in the generation of precancerous- leukemic stem/progenitor cells (pre-LSCs) also designated as precancerous stem cells (p-CSCs) followed by their malignant transformation into leukemic stem/progenitor cells (LSCs), showing abnormal proliferation and differentiation abilities (Figure 1).[4, 5, 11–14, 26, 32, 92, 115, 124–127] These molecular events subsequently culminate to the release of unfunctional leukemic blasts from BM into the bloodstream and their dissemination through the body's circulatory system. Among the leukemia types, there are acute and chronic lymphoid/lymphocytic/lymphoblastic leukemias (ALLs and CLLs) leading to deregulated lymphoid cell lineage and acute and chronic myeloid/myelogenous/myeloblastic leukemias (AMLs or CMLs) that are accompanied by the genetic alterations in he myeloid cell lineage in BM, and which lead to an accumulation of the unfunctional blood cells. In most cases, the development of leukemia is accompanied by specific chromosomal translocations in immature hematopoietic stem/progenitor cells that generate the abnormal fusion proteins as well as enhanced expression and activation of some hematopoietic growth factor and cytokine signaling cascades [hedgehog, Wnt/β-catenin, Notch, KIT and/or FMS-like tyrosine kinase 3 (FLT3) pathways] which may contribute to their malignant transformation.[11–14, 26, 32, 35, 43, 51, 127, 128] The accumulation of different genetic alterations in hematopoietic stem/progenitor cells generally results in more aggressive leukemia forms that are less responsive to current chemotherapeutic treatments and associated with a higher rate of cancer recurrence and death.[6, 8, 11–14, 17,18, 25, 26, 32, 51, 127]

The clinical treatment of leukemias may consist of chemotherapy, radiotherapy, molecular targeting therapy without or with allogeneic stem cell transplantation combined with immunosuppressive therapy (Figure 2).[11–14, 26, 32, 58, 76, 84, 85, 116] More specifically, the use of cytoreductive conditioning regimens, such as high-dose chemotherapy or ionizing radiations plus allogeneic stem cell transplantation, is generally performed as therapeutic intervention for treating the more aggressive leukemia forms at the advanced and late stages of disease or relapsed/refractory leukemias. The myeloablative treatment, which usually consists of a combination of chemotherapeutic drugs such as cyclophosphamide with busulfan or total body irradiation, permits eradicates the leukemic cells.[13, 66, 76, 129] The transplantation procedure is subsequently carried out with isolated BM- or PB-derived HSCs that have been collected from BM or by aphaeresis after their mobilization into PB by using a granulocyte-stimulating factor (G-CSF), granulocyte colony-stimulating factor (GM-CSF) and/or synthetic chemical compounds like bicyclam derivative, AMD 3100 (Plerixafor) (Figure 2).[13, 130, 131] Alternatively, bank-stored umbilical cord cells, including UC blood

and placenta cells and fetal tissues, may also be used as a HSC source for an allogeneic transplantation procedure when no appropriate graft donor is available.[11, 13, 132–134] In regard with this, UC blood also contains a substantial amount of $CD16^{-}/CD56^{+}$ natural killer cells that might be expanded in the presence of interleukin, IL-12 or IL-15 and that display a high rate of proliferation and cytotoxic effects against some cancers, and more particularly leukemias.[135] In fact, the intravenously infusion of allogeneic stem cell transplant generally leads to the engraftment and homing of immature HSCs to BM. (Figure 2).[11, 13, 65, 116] Hence, the new-engrafted HSCs can occupy the empty niche, and thereby this allows for the replacement of the HSCs and their progenies destroyed by the myeloablative treatment such as high-dose chemotherapy or total body irradiation. The BM-engrafted HSCs can repopulate the hematopoietic cells in BM and produce new functional blood cells, and thereby improve the immune response.[13, 65] Alternatively, autologous stem cell transplant after purging the leukemic cells or purified HSC transplant may also occasionally be used when no appropriate donors are available or for old patients or patients with co-morbidities.[13, 84, 136] Autologous transplantation offers the advantage of reducing the graft rejection and infection and to prevent the risk of the graft-*versus*-host disease and the immunogenic effect usually associated with allogeneic transplantation. More recently, it has also been reported that other treatment types consisting of reduced-intensity myeloablative conditioning regimens such as intermittent chemotherapy or mini-transplant by using smaller doses of chemotherapeutic drugs could be used in certain cases for the patients at high risk of developing severe secondary effects with the conventional myeloablative treatments.[13, 136] Moreover, the graft-*versus*-host disease, including the inflammatory effect, which is mediated usually by T cells from a donor, may also be prevented by retrieving T cells of the graft prior to the transplantation.[137] In addition, the chemoprotection against myelotoxicity induced by cytoreductive treatment may also be counteracted by genetic manipulations in HSCs or other hematopoietic cells, conferring them and their progenies resistance to certain cytotoxic effects of drugs, such as the expression of multidrug resistance-1 (MDR1) gene product, P-glycoprotein.[138]

For instance, CML is a myeloproliferative disease that is characterized in the most cases by the chromosomal translocation t(9;22) (q34;q11) called the Philadelphia (Ph^{+}) chromosome.[12, 13, 16, 26, 139] This chromosomal rearrangement generate a constitutively activated BCR-ABL fusion oncoprotein endowed with a tyrosine kinase activity which mediated its transforming effect, at least, in part, by speeding up cell division and inhibiting DNA repair. The treatment of patients with $BCR\text{-}ABL^{+}$ (Ph^{+}) CMLs consisting of molecular targeting of BCR-ABL protein by using a specific inhibitor of its tyrosine kinase activity such as imatinib mesylate, dasatinib or nilotinib may lead to a complete remission in the early chronic phase of the disease.[7, 8, 12, 13, 16–18, 26] Unfortunately, the persistence of primitive quiescent CML-LSCs or the occurrence of additional genetic abnormalities during disease progression to an accelerated phase and ultimately to a terminal phase, blast crisis may result in treatment resistant, disease relapse and a high rate of fatalities.[8, 12, 13, 16–18, 26, 46, 51, 127, 139–141] At the late stages of disease progression, including blast cryptis, the combination of diverse agents targeting distinct oncogenic cascades or high-dose chemotherapy plus stem cell transplantation may thus represent the more effective therapeutic options.[12, 13, 16–18, 26, 139, 142, 143] Similarly, the Ph^{+} AMLs and FIP1L1-PDGFRA positive chronic eosinophilic leukemia may also be treated by using the agents like imatinib mesylate.[7, 16, 18] Moreover, acute promyelocytic leukemia (APL), which is an AML subtype derived from a t(15;17) translocation, may generate a promyelocytic leukemia-retinoic acid receptor α (PML-RARα) fusion protein that induces an inhibition of myeloid differentiation.[144] Although the patients diagnosed with APL and other AML subtypes generally respond in the early stages to clinical therapy such as the combination of all-trans-retinoic acid (ATRA) for APL or cytarabine (ara-C) for AMLs plus anthracycline-based chemotherapy, the disease often progresses to the more aggressive

leukemia forms that are resistant to these treatment types.[4–6, 12, 13, 26] In fact, although a high rate of patients may show a complete remission with these chemotherapeutic treatments, the persistence of immature AML cells at an undetectable level with the available diagnostic methods may lead at a recurrence of leukemia. For patients at high risk of relapse or with refractory-relapsed AMLs, a potentially curative therapeutic treatment option consists then of using ATRA plus other cytotoxic drugs such as arsenic trioxide for APL or high-dose chemotherapy plus allogeneic stem cell transplants to eradicate the residual AML cells, thereby to achieving a potential curative treatment of patients.[4–6] Importantly, the data of a recent study have also indicated that BM-resident MSCs isolated from patients with acute myeloid leukemia (AML) may exhibit abnormal biological properties including a limited proliferation capacity and impaired differentiation ability.[145] Therefore, these observations underline the importance of providing new functional MSCs endowed with the immunomodulatory properties in BM-derived cell-based transplantation therapies for restoring the normal hematopoiesis in patients with AML.[65]

Cellular origin and clinical treatments of sarcomas

The sarcomas are the malignant solid tumors derived from connective or supportive tissues surrounding the organs, and which may originate at some parts of the body including in the bone, cartilage, muscles, fat, fibrous tissues, blood vessels, lymph vessels and nerve tissues.[64, 146–154, 154–164] Although the causes of the sarcoma development are not precisely known, it has been reported that certain genetic alterations, including specific mutations, inherited disorders, viral infection and/or high level of inflammation, can increase the risk of developing sarcomas. Among the most common forms of sarcoma occurring commonly in adults, there are the gastrointestinal stromal tumors (GISTs), which may arise in the gastrointestinal tract including the wall of the stomach, intestines, rectum or esophagus. GISTs are thought to originate from the interstitial cells of Cajal (ICCs) or a precursor of these cells found in the wall lining of the GI tract constituting a part of the autonomic nervous system, and which act as the pacemaker cells in controlling intestinal motility.[148, 150–152] GIST progression may result in the dissemination and metastatic spread of these cancer cells at diverse sites such as the liver, omentum and peritoneal cavity.

Other types of sarcomas, which occur more frequently in children than in adults, also include the bone cancers such as osteosarcoma and Ewing's sarcoma, retinoblastoma and rhabdomyosarcoma (Figure 1). More specifically, several lines of evidence have revealed that the bone osteoblastic and Ewing's sarcomas, which are among the most aggressive mesenchymal malignancies in childhood and young adults, may originate from the malignant transformation of primitive stem cell-like MSCs.[12, 146, 147, 149, 153–155] The osteoblastic sarcoma development, which is often accompanied by germinal mutations in *p53* and *Rb* tumor suppressor genes, may notably result in the aggressive cancer forms that can metastasize at distant sites including the lungs.[146, 147, 153, 165, 166] In the case of Ewing's sarcoma, which is a member of Ewing's family tumors (EFTs), the occurrence of a chromosomal translocation resulting in EWS-FLI-1 fusion oncoprotein that acts as an aberrant transcriptional activator, appears to contribute to tumor development.[154] Additionally, the ocular retinoblastoma appear to arise from tumorigenic retinal cells with properties like multipotent retinal stem/progenitors (RSCs) in the nerve tissues at the back of the eye (Figure 2).[156–159] The ocular retinoblastoma, which are often accompanied by leukocoria (white pupil) and misaligned eyes (strabismus) usually occurs in young children and its causes may be hereditary or nonhereditary (sporadic).[160] The retinoblastoma is generally associated with the mutations in the *Rb* tumor suppressor gene that gives an unfunctional Rb gene product. In fact, the mutant Rb protein remains always under its phosphorylated form and it does not interact with E2F transcription factor. Thereby, cell division occurs and leads to the malignant transformation of cells. The ocular retinoblastoma

progression may lead to metastatic spread and the formation of diverse secondary cancers including osteosarcoma and Ewing's sarcoma and usually has a poor prognosis.[167, 168]

In general, the treatment of the sarcoma depends on the location of the disease and the aggressiveness and grade of the tumors at the time of diagnosis. The localized and low grade sarcomas are usually treated by surgery, radiation therapy and/or chemotherapy, while high grade sarcomas including metastatic and relapsed sarcomas are treated by radiation, chemotherapy, alone or in combination with stem cell transplantations.[61–63, 87, 160, 169] Moreover, the treatment of metastatic GISTs, which frequently harbor the activating mutations in KIT (also known as CD117) and PDGFRA tyrosine kinase receptors, may also include diverse molecular targeting-based therapies including the use of agents such as dual KIT/PDGFA tyrosine kinase inhibitor, imatinib mesylate or sunitinib.[148, 150–152, 170, 171]

In addition, embryonic, alveolar and pleomorphic forms of rhabdomyosarcoma are rare types of sarcoma occurring principally in muscle tissues in children and younger adults. The rhabdomyosarcoma appear to arise of genetic and/or epigenic alterations in the embryonic muscle precursor or adult muscle-derived stem cells (MDSCs) and/or satellite cells that results in a defective skeletal muscle proliferation and differentiation.[32, 161–164] More particularly, different genetic alterations occurring in the *p53* and *Rb* tumor suppressor genes as well as the activation of *MYCN* and *Ras* proto-oncogenes, human telomerase reverse transcriptase (hTERT) catalytic subunit and/or different growth factor cascades such as hedgehog may lead to different rhabdomyosarcoma subtypes.[161, 164] The treatment of localized rhabdomyosarcomas primarily consists of chemotherapy, radiation therapy and in certain cases, surgery, when the tumor is accessible, alone or in combination. When the tumor is not resectable or has metastasized, the long-term survival of patients is poor and the disease remains incurable with these treatments. Another potential therapeutic approach to manage the metastatic rhabdomyosarcomas may thus consist of the high-dose chemotherapy and/or stem cell-based therapies such as the use of genetically-modified MSCs that can act as a carrier to specifically deliver the toxic gene products in MDSC or satellite cell-derived tumor cells.[63, 64, 66] Interestingly, the results from a recent preclinical study have also revealed the possibility of using the pharmacological agents inhibiting the cyclin D-dependent Cdk4 and Cdk6 kinase activity to possibly promote the myogenic differentiation in rhabdomyosarcoma, and thereby inhibit the tumor growth.[172]

Cellular origin and clinical treatments of cutaneous and non-cutaneous melanomas

Although the localized cutaneous melanomas diagnosed in the early stages are usually curable by surgical resection of malignant tumors, invasive melanomas that have penetrated deeper into the skin and spread to distant sites represent one of the most aggressive form of skin cancer that may cause the death of the patients.[3, 173] Cutaneous melanomas appear to arise from the malignant transformation of adult pluripotent epidermal neural crest stem cells (eNCSC) or their progenitors localized in bulge areas of hair follicles into tumorigenic cancer progenitors, and whose cells are the precursors of the pigmented cells, melanocytes that produce the pigment melanin that give the colors to our skin, hair, and eyes.[3, 11, 12, 105] Moreover, the change in the stromal environment of tumor cells including the activation of fibroblasts and their conversion into myofibroblasts may also contribute to melanoma progression.[174]

In general, an enhanced risk for an individual to develop cutaneous melanomas depends on several factors including sun exposure, familial genetic predisposition, such as the genetic alterations in *BRAF* (v-raf murine sarcoma viral oncogene homolog B1), *p53* and/or *p16* genes, and the activation of growth factor cascades, such as hedgehog and Notch pathways.[3, 173, 175] The potential management of invasive, metastatic and/or relapsed melanomas may consist of metastasectomy, chemotherapy such as dacarbazine (DTIC),

alone or in combination with other chemotherapeutic drugs and radiotherapy without or plus stem cell-based transplantation therapies.[3, 173] Moreover, certain patients with aggressive and incurable melanomas may also choose to enroll in novel clinical experimental trials with new treatments such as immunotherapy-based melanoma vaccines, chemoimmunotherapies with immunosuppressive agents such as interferon-α, gene therapies and anti-angiogenic therapy (thalidomine, angiostatin and endostatin), which represent the promising research areas on developing novel melanoma treatments.[176] In regard with this, it has recently been reported that the melanoma stem cells can be efficiently targeted by using cancer testis antigens (CTA)-directed immunotherapeutic strategies.[177] Moreover, the combined treatment with 5-fluorocy-tosine plus engineered NSCs expressing cytosine deaminase, which acts as a pro-drug activating enzyme, resulted in a significant reduction in the tumor border in animal models with established melanoma brain metastasis *in vivo.*[72]

In addition, the non-cutaneous malignant melanomas may also originate in different body compartments such as soft tissues and eyes and be associated with specific genetic alterations and changes in the stromal microenvironment.[174, 178–183] More specifically, the most common non-cutaneous melanomas, uveal melanomas are rare and aggressive intraocular primary cancers of the ureal tract, which is the pigmented layer of the eye that includes the iris, ciliary body, and choroids (Figure 2). Uveal melanomas are thought to derive from the neuroectodermal-like cells that give rise to the melanocytes in the pigmented layer of the uveal tract of the eyes. The potential curative treatments of uveal melanomas may consist of local tumor resection, radiotherapy, and ultimately to the enucleation procedure. Although the small and localized intraocular melanomas are generally not aggressive and curable by these therapeutic intervention types, the locally advanced and invasive forms, and more particularly the ciliary body or choroidal melanomas, are very serious and devastating diseases that may cause blindness and result in metastatic and lethal disease stages. The poor prognosis of patients with aggressive uveal melanomas underlines the need to further identify their precise cellular origin as well as the molecular mechanisms leading to the metastatic forms in order to offer ultimate hope for tumor control and vision preservation.[179] In respect with this, the molecular targeting of diverse oncogenic signaling elements including receptor tyrosine kinases, PI_3K/Akt, CXCR4 and angiogenic factors involved in the uveal melanoma progression and metastasis to the liver, offers great promise for developing new combination therapies against the aggressive and metastatic uveal melanomas.[178–184]

Cellular origin and clinical treatments of brain tumors

The embryonic, pediatric and adult brain tumors include distinct cancer subtypes with different cellular origins which may be associated with the inherited disorders and specific genetic alterations occurring in primitive stem/progenitor cells in the developing brain or adult central nervous system (CNS).[12, 22, 185–187] Among the brain tumors, some arise from embryonic neuroectodermal stem cells during embryogenesis (neuroblastoma, pheochromocytoma, ependymoblastoma and pineoblastoma) as well as from neural stem cells (NSCs) and/or more committed neuronal or glial cell lineage precursors (astrocytomas, oligodendrogliomas, ependymomas and mixed gliomas) in post-natal and adult life (Figure 2).[12, 22, 37, 47, 58, 94–97, 104, 185–189] Brain tumors are generally constituted by a heterogeneous population of cancer cells containing a mixture of the astrocytes, oligodendrocytes and/or ependymal cell-like tumor cells in different proportions.[190, 191] The malignant transformation of NSCs or their early progenies into brain tumor stem cells (BTSCs) may be accompanied by the sustained activation of distinct mitotic cascades such as EGF-EGFR, SHH-PTCH, Wnt/β-catenin or and/or Notch pathways as well as the changes in their local microenvironment, niche.[11, 12, 22, 32, 45, 189, 192] For instance, the primary glioblastoma multiformes (GBMs), which are among the most aggressive brain tumor forms,

are frequently associated with the overexpression of EGFR.[12, 22, 47, 96, 97, 193] In contrast, secondary GBMs are usually less aggressive cancers and usually progress more slowly from low-grade tumors, as compared to primary GBMs.[12, 22, 47, 194] Secondary GBMs appear to be often related with the occurrence of *p53* tumor suppressor gene mutations. Hence, these two GBM forms have different therapeutic management in the clinical practice.

The therapeutic treatment of the brain tumors in the clinics largely vary with the cancer subtype, its anatomic localization and grade at the time of diagnosis and may include surgery, radiotherapy and chemotherapy and stem cell transplant, delivered alone or in combination.[12, 58, 66, 77, 80, 86, 88] The targeted therapy with new drug classes that are able to penetrate the blood-brain barrier such as temozolomide or nitrosourea agents, such as carmustine (also called BCNU) and lomustine (CCNU), may also be used for treating patients with aggressive and recurrent brain tumors. In regard with this, certain recent experimental studies have also revealed the potential benefit of targeting the developmental signaling cascades such as hedgehog, EGFR, Wnt/β-catenin, Notch pathways or CDK1 and CDK2 checkpoint kinases by using the specific inhibitor, alone or in combination therapy to eradicate BTSCs, thereby improving the current therapies.[12, 26, 30–32, 49, 59, 195] For instance, it has been observed that a selective inhibitor of the smoothened (SMO) hedgehog signaling element, cyclopamine alone inhibited the self-renewal capacity of $CD133^+$ glioma cancer stem cell cultures established from human GBM tumor samples *in vitro*.[195] Moreover, the use of cyclopamine at a lower concentration in combination with the current therapeutic drug, temozolomide also induced an additive or synergistic anti-proliferative and apoptotic effect on the gliomasphere cells.[195] Importantly, a long-term cyclopamine treatment of gliomasphere cells expressing a high expression of the stemness genes (PTCH1 receptor, GLI1 transcription factor, Nanog, Oct-4, SRY-box containing gene 2 “SOX2”, BMI1 polycomb ring finger oncogene and proliferating cell nuclear antigen “PCNA”) also eradicated all of these BTSCs in culture, and induced the regression of glioma tumors established from the gliomasphere cells in nude mice *in vivo,* without systemic toxicity.[195] Interestingly, 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 of vessel-associated self-renewing CD133/nestin expressing BTSCs.[196] Additionally, the genetically-modified migrating NSCs or other stem cell types, which are able to migrate through the CNS and reach the extracranial neoplastic sites also offer great promise for specifically delivering the cytotoxic drugs to the brain tumor site.[64, 67–69, 71, 72] As a matter of fact, it has been observed that the transplantation of fetal-derived NSCs engineered to express IL-12 or tumor necrosis factor-α (TNF-α) related apoptosis inducing ligand (TRAIL), resulted in their specific recruitment within intracranial glioma, and the release of therapeutic gene product concomitant with an inhibition of tumor growth.[69, 73, 74]

Cellular origin and clinical treatments of epithelial cancers

The malignant solid tumors derived from multipotent adult stem/progenitor cells in epithelium represents the most common cancer group and includes the skin, head and neck, thyroid, lung, cervical, renal, liver, gastrointestinal, colon, bladder, pancreatic, breast, ovarian and prostatic cancers.[10, 14, 26, 29–32, 34, 36, 39, 42, 90, 91, 98–103, 106, 110–113, 117, 197–204] The epithelial cancers generally result from the accumulation of distinct genetic and/or epigenic alterations occurring in adult stem/progenitor cells resident within the basal compartment near the epithelial basement membrane concomitant with the changes in their local microenvironment that lead to in their transformation into tumorigenic cancer stem/progenitor cells with abnormal proliferation and differentiation abilities (Figure 1).[10–15, 26, 29–33] Moreover, the tumorigenic cancer stem/progenitor cells may also acquire a migratory phenotype during the epithelial-mesenchymal transition (EMT) program whose

molecular event may lead to their invasion in the stromal compartment and metastatic spread at distant tissues/organs in the body.[10–14, 26, 29–32]

Although the localized cancers may be successfully treated by tumor resection, radiotherapy, hormonal therapy and/or chemotherapy, the invasive and metastatic forms are the aggressive diseases associated with the development of resistance to current therapeutic options with a high rate of recurrence and death of cancer patients.[10–14, 26, 29–32] The combined use of adult stem cell- or genetically-modified stem cell transplant or the mobilization of HSCs, alone or in combination therapies with high-dose chemotherapy or ionizing radiation, may thus constitute potential therapeutic strategies for treating and curing the aggressive, metastatic and recurrent cancers such as kidney, lung, pancreatic, breast, ovarian and prostatic cancers.[11, 13, 58, 65, 66, 75, 76, 82–86, 88, 89, 205] However, the timing of the injection of HSCs during disease progression as well as the number of grafted cells are among the major factors influencing the success rate and survival of patients.

Of therapeutic interest, the recent identification of diverse deregulated growth factor cascades (EGF-EGFR. hedgehog, Wnt/β-catenin and/or Notch), oncogenic signaling elements (telomerase, Scr, Bcl-2, NF-kB, PI_3K/AKT and/or COX-2), ABC multidrug efflux pumps and DNA repair mechanisms that provide a critical function for the sustained growth, survival, invasion, metastases and/or treatment resistance of cancer stem/progenitor cells offers the possibility of targeting these signaling elements (Figure 2).[11–13, 20, 26, 30, 31, 33, 45, 206] This should allow us to eradicate the cancer-initiating cells, thereby improving the current clinical therapies and preventing the disease relapse. The targeting of the local microenvironment of cancer stem/progenitor cells, including the host cells such as myofibroblasts and immune cells that support their malignant transformation as well as the use of anti-angiogenic agents may also constitute an adjuvant treatment for counteracting the cancer progression to metastatic and lethal disease states (Figure 2).[12, 13, 26, 30, 31]

In addition, the use of specific delivery techniques for the administration of anti-carcinogenic drugs in tumor may also constitute promising approaches for targeting cancer stem/progenitor cells, and their early progenies which express specific biomarkers and oncogenic elements. Among the available strategies, there is the targeted delivery of therapeutic agents into tumors by using the conjugation/fusion of drugs to tumor-specific antibodies, encapsulation of chemotherapeutic drugs in liposomes, or other carriers such as nanoparticules, as well as the use of genetically-engineered stem/progenitor cells as vehicles.[207–210] More specifically, gene therapies by using genetically-modified stem cells as carriers for the delivery of anti-angiogenic or cytotoxic agents at specific tumoral sites represent, promising strategies for treating numerous aggressive and metastatic cancers (Figure 2).[11, 67, 69, 71]

Conclusions and perspectives

Recent advances on tissue-resident adult stem/progenitor cell biology and their malignant counterpart, cancer stem/progenitor cells, has significantly improved our understanding of the molecular events that may contribute to cancer initiation and progression to aggressive and metastatic disease stages, resistance to current clinical treatments and cancer recurrence. Further investigations are however necessary to further elucidate the causes leading to leukemia and solid tumor development. Specifically, it will be important to establish the oncogenic gene expression patterns specific to each cancer stem/progenitor cell type in order to identify better diagnostic biomarkers and prognostic indicators. These additional studies should allow us to develop new methods for preventing disease relapse or detecting residual disease after treatment. The development of new combination therapies by molecular

targeting the cancer-initiating cells and their local microenvironment and stem cell-based therapies is also of great clinical therapeutic interest for developing new effective treatments for curing the aggressive, metastatic, recurrent and lethal cancers.

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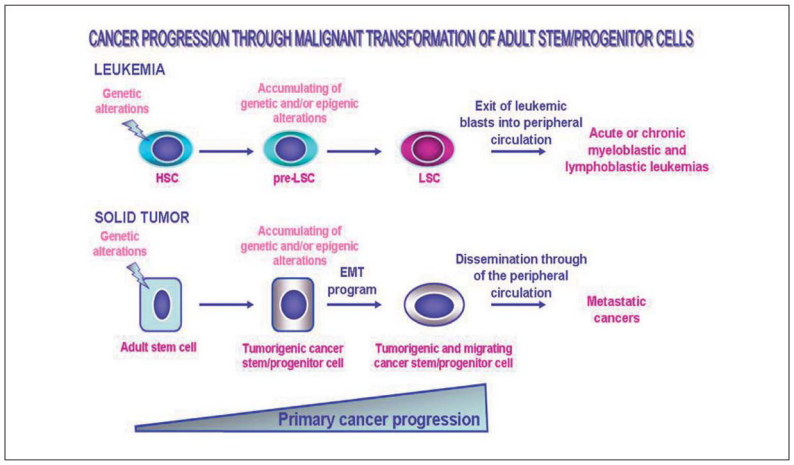

Figure 1.

Scheme showing the potential cellular oncogenic events associated with the malignant transformation of tissue-resident adult stem/progenitor cells into cancer stem/progenitor cells during the development of leukemias and solid epithelial tumors. The genetic alterations in bone marrow-resident hematopoietic stem cells (HSC), which may generate the non-malignant intermediate hematopoietic progenitor cells, the precancerous-LSC (pre-LSC) as well as the accumulating genetic and/or epigenic alterations in these pre-LSC immature cells leading to their malignant transformation into LSCs and leukemia development, are illustrated. Moreover, the accumulation of genetic and/or epigenic alterations in the epithelium-resident stem/progenitor cells occurring during primary cancer progression and whose molecular events may result in their malignant transformation into tumorigenic stem/progenitor cells and tumor formation is indicated. The acquisition of a migratory phenotype by tumorigenic stem/progenitor cells during the epithelial-mechenchymal transition (EMT) program which may result in their dissemination through systemic circulation and metastases at distant sites is also shown.

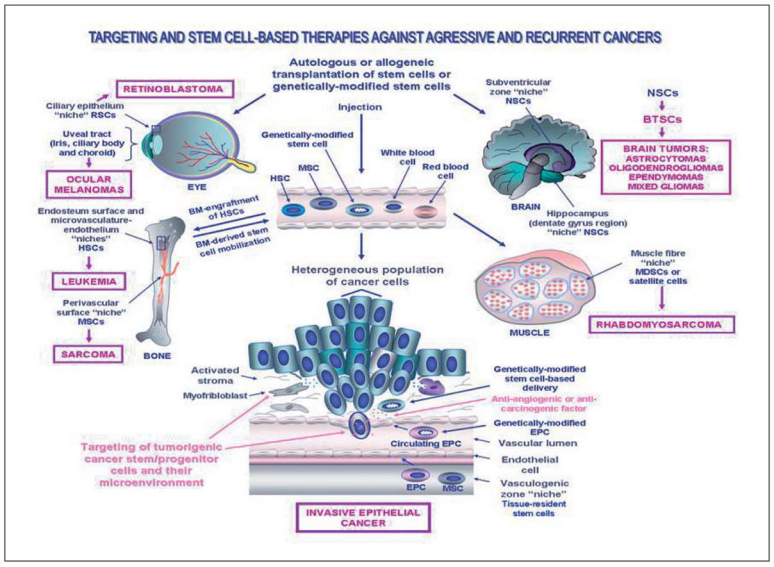

Figure 2.

Scheme showing the potential targeting and stem cell-based therapeutic applications in cellular and gene therapies against aggressive and recurrent cancers. The clinical treatment consisting of an injection of an autologous or allogeneic stem cell transplant of bone marrow (BM)-derived stem cells, peripheral blood (PB) HSCs or genetically-modified stem cells into diseased areas or peripheral circulation in the same patient or a host patient diagnosed with locally advanced or metastatic cancer is illustrated. The anatomic localization of the tissue-resident adult stem/progenitor cells and their putative niches in the human adult eye, bone, brain, muscle and epithelium as well as their malignant transformation into cancer stem/progenitor cells are shown. The aggressive cancers including leukemia, sarcomas, brain tumors and invasive epithelial cancer that might benefit the targeting and/or stem cell-based therapies are also indicated. BTSCs, brain tumor stem cells; EPC, endothelial progenitor cell; HSCs, hematopoetic stem cells; MDSCs, muscle-derived stem cells; MSCs, mesenchymal stem cells; NSCs, neural stem cells and RSCs, retinal stem cells.