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Malignant Stem Cell-Targeted Treatment in Therapeutic Strategies Against Cancer and Leukemia

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The cancer stem cell hypothesis suggests that only a small subpopulation of malignant cells — cancer stem cells, escape the normal self-renewal giving rise to abnormally differentiated neoplastic cells. Understanding the molecular basis, gene expression and signalling pathways which contribute to the maintenance of malignant stem cells may help gain an insight into the cellular, molecular and genetic mechanisms of cancer, thus providing new approaches for cancer stem cell elimination- and/or differentiation therapies.

Key words: normal and cancer stem cells, cell signalling pathways, gene expression, differentiation therapy, elimination therapy.

Introduction

The results from different studies suggest that malignancies are clonal diseases and single cells — *cancer stem cells (CSCs)* are involved in tumor growth [9, 20]. The concept for stem cell origin of neoplasms has been related to the "embryonal rest" theory of cancer (mid-19th century) suggesting that tumors arise from embryo-like cells and that "dormant"embryonic remnants could be activated to become cancer [18]. Recent hypotheses and theories that malignancies could arise in different organs from tissue stem cells in adults are updated versions of the "embryonal rest" theory of carcinomas. The relationships of normal stem cells — embryonal, germinal and somatic, to cancer stem cells have been further examined and cell signalling pathways (influenced by tissue microenvironment to control normal and/or malignant cell development), have been clarified. Understanding the signals and cell growth factors involved in normal–and cancer stem cell development lead to insights in treating malignant diseases as cancer and leukemia by inducing their differentiation (differentiation therapy) and/or elimination therapy.

In the present *mini-review*, the specific properties of normal–and cancer stem cells providing an insight into the molecular/genetic mechanisms of malignancies [27] and a new therapy targeting cancer stem cells (CSCs) in experimental models and clinical therapeutic niches [7] have been described.

Biological properties of normal stem cells

Studies on the biological properties of normal stem cells (embryonal, germinal and somatic/adult) are focused on their self-renewal and differentiation. Stem cells are defined as undifferentiated cells that can renew themselves and also can generate mature cells and tissues through differentiation [1]. The most important features of stem cells in adult tissues are quiescence, asymmetrical division and multi potency (a capacity for differentiation in different cell types). By asymmetrical division every stem cell could produce one daughter cell (remaining a stem cell) and other cells (rapidly proliferating progenitor cells, committed to differentiation and giving differentiated or apoptotic cells). One of the most important functions in stem cell biology is the regulation of self-renewal [12, 21].

The high self-renewal potential of stem cells and their plasticity make them candidates for gene delivering as well as for application in regenerative medicine and tissue engineering [10, 11].

Cancer stem cell hypothesis and identification

Cancer stem cells are small populations of tumor cells, capable of self-renewal and giving rise of all components of heterogeneous tumors.

The concept of cancer stem cells arose from the similarities between normal stem cells (especially embryonic cells) and cancer cells [20]: nephroblastomas, neuroblastomas and theratocarcinomas are used as examples of possible tumors developing from "embryonic rest" in children. Another principle in the cancer stem cell hypothesis [1] is the alteration of genes involved in inhibiting normal stem cell proliferation and programmed cell death (apoptosis). Examples of genetic mutations in epithelial and hematopoietic cancers show a significance of altered gene expression manifested as "maturation arrest" of cell lineage at a specific state of differentiation. The "cancer stem" cell hypothesis was first proposed for acute myelogenous leukemia (AML) demonstrating that only a small population of the leukemic cells (leukemia stem cells) were able to self-renew and extensive proliferation [3]. Gene mutations that alter and disregulate normal stem cell self-renewal have also been observed in different malignancies and more recently this concept has been extended to other forms of leukaemias, lymphomas and multiple myeloma, breast cancers, brain tumors, etc [2, 19, 23, 24]. Tumor stem cells have been also identified in melanoma models [5] and in cases of prostate carcinogenesis [8, 28].

Similar genes and signalling pathways may regulate self-renewal of normal and tumor stem cells

Normal and/or neoplastic stem cell functions could be determined by a common set of genes [13]. The authors showed that the Polycomb group gene Bmi-1 has a key role in regulation – the proliferating activity of normal stem/progenitor cells and the capacity of leukemic stem cells to proliferate. It is important that the proliferative potential of leukemic stem cells lacking Bmi-1 is compromised and they undergo proliferation arrest, showing signs of differentiation and apoptosis. These experimental studies indicate the essential role of Bmi-1 in regulating the proliferative activity of both – normal hematopoietic and leukemic stem cells.

It is also well known fact that tumors may often originate from the malignant transformation of normal stem cells [20], e.g., disruption of cell cycle inhibition in normal development may contribute to the formation of tumor–and leukemia stem cells [4]. Inter-

estingly, similar signalling pathways/cascades and cell growth factors (epidermal growth factor, hedgehoh, Wnt/beta-catenin, tumor growth factor beta, integrin, etc.) may regulate the proliferation and/or differentiation of normal and cancer stem cells during cancerogenesis and leukemogenesis [15]. Therapies targeting cancer stem cells focus on pathways such as Wnt, Shh and Notch which are required for the maintenance of cancer stem cells, but also on the ABC transporter family and other specific molecular properties of neoplastic stem cells [14]. A detailed understanding of normal and cancer stem cells' self-renewal regulation and signalling pathways mediating pathogenesis of malignancies will be of critical importance in developing more effective cancer therapies.

Stem cell differentiation and elimination therapy

Understanding the signals that control normal development may eventually lead us to insights in treating cancer by inducing its differentiation (cancer stem cell differentiation therapy). Cancer stem cells are more resistant to conventional chemotherapy than other more differentiated cancer cells. Therapies can kill or induce differentiation of cancer stem cells could better contribute to curing patients. Such an example are retinoids — retinoid and all-trans-retinoid acids (RA, ATRA), which induce differentiation therapy and acquire a therapeutic niche in treatment of acute promyelocytic leukemia (APL). The ability of RA, ATRA and vitamin A as differentiating agents to prevent cancer is currently under examination: they can invert malignant processes through modulation of transduction signal mediated by nuclear receptors. By this therapy ATRA-based induction therapy followed by chemotherapy, APL has become a curable disease [17]. Therapeutic results with retinoids have been achieved in the treatment of different solid tumors (squamous cell carcinomas, prostate carcinomas, prostate adenocarcinomas, neuroblastomas and hepatocarcinoma — 22). Retinoids can also induce differentiation in precancerous cells and are used as chemopreventive agents [25].

SAHA and other histone deacetylase (HDAC) inhibitors are in clinical trials suggesting that can induce tumor stem cell differentiation [26].

Recent data have shown that chemotherapy with a proteasome inhibitor (bortezomib) killed leukemia stem cells, but not normal hematopoetic stem cells [6]. Cell surface markers (adhesion receptors) which are differentially expressed between normal and cancer stem cells could be also a new target for antibody-based therapy [16].

The use of viral-based gene constructs inducing tumor destruction and cytotoxicity in neoplastic cells, has also been suggested as an effective stem cell therapeutic strategy [13].

Another way to increase the efficacy of cancer therapy is to eliminate cancer stem cells (cancer stem cell elimination therapy). The most common example of such a therapy is transplantation of allogeneic hematopoietic stem cells with graft versus leukemia/tumor effect. Transplantation of allogeneic hematopoietic stem cells can be curative in leukemias that have a poor prognosis with conventional chemotherapy.

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