

Cancer stem cells

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ABSTRACT

There are two hypotheses that explain tumor progression. The first one, the stochastic hypothesis, assumes that any cell within a tumor has the capacity to form and maintain the tumor mass. The second, the so-called hierarchical hypothesis, suggests the existence of a group of cells with a stem phenotype which, like in normal tissues, preserves tumors through a continuous production of progeny. These stem cells are in a particular niche, have a higher resistance to chemotherapy and radiotherapy, and are also capable of invading and migrating to other tissues. This review describes the cancer stem cells (CSCs), their function inside a tumor and the current knowledge about these cells.

Key words. Cancer. Cancer stem cells. Self-renewal. Differentiation. Therapeutic resistance.

INTRODUCTION

Cancer is a group of complex diseases originated by the accumulation of multiple DNA mutations in somatic cells, which together, lead to uncontrolled proliferation, apoptosis resistance and other malignant characteristics of these diseases.¹ The mutated genes interact with other genetic factors and not well understood environmental cues. Cancer cells present also epigenetic changes and deep interactions with their individual microenvironment, which leads to tumor heterogeneity.^{2,3} This heterogeneity is an overriding factor for disease progression since it provides a mechanism for acquired treatment resistance as well as the possibility to adapt to diverse tissue microenvironment, key for invasion and metastasis. Despite this, it has been suggested recently that some cancers still present a

Células troncales cancerosas

RESUMEN

Existen dos teorías para explicar la progresión tumoral. La primera, llamada estocástica, plantea que cualquier célula dentro del tumor tiene la capacidad de formar y mantener la masa tumoral. La segunda, denominada jerárquica, plantea la existencia de un grupo de células con fenotipo troncal (stem), que de manera similar a los tejidos normales adultos, mantiene al tumor mediante la producción continua de progenie. Estas células troncales se encuentran dentro de un nicho particular y poseen mayor resistencia a fármacos y radioterapia, además de ser capaces de invadir y migrar a otros tejidos. La presente revisión trata de describir las células troncales cancerosas (CTC's), las funciones de éstas dentro de un tumor, así como el conocimiento actual de las mismas.

Palabras clave. Cáncer. Células troncales cancerosas. Autorenovación. Diferenciación. Resistencia terapéutica.

hierarchical cell structure similar to the tissue of origin, which implies the existence of tumor cells capable of sustaining growth of the neoplasm.^{4,5} Therefore, there are two hypotheses, not mutually exclusive, that explain the neoplastic progression (Figure 1):

- The stochastic hypothesis suggests that all cells within a tumor are potentially tumorigenic; it proposes that the tumor is relatively homogeneous.⁶
- The hierarchical hypothesis assumes that tumors are organized in a hierarchy of heterogeneous cell populations with different biological properties, and the ability to sustain tumor formation and growth lies mainly in a small proportion of tumor cells called cancer stem cells.⁷⁻¹¹

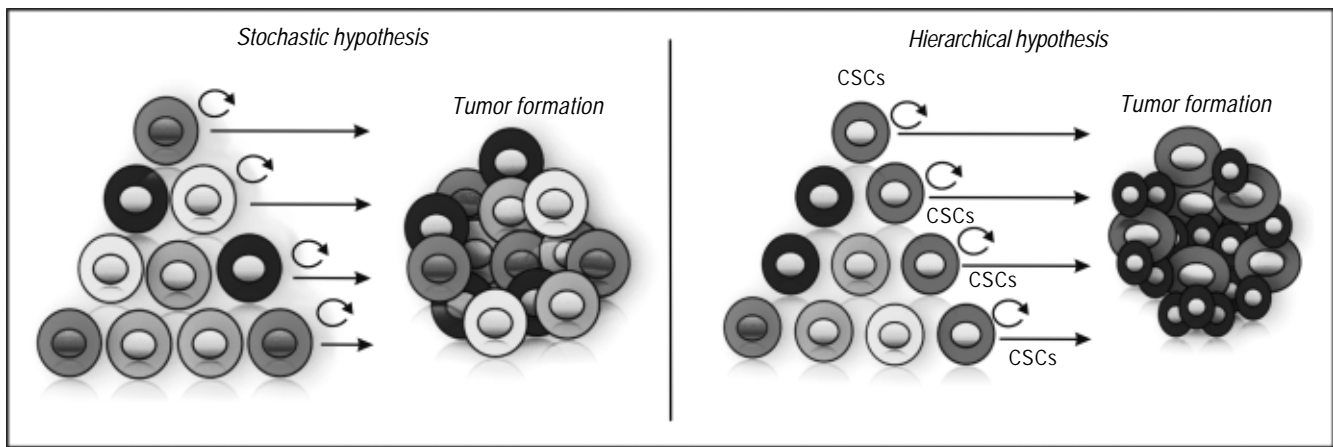


Figure 1. A. The Stochastic hypothesis: Suggests that all cells within a tumor are potentially tumorigenic; all cells are capable of self-renewing. B. The hierarchical hypothesis assumes that the ability to sustain tumor formation and growth lies mainly in CSCs.

According to this model tumors are originated either from normal stem cells or progenitor cells through deregulation of self-renewal processes.¹² These results in tumors directed by a cellular sub-component that retains stem cells properties.^{8,11,12} Only one specific group of the cancer cells population has the capacity to sustain tumor growth *in vivo*, while the rest of the population (differentiated cells) cannot.^{6,13}

STEM CELLS

There are two ways to classify Stem cells (SCs), the first one according to their differentiation potential in totipotent, pluripotent and multipotent cells. The second one according to the tissue of origin in embryonic and adult stem cells.¹⁴ SCs are defined by the capacity to self-renew indefinitely and generate, by asymmetric or symmetric division, daughter cells that can differentiate into several cell types of the specific mature tissue.^{6,15} Although stem cells can self-renew, they are generally quiescent, spending most of their time in G0.¹⁶

The ability to divide asymmetrically generates two cells, one that is identical to the mother cell in terms of stemness, and a second one that is committed to differentiate into specific cell lineages.^{8,17} The daughter cell with conserved stemness remains in its own compartment (the stem cell niche), whereas the committed daughter cell continues with cell divisions. These latter cells, known as progenitor cells, lead finally to differentiated cells. This type of division is believed to be dominant in normal tissue homeostasis; nevertheless, to date there is not enough evidence that sustain a

preference of asymmetric over symmetric way of division.¹⁸ The symmetric division is used by the SCs when they need to expand in number during development injury.¹⁹ This kind of division is defined as the generation of daughter cells that are destined to acquire the same fate.²⁰ Most SCs are able to switch between both types of division, the mode of division reflects a key adaptation that is crucial for adult regenerative capacity. Finally, the balance of SCs numbers depends on internal and external cues.^{18,19} It is crucial to understand the regulation of normal SCs self-renewal to also understand the regulation of cancer cell proliferation, since cancer is considered to be a disease of unregulated self-renewal.²¹

The stem cell population within a normal tissue is defined by certain common characteristics:^{6,11,17,22,23}

- Self-renewal, which maintains stem population over time.
- Regulation of the number of stem cells through a strict balance between cell proliferation, cellular differentiation and cell death.
- Ability to generate a wide range of differentiated cells.

The *in vivo* microenvironment that regulates stem cell survival, self-renewal, and differentiation is called niche. Key components and interactions of the niche include growth factors, cell-cell contacts, and cell-matrix adhesions.²⁴ Likewise, it has been proved that several transcription factors are required for the maintenance of pluripotency, such as Oct4, Rex1, Sox2 and TDGF1.²⁵

SCs show properties that provide for a long lifespan, like relative quiescence, active DNA repair system and resistance to apoptosis and several drugs

and toxins. It is alleged that CSCs can also have these resistance mechanisms.¹⁶

Isolation methods

SCs are rare in most tissues, therefore, they need to be identified prospectively and purified to study their properties.²¹ Nowadays, SCs are recognized by their immunophenotypic profile, for example hematopoietic SCs express CD34 y CD90, neural stem cells (NSCs) CD133 and nestin.^{23,26,27}

An important marker for isolation and analysis of SCs is conferred by ABC transporters that gives them the property of drug transporting cells. Most cells accumulate fluorescent dyes like Hoechst 33342 and rhodamine 123, but SCs do not, since these dyes are expelled by ABCG2 and ABCB1 among others. Because they don't accumulate these compounds, SCs can be sorted by collecting cells that contain a low level of Hoechst 33342 fluorescence. These cells are known as "side population" or "dull cells".¹⁶

Another type of isolation is the use of sphere culture system, first used by Reynolds and Weiss in 1992 to identify NSCs. This method has permitted the in vitro characterization of SCs, establishing that the neurospheres are multi-potential floating clusters cells and are derived from clonal expansion of a single NSC.²⁷ This culture system has also been used to identify other SCs like mammary stem and progenitor cells.¹²

Evidence of the existence of CSCs

In 1875 Conheim proposed that cancer was the development of a misplaced embryonic stem cell in

the adult organism deriving in a carcinogenic process,^{28,29} but the concept that only a subpopulation of cancer cells (CSCs) are responsible for the preservation of a tumor arose about 50 years ago.⁴ It was until 1994 when Lapidot, T. *et al.*, first identified the CSCs in a purified cell population of acute myeloid leukemia.

These cells identified by specific cell surface markers, had the ability to form tumors efficiently after injecting them into nude mice, while other cell populations of the same tumor did not.³⁰ Since then, this functional assay has allowed the identification of CSCs in many tumor types including breast, brain, prostate, pancreas, head and neck, colon, lungs, skin, liver and ovary (Table 1).³ A classic example of this identification process is used in breast cancer. In 2003, Al-Hajj's group demonstrated through xenografts that this tumor is heterogeneous and that breast CSCs are the only cells capable of establishing this tumor after transplanting them into NOD/SCID mice.^{8,22,31,32} Despite the progress in this area, it still remains unknown if cancer stem cells originate from somatic stem cells or cells in a higher state of differentiation that revert to the stem status by mutations and epigenetic changes that occur.

CANCER STEM CELLS

The idea of the cancer stem cells arose from the observation of striking similarities between the self-renewal mechanisms of stem cells and cancer cells.²⁶ As mentioned above, CSCs could originate by mutations in undifferentiated tissue stem cells, progenitor cells, and differentiated cells.^{11,22,33} A mutational event occurring in a progenitor cell may not be as

Table 1. Phenotypes of CSCs identified to date.

Tumor	CSC marker	References
Brain	CD133+/A2B5	6, 11, 17, 22, 26, 27, 35, 46
Breast	CD44+CD25-/low/ESA+/CD29+CD133+/Lin-/ALDH1+	5, 6, 9, 12, 13, 17, 22, 35, 43, 46
Ovaries	CD133/SP/CD44+CD117+	17
Lung	CD133+/SP-C+/CCA+	17, 35, 46
Prostate	CD44+/CD133+/2βHigh/CD133+	21, 27, 31
Pancreas	CD44+/CD24+/ESA+/CD133+	17, 35, 36, 43
Hepatocellular	CD133+/CD90+	15, 17, 35
Hematologic	CD33+/CD34+/CD38-/CD123+/CD90-	6, 17, 22, 39, 46
Colon	CD133+/CD44+/CD166+/Lin-/ESA+	10, 17, 35, 46
Head and neck	CD44+	17, 35
Retinoblastoma	ABCG2+	46
Melanoma	ABCB5+	35
Mesenchymal	SP	35

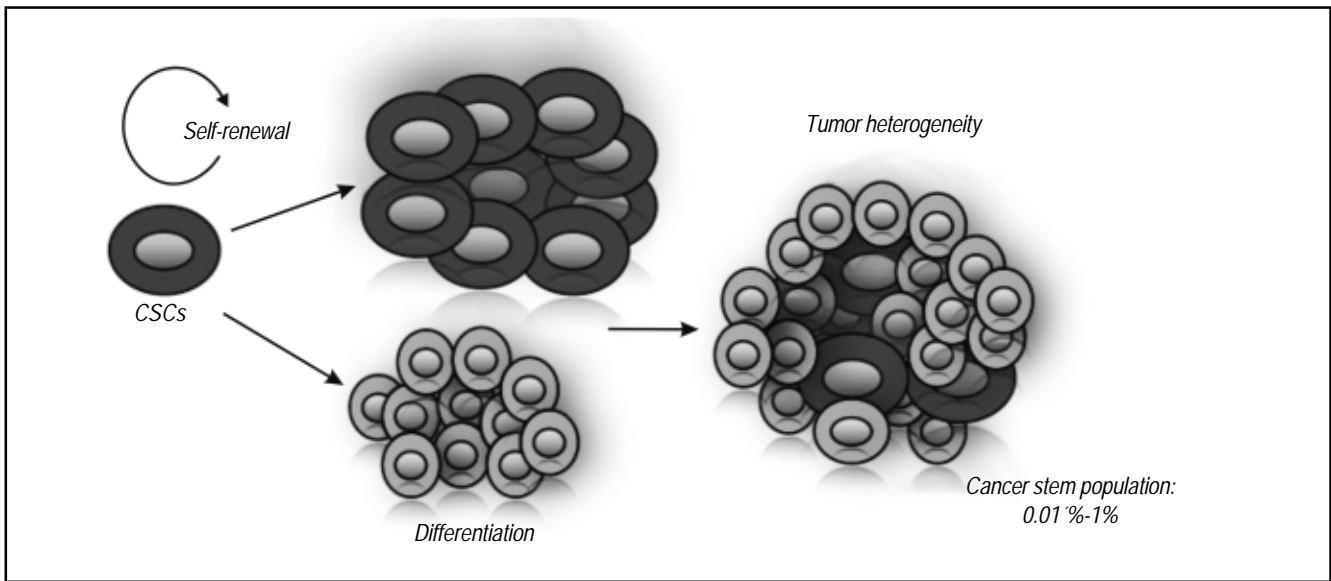


Figure 2. Characteristics of CSCs: Differentiation and self-renewal; these processes results in a heterogeneous tumor population. CSCs represent only the 0.01-1% of the tumor mass.

dangerous as in a stem cell, because this cell has limited self-renewal ability and it becomes clonally exhausted as it generates differentiated cells.²⁷

Additionally, it has been proposed many hypothesis concerning the origin of CSCs:^{28,34}

- Loss of regulation of the microenvironment (including the niche).
- Loss of asymmetric division. Polarity loss may lead to the lack of this type of division and the consequent accumulation of these cells. It is thought that they only divide symmetrically.
- Cell fusion.
- Horizontal gene transfer. The SC has the capacity of introducing apoptotic bodies that re-program their genetic load, turning it in tumorigenic.

The genetic program that controls self-renewal and differentiation plays a key role in the generation of CSCs. It is known, that as SCs, CSCs have the ability to proliferate indefinitely by deregulated self-renewal capacity^{6,8,11,12} (Figure 2).

Progenitor cancer cells, which represent most of the tumor population, have a high rate of proliferation,⁵ and, unlike CSCs that have a stem phenotype and a small number of cells within the tumor (0.01-1%), together with a smaller rate of proliferation³⁵ (Figure 2).

It has been suggested that eliminating this differentiated progeny and maintaining CSCs will result in tumor relapse.⁷

Five key observations define the existence of a CSCs population (Table 2):¹⁰

- Only a minority of cells within a tumor have tumorigenic potential when transplanted into immunodeficient mice.³⁶
- They self-renew and proliferate.^{26,27}
- They generate clusters of clonally derived cells resembling spheres.^{26,27}
- Tumorigenic cancer cells are characterized by a profile of specific surface markers and can be isolated by flow cytometry or other immunoselection methods.³⁶
- The tumor mass derived from tumorigenic cancer cells contains mixed population of tumorigenic cancer cells and non tumorigenic, recreating a phenotypically heterogeneous population.⁶

Table 2. Features of CSCs.

Characteristics of CSCs
<ul style="list-style-type: none"> • Self-renewal • Resistance to noxious stimuli • Increased activity of survival cascades • Differentiation • Symmetric division/asymmetric division • Invasion and metastasis • Reduced rate of proliferation • Higher number of drug resistance pumps

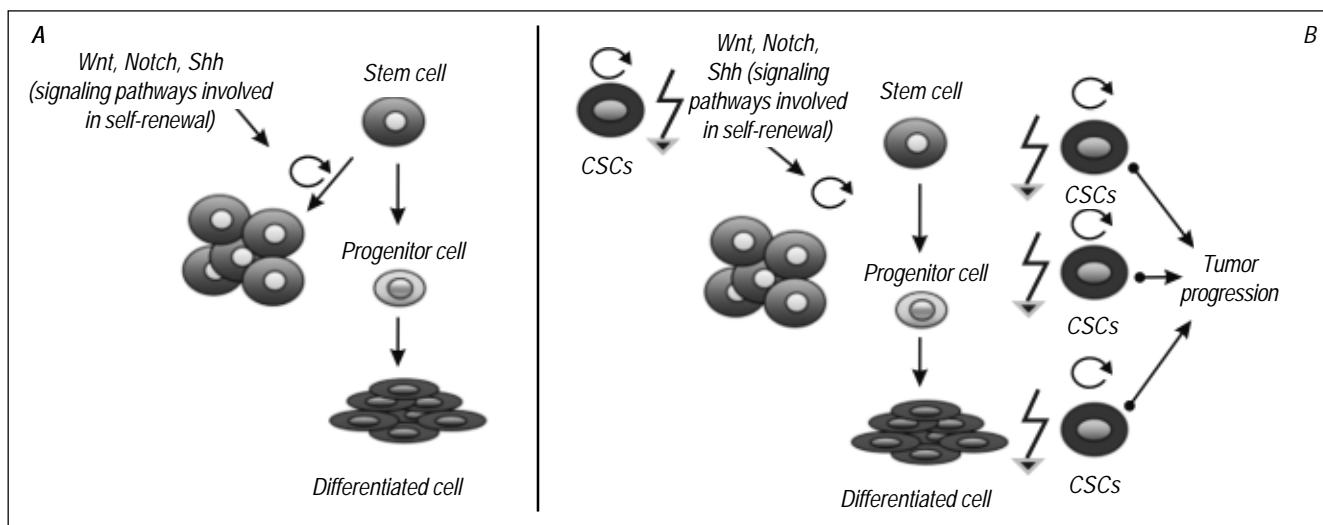


Figure 3. A. Self-renewal and differentiation of SCs. Crucial signaling pathways regulating SCs self-renewal. B. Alterations in stem cell's process of self-renewal and differentiation that could originate CSCs.

This process is very similar to the process where somatic stem cells can both self-renew to maintain the stem population, and also produce differentiated progeny to create specific mature cell types of an organ.⁶

The symbiotic relationship with the niche is totally perturbed in CSCs, and it remains incompletely understood.²⁹ The interactions within may have an important role in maintaining a population of tumor cells with characteristics of self-renewal.³⁷

The CSCs can be defined experimentally for their ability to continuously generate tumors. Today, the practical definition and the gold standard to define the stemness of the cancer cells has been the ability to generate a phenocopy of the original malignancy in immunocompromised mice.¹⁷

Signaling pathways of self-renewal and carcinogenesis

Because CSCs share common properties with normal stem cells, it is reasonable to assume that they have regulatory mechanisms in common^{6,17,38} (Figure 3). In this regard, it has been found that several CSCs express markers associated with adult stem cells like CD133, ALDH, ABCG2, Fgfr1 y Sox1, and even the pluripotent stem cell marker OCT 4.^{2,8,12,15,22,26,27,31,33,35} Likewise, recent studies showed that the expression of several genes and the activation of signaling pathways are involved in regulating differentiation and self-renewal processes. Among them are the signaling pathways initiated by Sonic Hedgehog (Shh), Notch and Wnt, which play

an important role in regulating stem cell self-renewal.^{2,4,6,8,14,15,17,21,39-41} The molecular expression profile and other characteristics of the CSCs involved in oncogenesis remains unclear.²

CSCs in tumor growth

It has been proposed that CSCs are involved in tumor growth but the exact number of cancer stem cells involved in this process and the importance of the different percentages of CSCs found in tumors remains unclear.² The percentage of CSCs is determined mainly by the particular characteristics of the cancer stem cell that started the tumor as well the microenvironment and the frequency in which additional CSCs are created.² Thus, it was found that the percentage of CSCs present in a tumor may represent the tumor subtype or stage of progression: With larger number of CSCs present, the clinical outcomes are worse. The presence of many cancer stem cells may indicate a higher rate of proliferation of tumor cells, as well as a tumor with greater genetic instability, lack of differentiation, or gain of a selective advantage under certain microenvironmental conditions like the presence of cancer treatment.² Similar to normal SCs, CSCs have a higher number of DNA repair mechanisms, increased activity of survival signaling cascades, higher apoptotic threshold (compared to other cancer cells), higher number of multi-resistant drug pumps (ABC-transporters, that at the same time allows them to be isolated as side population) and a lower rate of proliferation.⁸ These mechanisms give

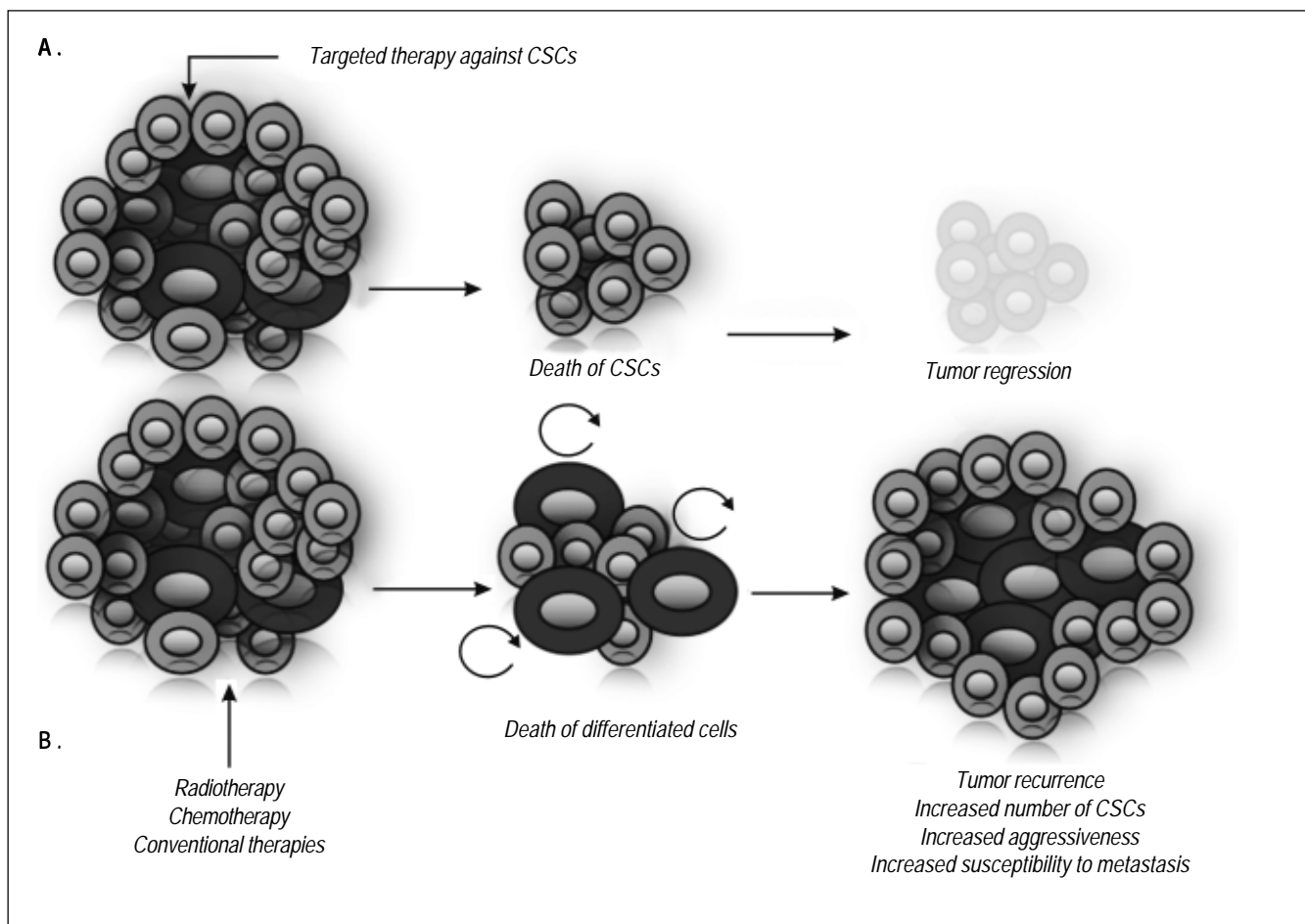


Figure 4. A. Ideal course of therapy that eliminate CSCs. B. Conventional cancer therapies.

them greater protection of their genetic material, the ability to maintain the tumor mass, and to establish secondary tumors as well as resist and evade anti-tumor therapies.⁴²

Implications and therapeutic targets for CSCs

The successful elimination of cancer requires an anti tumor therapy that affects the differentiated cells as well as the cancer stem cell population.^{8,43} It is thought that quiescent CSCs are more resistant to chemotherapy and to targeted therapies;^{22,35} this may be due to intrinsic or extrinsic resistance that favors the selection of stem clones able to survive therapy. Today, conventional cancer therapies including surgery, chemo, radio and immunotherapy quickly eliminate differentiated tumor cells, reducing the tumor mass, but in general, leaving the potentially initiating tumor cells (CSCs).^{8,10,43} Many researchers have suggested an association of reacti-

ve oxygen species (ROS) and radio-resistance in CSCs.⁴⁴ Therapies that are directed exclusively against the differentiated cancer cells, but fail to eradicate the CSCs compartment will result in relapse and proliferation of more aggressive tumor cells and even more resistant to cancer therapies, causing the patient's death^{10,11,12,22,43} (Figure 4).

For these reasons, an ideal course of therapy should eliminate the differentiated cancer cells while at the same time, specifically, selectively and rapidly eliminate also the CSCs, thus, avoiding toxic side effects to other cell types⁴³ (Figure 4). This will require specific identification of therapeutic targets that occur exclusively in CSCs.³⁹

Recent studies have reported that treatment with an inhibitor of tyrosine kinase EGFR/HER2 (Lapatinib) does not lead to an increase in breast cancer stem cell population, thus, opening the possibility that certain inhibitors can and even go against signaling pathways that regulate CSC self-renewal.^{12,45} For example, it has been recently initiated a clinical

trial using gamma-secretase inhibitors that block the Notch pathway in combination with chemotherapy in the neoadjuvant setting for breast cancer.⁴⁴ Using Imatinib (a small-molecule inhibitor) in chronic myelogenous leukemia, a disease that arises from a CSC, confers a substantial survival benefit, despite the fact that this compound does not eradicate the CSC population.²⁹ Cyclopamine is a stem-cell inhibitor that blocks the Hedgehog-Patched receptor signaling protein Smoothed. Inhibiting such receptors and signaling molecules could inhibit CSCs.¹⁶

Identifying specific and non-toxic inhibitors of ABC1, ABCG2 and ABCC1 is necessary to block the properties of drug transporters that these compounds confer to the CSCs. For example, Fumitremorgin C is a natural product that specifically inhibits ABCG2. Nevertheless, it is a complicated task, because SCs depend on the expression of drug transporters to survive drug therapy. Targeting drug transporters could involve killing normal SCs.¹⁶

In the field of immunotherapy, it has been proposed that purified tumor CSCs from a patient could be irradiated and used to immunize the patient or to activate the donor's immune cells against the tumor cells.¹⁶

The identification of these targets and the development of anti tumoral agents against them will require not only a deep understanding of the biology of normal stem cells but also of cancer biology, including knowledge of which SC features are retained by CSCs.^{17,29} From the clinical perspective, it is necessary to decipher the mechanisms of chemo- and radio-resistance operating in CSCs in order to propose new strategies that increase the response to this therapies in our patients.³⁵

ACKNOWLEDGMENTS

We thank Dr. Magali Espinosa for helpful discussions and unconditional backup, Dr. Gisela Ceballos, Dr. Denise Campos, Q. F. B. Karla Méndez and Biol. Exp. Iván Bahena for their support.

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*Recibido el 25 febrero de 2010
 Aceptado el 3 agosto de 2010.*