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Cancer Stem Cells as a Result of a Reprogramming-Like Mechanism

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1. Introduction

The treatment of cancer is generally based on histological grade, respectability and the presence or absence of metastasis. Because interventions after the manifestation of metastasis are notoriously ineffective for most cancers, great effort is invested in the development of targeted therapies to eradicate or suppress the growth of cancer. A complete understanding of the cancer process requires more detailed knowledge of the mechanisms maintaining neoplastic growth and it is a prerequisite not only for understanding the genesis of human cancer but also for the identification of molecular events responsible for cancer maintenance. New drugs must be designed against the mechanisms that are responsible for cancer maintenance not for the initial event that transform a normal cell into cancer cell, because it is possible that the first alteration of the cancer cell will have no function in the subsequent steps of cancer development. Much effort is currently being expended to target the mutated oncogenes and tumour suppressor genes that control neoplastic cell growth directly. Inactivation of oncogene(s) can cause cancer remission, implying that oncogenes are the Achilles' heel of cancers. This current "hands on" model of cancer has kept oncogenes firmly in focus as therapeutic targets and is in agreement with the fact that in human cancers all cancerous cells, with independence of the cellular heterogeneity existing within the tumour, carry the same oncogenic genetic lesions. However, many of the new classes of agents targeting the oncogenes usually do not show a permanent clinical benefit. These clinical observations suggest that oncogene-induced tumourigenesis is not reversible through the unique inactivation of the gene defect(s) initiating cancer development. But, what are the mechanisms of tumor relapse by which tumors evolve to escape oncogene dependence? Several recent studies of the effect of

oncogenes in stem cells in cancer development (Barker et al., 2009; Perez-Caro et al., 2009; Zhu et al., 2009; Bussard et al., 2010; Jacques et al., 2010; Nakagawa et al., 2010; Saring et al., 2010; Zhang et al., 2010) implicate that tumor reprogramming (where the maintenance of oncogene expression is not critical for the generation of differentiated tumor cells) might represent a potentially important mechanism of tumour development for many types of cancer and that, if this is the case, the oncogenes that initiate tumor formation might be dispensable for tumor progression and/or maintenance. The practical implications that this new point of view has for the therapy of cancer are obviously enormous (Castellanos et al., 2010). This chapter addresses the impact of these results toward a better understanding of carcinogenesis and proposes research avenues for tackling these issues in the future.

2. The cancer stem cell (CSC) concept

The cancer stem cell (CSC) theory hypothesizes that a cancer maintains a hierarchical organization similar to a normal tissue. Thus, the tumor mass is the result of differentiated progeny of rarer CSCs with self-renewal capacity (Sanchez-Garcia et al., 2007). Chronic myeloid leukemia (CML) is universally regarded as providing the strongest evidence in support of the CSC concept. Fialkow and his colleagues first suggested that CML arose from rare transformed hematopoietic stem cells (HSC) nearly 40 years ago, when they showed that both granulocytes and red blood cells from CML patients were derived from a common cell (Fialkow et al., 1977). However, the term tumor/cancer stem cell was first coined nearly 40 years ago to highlight the observation that only a minority of multiple myeloma cells were capable of clonogenic growth (Hamburger and Salmon, 1977). The last decade has witnessed an increasing re-appreciation of the role of these heterogeneous cellular cues in cancer development and therapy. This re-evaluation represents a rather crucial detour from the widely held view that the neoplastic phenotype resulted from uncontrolled proliferation of tumor cells. The CSC concept would explain not only the low clonogenic capacity of most malignancies, but also why complete treatment responses translate into cures in only a minority of cancer patients. Initial responses in cancer represent therapeutic effectiveness against the bulk cancer cells, while rarer resistant CSCs could be responsible for relapse. Accordingly, improving the results of cancer therapy would require identification and better understanding of the biology of CSC (Perez-Caro et al., 2009; Saito et al., 2010) (**Figure 1**). Within this framework, fundamental determinants of neoplastic disease are to be found within the CSC and, thus the role of CSC regarding cancer biology, management and therapy needs to be evaluated (Sanchez-Garcia, 2009). It should be noted that partial tumor responses to therapy mean little if CSCs are the major cells determining outcome (Sanchez-Garcia, 2009). Because of the difficulty of assessing the effects of therapies on the rare CSCs responsible for cancer maintenance and relapse, the development of new clinical approaches will require new clinical paradigms and methodologies that should rely heavily on preclinical modelling, using novel preclinical assays to evaluate the fate of CSC (Sanchez-Garcia et al., 2007). Preclinical studies should assess the effects of therapies on CSC and differentiated cancer cell populations. This could allow us to take directly to the patient a fully functional new approach (**Figure 1**).

A related concept is that the exact definition of “stemness” is elusive and stemness may be more of a continuum or a property that may be regained in cancer, which would suggest that neither the hierarchical nor the stochastic model are exclusively right.

Furthermore, we must call the attention to the fact that the fundamental concept essential to the CSC hypothesis does not have anything to do with the absolute frequency of these cells within the tumour; indeed, what the model states is that there is a functional heterogeneity within the tumor cellular components, and that there is only a defined population of cells that can initiate/maintain malignant growth in vivo while the remaining cells cannot. Thus, the therapeutic implications of the CSC concept are equally important whatever their frequency is within each tumour type: they are the cells that must be effectively targeted to achieve a definitive cure on the long round (Perez-Caro et al., 2009; Saito et al., 2010) (Figure 1).

3. Stem cells and cancer initiation

The nature of the cell in which the initiating mutation occurred in human cancer has received little attention during the last decades. Since the process of carcinogenesis need to accumulate a number of oncogenic events during long periods of time, only cells with self-renewal capacity, would be in the tissue enough time to accumulate the oncogenic alterations necessary for the complete cell transformation. This fact seems to be particularly evident, in tumors originated in tissues with high cellular turnover, as the skin, the intestine or the breast, where normal stem cells should be the target for the oncogenic initiation event (Al-Hajj et al., 2003; Singh et al., 2004; Wang et al., 2009; Jacques et al., 2010). For more differentiated cells to originate epithelial cancer, it would be necessary that the first oncogenic event to induce a fully tumor phenotype, or at least be able to trigger a partial stem cell-like program that permit the differentiated progenitor to acquire surviving and self-renewal capabilities, and probably new adhesion properties near the basal membrane to avoid being expelled from the tissue under the normal cellular turnover. In recent years, there is growing evidence that stem cells are the cells of origin for several types of cancer (Sanchez-Garcia et al., 2007; Vicente-Dueñas et al., 2009). An example is provided by the chronic myelogenous leukaemia (CML), a granulocytic disease (Melo and Barnes, 2007). However, the *BCR-ABL* translocation, pathognomonic of this disease, does not arise in a granulocyte, but rather in a cell at the beginning of the hematopoietic differentiation tree (Jamieson et al., 2004).

4. Caveats for identification of CSC in human cancer

In human cancer the definition of the identity of CSCs comes from experiments of serial transplantation of flow cytometry-sorted cell populations into immunocompromised mice. The CSC-containing population should recapitulate the cellular heterogeneity present in the primary human cancer and must have the capacity for self-renewal on serial passaging (Cobaleda and Sanchez-Garcia, 2009). However, there are many technical issues concerning the isolation and determination of CSC capabilities from human cancer samples, ranging from the methods of selection of the cells themselves to the choice of the recipient animals where the cells can reveal their potential and to the injection site within the recipient (Cobaleda and Sanchez-Garcia, 2009). To avoid these caveats an alternative way to study the CSC population is to use mice as a system model.

5. Identification of CSC in mouse models of human cancer

Much of our current conceptualization of how tumorigenesis occurs in humans is strongly influenced by mouse models of cancer development (Perez-Losada et al., 2002; Sanchez-

Martin et al., 2002; Perez-Mancera et al., 2005a; Perez-Mancera et al., 2005b;). But studies in mice in which the oncogenic alteration(s) is not directed to the specific cells of origin, as it normally occurs in most current mouse models, should be interpreted cautiously (Vicente-Dueñas et al., 2010)

The genetic alterations found in human cancer seem to occur during specific periods of time and restricted to a few specific cells. In several cases, like in the case of CML, the cancer cell-of-origin is a stem/progenitor cell, and this explains the stem properties that allow the CSCs to maintain the tumor mass. However there are also many cancers where most probably the cancer cell-of-origin would be a more differentiated cell (Cobaleda et al., 2007). In these cases, the combination of the reprogramming capabilities of the oncogenic alteration and the intrinsic plasticity of the target cell (i.e., its susceptibility to the reprogramming) determine the final outcome of a CSC. Since not all the cells present the same susceptibility to reprogramming, and not all the oncogenes possess the same reprogramming capacities (i.e., the ability to confer stem cell features to the target cell), the targeting of the oncogenic alteration to the wrong cellular compartment is a likely cause of failure in the generation of accurate mouse models of human cancer. Considering these facts, three independent groups have already shown that the genotype-phenotype correlations found in human cancer can be established in mice by specific targeting of stem cells (Barker et al., 2009; Perez-Caro et al., 2009; Zhu et al., 2009).

6. Cancer as a reprogramming-like disease

In a normal stem cell-driven tissue, genetic programming of stem cells is all what is required to (re)constitute all differentiated cells forming the tissue and the genetic information responsible for the stem cell programming is not anymore expressed within the differentiated cells that form the tissue. As we have mentioned before, in the last years, many evidences have been accumulated indicating that cancers are also hierarchically organized tissues which can be created and maintained like a normal stem-cell-based tissue (Etzioni et al., 2003; Sanchez-Garcia et al., 2007; Jemal et al., 2009). The most challenging arena in which to prove this concept are those tumors whose main cellular components are terminally differentiated cells. A clear example of this kind of tumors is the chronic phase of CML. To elucidate if CML is a stem cell-driven tissue, we developed mice limiting *BCR-ABL* expression to the Sca1⁺ cells (Sca1-BCRABL mice) (Sanchez-Garcia et al., 2009). Thus, our Sca1-BCRABL is a very suitable *in vivo* model to study the consequences of ectopic expression of *BCR-ABL* targeted to stem cells. However, in human CML and in most animal models of cancer, the oncogenic alteration(s) is(are) present in all the cellular types that compose the tumoral tissue, from the cancer cell-of-origin to the terminal differentiated granulocytes. In our stem cell-driven Sca1-BCRABL model, the expression of the oncogene is restricted to the stem/progenitor compartment but is nevertheless capable of generating a full-blown CML with all its differentiated cellular components. Of course, the demonstration that CML development can be established in mice by limiting oncogene expression to Sca1⁺ cells implies that abolishing oncogene function does not interfere with the formation of differentiated tumor cells, and suggest that the oncogene imposes a gene regulatory state in stem cells that somehow persists during hematopoiesis and which imposes a tumor phenotype reflective of the usual CML, an observation that seems to apply to other cancer-initiating gene defects (Sanchez-Garcia et al., 2009). Therefore, we hypothesize that the oncogene mediates tumorigenesis through epigenetic/genetic

modification of target genes that remain in this modified state in the mature tumor even in the absence of *BCR-ABL* in agreement with a reprogramming role for *BCR-ABL* in regulating CML formation. Supporting these observations, it has been recently shown that only stem cells, but not astrocytes, gave rise to brain tumors, independently of their location. This suggests a cell-autonomous mechanism that enables stem cells to generate brain tumors, underlining an important role of stem cells and the relevance of initial genetic mutations in the pathogenesis and phenotype of brain tumors.

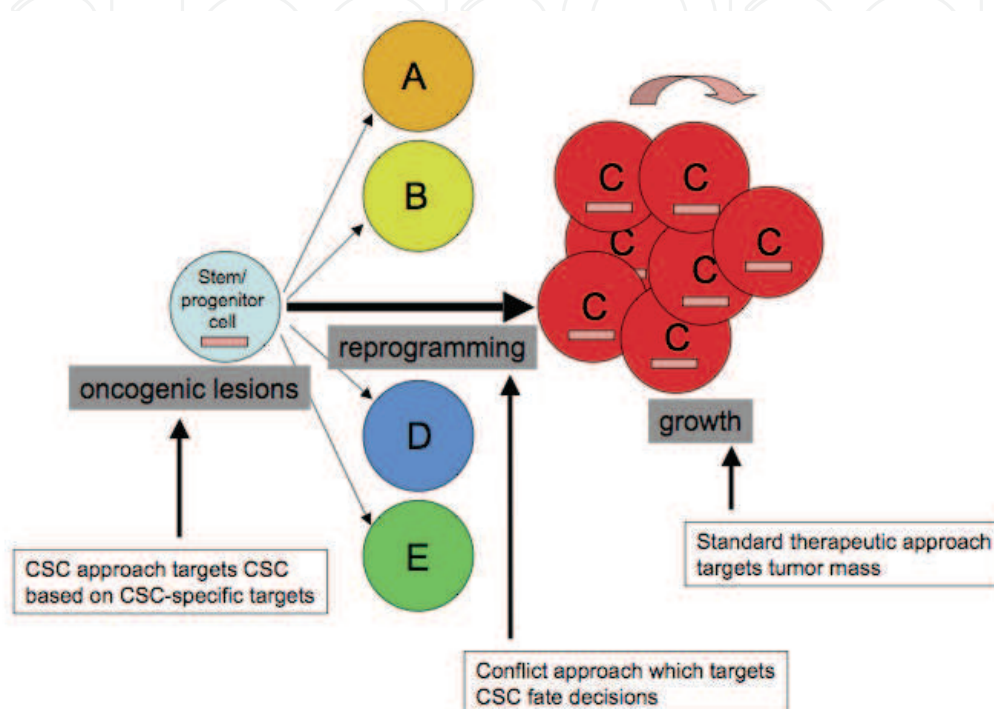


Fig. 1. Approaches to target CSC.

Recent breakthroughs have shown that reprogramming of differentiated cells can be achieved by the transient expression of a limited number of transcription factors that can “reset” the epigenetic status of the cells and allow them to adopt a new plethora of possible fates. Several of these reprogramming factors were previously known for their oncogenic activity, already connecting the role of oncogenes with tumoral cell fate reprogramming. Furthermore, it has recently been shown that the elimination of p53, whose function is to prevent the survival and expansion of cells with genetic damage, greatly enhances the reprogramming efficiency in the generation of induced pluripotent cells (iPS) (Castellanos et al., 2010). These p53-null reprogrammed cells carry, however, several types of mutations (Castellanos et al., 2010). These results confirm the fact that the absence of the tumor suppressor does not have an instructive role in tumorigenesis, but just a permissive one, so p53 would prevent cells with damage from being successfully terminally reprogrammed. This indicates that the driving force of the reprogramming process are the reprogramming factors themselves, and that just the necessity of maintaining genetic integrity prevents the reprogrammed cells with any kind of damage to progress along the newly programmed pathway. As a logical consequence, it has recently been proposed that cancer stem cells might arise through a reprogramming-like mechanism and that, if this is the case, perhaps the oncogenes that initiate tumor formation might be dispensable for tumor progression

(Castellanos et al., 2010). Further to this, it has also been shown in the haematopoietic and nervous systems that the susceptibility of cells to reprogramming is inversely proportional to their degree of differentiation, and that hematopoietic stem cells (HSC) are 300 times more prone to be reprogrammed than B or T cells (Castellanos et al., 2010). Our results show that this stem cell reprogramming is indeed possible in the case of *BCR-ABL*. But perhaps the most crucial question is whether these hands-off regulation mechanisms can be found in other cancer types, especially tumors of epithelial origin, which represent the bulk of human cancers. Importantly, a small subset of *Sca1-BCR-ABL* mice develops additional solid tumors. Considering that *Sca1* has been identified as a almost universal stem cell marker in many different tissues, these data would suggest that the view of cancer as a reprogramming-like disease is not specific to only hematopoietic tissues, but rather represents a broader mechanism for deregulation of stem cell differentiation, providing a paradigm that can be applied to solid-organ cancers and, together with all the above discussed findings, provide enough experimental evidence to support the view of cancer as a reprogramming-like disease (Castellanos et al., 2010).

This model of cancer (**Figure 1**) is very informative with respect to the fact that the oncogenic mutations can have different roles in CSC versus differentiated cancer cells, and explains why targeted therapies like imatinib can eliminate the latter without affecting the former. However, we should be cautious in interpreting the data as a mimicking of human disease as mouse cells are more prone of transformation than human cells and thus one mutation can lead to full blown cancer in the mouse transgenic model but not in human. Furthermore, the regulation of certain genes/pathways might differ between mouse and human.

There are many evidences now suggesting that human cancer could be considered as a reprogramming-like disease. If the potential growth of cancer depends on CSCs and on oncogenes that can function in a hands-off manner, it would be important to know how to eradicate these cells and/or inactivate the reprogramming mechanism (Castellanos et al., 2010) (**Figure 1**).

7. Conclusions

There are many evidences now suggesting that human cancer could be considered as a reprogramming-like disease (Castellanos et al., 2010). If the potential growth of cancer depends on CSCs and on oncogenes that can function in a hands-off manner, it would be important to know how to eradicate these cells and/or inactivate the reprogramming mechanism (**Figure 1**). The coming years will show whether this optimism is well founded, or whether the immense complexity of this disease will continue to confound our best endeavours to tackle cancer.

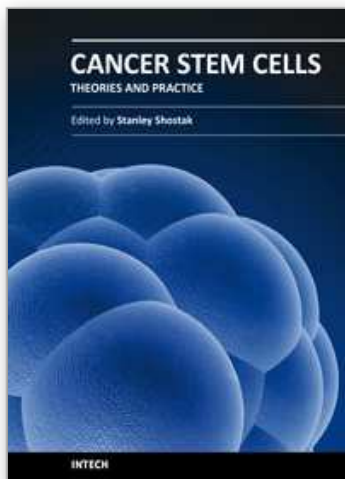
8. Acknowledgements

Research in our groups is partially supported by FEDER and by MICINN (SAF2009-08803 to ISG), by Junta de Castilla y León (Proyecto Biomedicina 2009-2010 to ISG, and Proyecto Biomedicina 2010-2011 to CVD), by MEC OncoBIO Consolider-Ingenio 2010 (Ref. CSD2007-0017) to ISG, by NIH grant (R01 CA109335-04A1) to ISG, by Sandra Ibarra Foundation to ISG, and by Group of Excellence Grant (GR15) from Junta de Castilla y Leon to ISG and JJC.

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Cancer Stem Cells Theories and Practice

Edited by Prof. Stanley Shostak

ISBN 978-953-307-225-8

Hard cover, 442 pages

Publisher InTech

Published online 22, March, 2011

Published in print edition March, 2011

Cancer Stem Cells Theories and Practice does not 'boldly go where no one has gone before!' Rather, Cancer Stem Cells Theories and Practice boldly goes where the cutting edge of research theory meets the concrete challenges of clinical practice. Cancer Stem Cells Theories and Practice is firmly grounded in the latest results on cancer stem cells (CSCs) from world-class cancer research laboratories, but its twenty-two chapters also tease apart cancer's vulnerabilities and identify opportunities for early detection, targeted therapy, and reducing remission and resistance.

How to reference

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Carolina Vicente-Dueñas, Isabel Romero-Camarero, Teresa Flores, Juan Jesús Cruz and Isidro Sanchez-Garcia (2011). Cancer Stem Cells as a Result of a Reprogramming-Like Mechanism, Cancer Stem Cells Theories and Practice, Prof. Stanley Shostak (Ed.), ISBN: 978-953-307-225-8, InTech, Available from: <http://www.intechopen.com/books/cancer-stem-cells-theories-and-practice/cancer-stem-cells-as-a-result-of-a-reprogramming-like-mechanism>

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