DE GRUYTER Biol. Chem. 2014; 395(11): 1315–1320

Minireview

Alberto Martín-Lorenzo, Inés Gonzalez-Herrero, Guillermo Rodríguez-Hernández, Idoia García-Ramírez, Carolina Vicente-Dueñas* and Isidro Sánchez-García*

Early epigenetic cancer decisions

Abstract: A cancer dogma states that inactivation of oncogene(s) can cause cancer remission, implying that oncogenes are the Achilles' heel of cancers. This current 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, recent studies of the interactions between an oncogene and its target cell have shown that oncogenes contribute to cancer development via developmental reprogramming of the epigenome within the target cell. These results provide the first evidence that carcinogenesis can be initiated by epigenetic stem cell reprogramming, and uncover a new role for oncogenes in the origin of cancer. Here we analyse these evidences and discuss how this vision offers new avenues for developing novel anti-cancer interventions.

Keywords: cancer; cancer stem cell; cancer therapy; oncogenes; stem cells; tumoural reprogramming.

DOI 10.1515/hsz-2014-0185
Received April 15, 2014; accepted May 9, 2014; previously published online September 2, 2014

***Corresponding authors: Carolina Vicente-Dueñas and Isidro Sánchez-García,** Experimental Therapeutics and Translational Oncology Program, Instituto de Biología Molecular y Celular del Cáncer, CSIC/Universidad de Salamanca, Campus M. de Unamuno s/n, E-37007 Salamanca, Spain; and Institute of Biomedical Research of Salamanca (IBSAL), 37007 Salamanca, Spain, e-mail: cvd@usal.es, isg@usal.es
Alberto Martín-Lorenzo, Inés Gonzalez-Herrero, Guillermo Rodríguez-Hernández and Idoia García-Ramírez: Experimental Therapeutics and Translational Oncology Program, Instituto de Biología Molecular y Celular del Cáncer, CSIC/Universidad de Salamanca, Campus M. de Unamuno s/n, E-37007 Salamanca, Spain; and Institute of Biomedical Research of Salamanca (IBSAL), 37007 Salamanca, Spain

Introduction

Since the discovery that human cancers contain activated oncogenes, many efforts have been made to elucidate the causal role that these oncogenes play in cancer development. These previous works have shown that oncogene expression is not only required for initiation of cancer but also for the maintenance of the disease and have kept oncogenes firmly in focus as therapeutic targets. In mouse models where oncogene expression is driven by tissue-specific promoters, tumours arise at high frequencies, but disappear again when the inducing stimulus is switched off (Chin et al., 1999; Huettner et al., 2000; Boxer et al., 2004), suggesting that oncogenes are the Achilles' heel of cancers (Weinstein, 2002). Overall, these observations define a homogenous role for oncogenes within cancer cells (Figure 1A), as brief inactivation of the single tumour-inducing oncogene can cause remission in these model systems. These observations are consistent with a role for oncogenes in regulating tumour mass formation in a similar way to the control of cell-fate determination as a function of lineage-specific factors (Vicente-Duenas et al., 2013, 2014).

This current model of cancer is in agreement with the fact that in human cancers, all cancerous cells carry the same oncogenic genetic lesions. However, it is also a very well-known fact that cancers are composed of heterogeneous cell types (Hanahan and Weinberg, 2011), suggesting that, in the control of oncogenesis, the nature of the target cells suffering the effects of oncogenic activity might play an important role. In fact, therapy based on the current working model of cancer fails to eradicate tumours in humans, as is well illustrated by the BCR–ABL kinase inhibitors such as imatinib/STI571, which can target the differentiated tumour cells of chronic myeloid leukaemia (CML) but fail to eradicate the BCR-ABL-expressing leukaemia stem cells (Chomel et al., 2011; Chu et al., 2011; Corbin et al., 2011; Hamilton et al., 2012; Kumari et al., 2012). On the contrary, these observations are compatible with the cancer stem cell (CSC) theory of cancer that suggests that tumours are hierarchically organized tissues

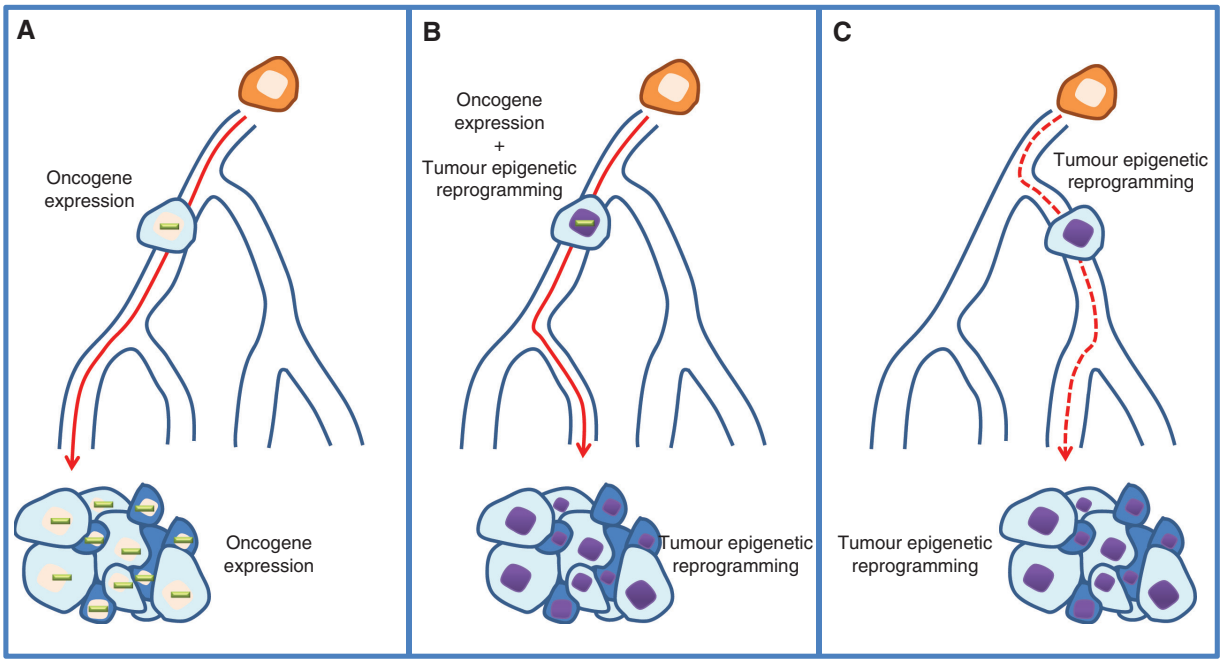

Figure 1 Cellular architecture, drivers and development in cancer.
(A) Current working model for the development of cancer in humans. In the current view of the initiation and progression of cancer, an initiating hit is required to immortalize a target cell. Such cells are then destined to acquire additional genetics hits over time. The acquisition of additional hits further deregulates the behaviour of the tumour cells, thus leading to a subclonal genetic heterogeneity within tumour cells. Specific subclones of tumour cells may contribute to the initiation, treatment resistance or relapse. (B) The tumour stem cell reprogramming model. In human cancer and in most animal models of cancer, the oncogenic alterations are expressed in all the cellular types that compose the tumoural tissue, from the target cell to the terminal differentiated tumour cells. In our model, carcinogenesis can be initiated by epigenetic stem cell reprogramming, uncovering a new role for oncogenes in the origin of cancer: the expression of the oncogene is restricted to the stem/progenitor compartment, but this restricted expression pattern is nevertheless capable of generating a full-blown cancer with all its differentiated cellular components. The demonstration that cancer development can be established in mice by expressing the oncogene only in stem/progenitor cells implies that the oncogene can impose an epigenetic regulatory state in these stem cells that somehow persists during hematopoiesis. These (epi)genetic changes would not interfere with normal hematopoietic development, but become active in the process of terminal differentiation, leading to the appearance of specific tumour differentiated cells. (C) Is epigenetic tumour stem cell reprogramming the driver of cancer? The key question emerging from these findings is how a cell can escape the normal regulatory mechanisms governing epigenetic modifications such that oncogenic gene-expression patterns can persist, without having DNA-sequence mutation. It will be challenging to test whether epigenetic modifications (epigenetic tumoural stem cell reprogramming) without gene mutations can indeed drive cancer development.

(Reya et al., 2001; Pardal et al., 2003; Perez-Losada and Balmain, 2003). If that was indeed the case, then cancer could be created and maintained similarly to any other normal stem cell-driven tissue, like the hematopoietic system. In a normal stem cell-driven tissue, genetic programming of stem cells is all that is required to (re)constitute all differentiated cells forming the tissue, and the genetic information responsible for the stem cell programming does not need to be anymore present within the differentiated cells that form the tissue, implying a different function for oncogenes within CSCs. Thus, we reasoned that a similar organization could be underlying cancer formation (Vicente-Duenas et al., 2013, 2014). In order to initially address this biological question, we have used oncogenic lesions of different types linked to specific hematopoietic cancers and proved that they can re-programme target stem cells through epigenetic changes, into a differentiation state from which tumour cells with different properties emerge heterogeneously (Perez-Caro et al., 2009; Vicente-Duenas et al., 2012a,c, Romero-Camarero et al., 2013).

Limiting oncogene expression to stem cells induces cancer in mice

A major barrier for the understanding of the contribution that CSCs make to the development and maintenance of cancer and their suitability as a target was the lack of a

system to limit oncogene expression to the CSC compartment. To elucidate whether cancer is a stem cell-driven tissue, we used the Sca1 locus control region to limit oncogene expression to the stem cell compartment in a transgenic mouse setting (Perez-Caro et al., 2009). We have initially focused on the effects of the *BCR-ABLp210* oncogene, linked to CML in humans (Koeffler and Golde, 1981a,b; Melo and Barnes, 2007). CML is widely accepted to be a stem-cell disorder where the specific BCR-ABL inhibitor STI571 is able to eliminate the BCR-ABL-expressing differentiated cells that constitute the bulk of the tumour, but it cannot eliminate BCR-ABL-expressing CSCs (Chomel et al., 2011; Chu et al., 2011; Corbin et al., 2011; Hamilton et al., 2012; Kumari et al., 2012).

When the expression of BCR-ABL is restricted to the $Sca1^+$ cells in mice, these *Sca1-BCR-ABLp210* mice fully develop CML. In these *Sca1-BCR-ABLp210* mice, although initiation takes place within the stem cell/progenitor population, the oncogene is switched off in the tumour differentiated cells which constitute the bulk of the tumour. In the paper by Perez-Caro et al. (2009), quantitative RT-PCR analysis of *BCR-ABL* transcripts was used to define patterns of *BCR-ABL* gene expression in pure populations of hematopoietic cells. Overall, *BCR-ABL* is not expressed in lineage-positive hematopoietic progenitors, but it could be that BCR-ABL target genes could continue to be expressed in the absence of BCR-ABL. These genes could be targets of a 'hit and run' mode of action in which *BCR-ABL* turns genes on in stem cells but is not required for maintaining their expression at later stages of development. However, neither BCR-ABL protein nor downstream signalling was detected in $Sca1^+Lin^+$ cells of *Sca1-BCR-ABLp210* mice. The data support the hypothesis that BCR-ABL downstream targets are switched off after the silencing of *BCR-ABL*. It might appear then counter-intuitive and surprising that cancers develop efficiently in these mice as in actual human cancers all cancerous cells carry the oncogenic genetic lesions, not only the CSCs (Figure 1A). Nevertheless, CML arises in these mice indicating that silencing of *BCR-ABL* is not critical for generation of differentiated tumour cells and suggesting a tumour stem cell reprogramming role for BCR-ABL in regulating cancer formation (Figure 1B).

To determine whether the continuous presence of BCR-ABL is necessary for the maintenance of CSCs we treated diseased *Sca1-BCR-ABLp210* mice with the specific BCR-ABL inhibitor STI571 and we found that the course of the CML disease was not modified upon treatment. These observations demonstrate that blocking BCR-ABL function (or at least abolishing its tyrosine-kinase activity) is not efficient in eliminating the CSCs, indicating that mouse CSC are not oncogene addicted. These findings were later corroborated in human patients by showing that human CSC are not oncogene addicted either (Chomel et al., 2011; Chu et al., 2011; Corbin et al., 2011; Hamilton et al., 2012; Kumari et al., 2012). Overall, these observations are in agreement with the development of CML following our tumour stem cell reprogramming model (Figure 1B).

But because we wanted to address the question of whether CSCs are required continuously for maintenance of the CML disease, we used a model in which $Sca1^+$, *BCR-ABL*-expressing cells are deleted in the presence of gancyclovir. After elimination of the CSC, we were able to eradicate the whole tumour (Perez-Caro et al., 2009). These observations formally prove that CSCs are required continuously for maintenance of the CML disease. However, abolishing BCR-ABL function is not critical for the generation of differentiated tumour cells. In our view, this constitutes the most convincing evidence to date that these cancers arise and are driven by a cell-fate change within the stem cells, and that this population is the ultimate target for cancer therapy. In total, the data suggest a tumour stem cell reprogramming role for BCR-ABL in regulating cancer formation.

Considering these evidences, and although human CML is a paradigmatic stem-cell driven cancer, we reasoned that a similar experimental approach to the one we used with *BCR-ABL* could also allow us to reproduce in the mouse the genotype-phenotype correlation (specific oncogene-specific tumour) found in other types of human cancers. The most challenging systems in which to test this hypothesis are those tumours whose main constituent cell type is a mature differentiated cell, such as multiple myeloma (MM) or mature B-cell lymphoma. In recent reports we have showed that MM (by using the *MafB* oncogene) and B-cell lymphoma (by using the *MALT1* oncogene) phenotypes and biology can be faithfully recapitulated in mice in which specific oncogene ectopic expression is limited to stem cell antigen 1 $(Sca1)^+$ cells, implicating for the first time stem cells in the pathogenesis of MM and B-cell lymphoma. Of course, the demonstration that MM and B-cell lymphoma development can be established in mice by limiting oncogene expression to $Sca1^+$ cells implies that abolishing oncogene function does not interfere with the differentiated tumour cell formation, and suggest that the oncogene imposes a gene regulatory state in stem cells that somehow persists during hematopoiesis and which imposes a tumour phenotype reflective of the usual MM and B-cell lymphoma (Vicente-Duenas et al., 2012a,b,c). Therefore, we hypothesize that the cancer-initiating oncogenes mediate tumourigenesis through epigenetic

modification of target genes that remain in this modified state in the mature tumour even in the absence of the oncogene in agreement with an epigenetic tumour stem cell reprogramming model for oncogenes in regulating cancer formation (Figure 1B).

Epigenetic tumour stem cell reprogramming: how does an oncogene program stem cells to make a cancer?

In human pathologies and in most animals models of cancer, the oncogenic alteration(s) is(are) present in all the cellular types that compose the tumoural tissue, from the CSCs to the more differentiated types (Figure 1A). In our stem cell-driven cancer model, the expression of the oncogenic alteration is restricted to the progenitor compartment but is nevertheless capable of generating a full-blown tumour with all its differentiated cellular components, showing a tumour stem cell reprogramming for (some) oncogenes in regulating cancer formation (Figure 1B). Of course, this model implies that the oncogenic activity in the CSC compartment causes epigenetic latent alterations that are responsible for the later appearance of the tumoural phenotype (Vicente-Duenas et al., 2013).

In order to gain even more insight into the mechanism by which oncogene can induce the reprogramming of stem cells into tumour differentiated cells, we have generated *in vivo* genome-scale maps of DNA methylation from both stem cells and mature B-cells from Sca1-MafB mice (Vicente-Duenas et al., 2012c). We found that a substantial number of CpG islands and promoters are specifically hypermethylated or hypomethylated in the stem cells of Sca1-MafB mice, setting a pattern inherited throughout B-cell development. Thus, the results presented in our study demonstrate a novel molecular mechanism involved in tumour initiation, by showing that stem-progenitor cells can be epigenetically reprogrammed to give rise to terminally differentiated tumour plasma cells by MafB (Vicente-Duenas et al., 2012c). To our knowledge, these results represent the most convincing evidence to date that cancer development can arise and be driven by a tumour cell-fate change within the stem cells. The key question emerging from these findings is how a cell can escape the normal regulatory mechanisms governing epigenetic modifications such that oncogenic gene-expression patterns can persist, without having DNA-sequence mutation. It will be challenging to test whether epigenetic modifications (epigenetic tumoural stem cell reprogramming) without gene mutations can indeed drive cancer development (Figure 1C). However, the clinical implications of such oncogenic routes would be far reaching.

This tumoural epigenetic reprogramming is conceptually different from the "epigenetic progenitor" model of cancer, proposing that cancer formation involves a general, non-targeted epigenetic disruption at the level of progenitors cells, followed by an initiating mutation and then by genetic and epigenetic plasticity. However, in both contexts, epigenetic alterations in cancer serve as potent surrogates for genetic mutations and are driving forces of the initial tumoural development (Feinberg et al., 2006; Iacobuzio-Donahue, 2009).

Tumour suppressors can act as barriers for epigenetic tumoural stem cell reprogramming

In analogy to what happens in reprogramming to pluripotency (Zhao et al., 2008; Banito et al., 2009; Hong et al., 2009; Kawamura et al., 2009; Krizhanovsky and Lowe, 2009; Li et al., 2009; Marion et al., 2009; Utikal et al., 2009), the efficiency of the oncogene-induced tumoural reprogramming of normal HS/P-Cs to terminally differentiated malignant cells is enhanced by *p53* deficiency, at least in the cases of BCR-ABL (CML), Malt1 (MALT B-cell lymphoma) and MafB (MM) (Velasco-Hernandez et al., 2012; Vicente-Duenas et al., 2012a,b). These results suggest that the absence of the tumour suppressor does not have an instructive role in the genesis of tumour cells, but just a permissive one, preventing cells with damage from being successfully terminally reprogrammed. In addition, this further supports the interpretation that the driving force of the tumoural reprogramming process is the oncogene itself, and that it is just the need of maintaining genetic integrity that prevents the reprogrammed cells with any kind of damage to progress along the newly programmed malignant pathway (just like in iPSCs generation). Along these lines, transient restoration of *p53* slows down CML disease progression and significantly extends the survival of leukemic animals (Velasco-Hernandez et al., 2012), being the mechanism responsible for this effect the p53-mediated apoptotic death of primitive leukaemia cells, suggesting that reestablishing *p53* function may be a therapeutic strategy for the eradication of leukemic stem cells and to prevent disease progression.

Conclusions and future directions

Despite a better understanding of the biology of tumour cells, the treatment of most cancers has not significantly changed for the past four decades and the decreasing mortality has been mostly the result of early detection and prevention rather than the consequence of effective therapeutics (Etzioni et al., 2003; Chabner et al., 2005; Huff et al., 2006). Thus, the cells and genetic lesions responsible for maintaining the disease remain an intriguing and exciting topic of research, as these cells have been posited to be responsible for resistance to conventional therapies, recurrence, and metastasis (Reya et al., 2001).

We have shown that cancer growth and elimination was achieved by targeting oncogene expression to the CSCs only (Perez-Caro et al., 2009). Thus, if the growth potential of a cancer depends on CSCs and on oncogenes that can function in an epigenetic tumoural stem cell reprogramming manner, it seems important to know how to eradicate these cells and/or inactivate the epigenetic tumoural stem cell reprogramming mechanism. Similarly, assessing the ability of any candidate therapy to destroy these cells would seem crucial to predicting its efficacy (Vicente-Duenas et al., 2013, 2014).

But perhaps the most crucial question of all is whether epigenetic tumoural stem cell reprogramming regulation mechanisms can be found in other cancer types, especially tumours of epithelial origin, which represent the bulk of human cancers. Importantly, a small subset of *Sca1-BCR-ABLp210* mice develops additional solid tumours. Considering that Sca1 has been identified as an almost universal stem cell marker in many different tissues, these data suggest that epigenetic tumoural stem cell reprogramming as a driver of cancer is not specific to only hematopietic tissues, but rather represents a broader mechanism for that can be applied to solid-organ cancers.

Acknowledgments: We are indebted to all members of Lab 13 at IBMCC for useful discussions and for his critical reading of the original manuscript. Research in our group is partially supported by FEDER and by MICINN (SAF2012-32810), by NIH grant (R01 CA109335-04A1), by the ARIMMORA project (FP7-ENV-2011, European Union Seventh Framework Program), by Junta de Castilla y Leon (BIO/SA06/13), and by the Deutsche José Carreras Leukämie-Stiftung (DJCLS project 13/26). All Spanish funding is co-sponsored by the European Union FEDER program. ISG is an API lab of the EuroSyStem project and a partner within the Marie Curie Initial Training Network DECIDE (Decision-making within cells and differentiation entity therapies) funded by the European Union's Seventh Programme under grant agreement n° 315902.

References

Banito, A., Rashid, S.T., Acosta, J.C., Li, S., Pereira, C.F., Geti, I., Pinho, S., Silva, J.C., Azuara, V., Walsh, M., et al. (2009). Senescence impairs successful reprogramming to pluripotent stem cells. Genes Dev. *23*, 2134–2139.

Boxer, R.B., Jang, J.W., Sintasath, L., and Chodosh, L.A. (2004). Lack of sustained regression of c-MYC-induced mammary adenocarcinomas following brief or prolonged MYC inactivation. Cancer Cell *6*, 577–586.

Corbin, A.S., Agarwal, A., Loriaux, M., Cortes, J., Deininger, M.W., and Druker, B.J. (2011). Human chronic myeloid leukemia stem cells are insensitive to imatinib despite inhibition of BCR-ABL activity. J. Clin. Invest. *121*, 396–409.

Chabner, B.A. and Roberts, T.G., Jr. (2005). Timeline: chemotherapy and the war on cancer. Nat. Rev. Cancer *5*, 65–72.

Chin, L., Tam, A., Pomerantz, J., Wong, M., Holash, J., Bardeesy, N., Shen, Q., O'Hagan, R., Pantginis, J., Zhou, H., et al. (1999). Essential role for oncogenic Ras in tumour maintenance. Nature *400*, 468–472.

Chomel, J.C., Bonnet, M.L., Sorel, N., Bertrand, A., Meunier, M.C., Fichelson, S., Melkus, M., Bennaceur-Griscelli, A., Guilhot, F., and Turhan, A.G. (2011). Leukemic stem cell persistence in chronic myeloid leukemia patients with sustained undetectable molecular residual disease. Blood *118*, 3657–3660.

Chu, S., McDonald, T., Lin, A., Chakraborty, S., Huang, Q., Snyder, D.S., and Bhatia, R. (2011). Persistence of leukemia stem cells in chronic myelogenous leukemia patients in prolonged remission with imatinib treatment. Blood *118*, 5565–5572.

Etzioni, R., Urban, N., Ramsey, S., McIntosh, M., Schwartz, S., Reid, B., Radich, J., Anderson, G., and Hartwell, L. (2003). The case for early detection. Nat. Rev. Cancer *3*, 243–252.

Feinberg, A.P., Ohlsson, R., and Henikoff, S. (2006). The epigenetic progenitor origin of human cancer. Nature Rev. Genet. *7*, 21–33.

Hamilton, A., Helgason, G.V., Schemionek, M., Zhang, B., Myssina, S., Allan, E.K., Nicolini, F.E., Muller-Tidow, C., Bhatia, R., Brunton, V.G., et al. (2012). Chronic myeloid leukemia stem cells are not dependent on Bcr-Abl kinase activity for their survival. Blood *119*, 1501–1510.

Hanahan, D. and Weinberg, R.A. (2011). Hallmarks of cancer: the next generation. Cell *144*, 646–674.

Hong, H., Takahashi, K., Ichisaka, T., Aoi, T., Kanagawa, O., Nakagawa, M., Okita, K., and Yamanaka, S. (2009). Suppression of induced pluripotent stem cell generation by the p53-p21 pathway. Nature *460*, 1132–1135.

Huettner, C.S., Zhang, P., Van Etten, R.A., and Tenen, D.G. (2000). Reversibility of acute B-cell leukaemia induced by BCR-ABL1. Nat. Genet. *24*, 57–60.

Huff, C.A., Matsui, W., Smith, B.D., and Jones, R.J. (2006). The paradox of response and survival in cancer therapeutics. Blood *107*, 431–434.

Iacobuzio-Donahue, C.A. (2009). Epigenetic changes in cancer. Annu. Rev. Pathol. *4*, 229–249.

Kawamura, T., Suzuki, J., Wang, Y.V., Menendez, S., Morera, L.B., Raya, A., Wahl, G.M., and Izpisua Belmonte, J.C. (2009). Linking the p53 tumour suppressor pathway to somatic cell reprogramming. Nature *460*, 1140–1144.

Koeffler, H.P. and Golde, D.W. (1981a). Chronic myelogenous leukemia – new concepts (first of two parts). N. Engl. J. Med. *304*, 1201–1209.

Koeffler, H.P. and Golde, D.W. (1981b). Chronic myelogenous leukemia – new concepts (second of two parts). N. Engl. J. Med. *304*, 1269–1274.

Krizhanovsky, V. and Lowe, S.W. (2009). Stem cells: the promises and perils of p53. Nature *460*, 1085–1086.

Kumari, A., Brendel, C., Hochhaus, A., Neubauer, A., and Burchert, A. (2012). Low BCR-ABL expression levels in hematopoietic precursor cells enable persistence of chronic myeloid leukemia under imatinib. Blood *119*, 530–539.

Li, H., Collado, M., Villasante, A., Strati, K., Ortega, S., Canamero, M., Blasco, M.A., and Serrano, M. (2009). The Ink4/Arf locus is a barrier for iPS cell reprogramming. Nature *460*, 1136–1139.

Marion, R.M., Strati, K., Li, H., Murga, M., Blanco, R., Ortega, S., Fernandez-Capetillo, O., Serrano, M., and Blasco, M.A. (2009). A p53-mediated DNA damage response limits reprogramming to ensure iPS cell genomic integrity. Nature *460*, 1149–1153.

Melo, J.V. and Barnes, D.J. (2007). Chronic myeloid leukaemia as a model of disease evolution in human cancer. Nat. Rev. Cancer *7*, 441–453.

Pardal, R., Clarke, M.F., and Morrison, S.J. (2003). Applying the principles of stem-cell biology to cancer. Nat. Rev. Cancer *3*, 895–902.

Perez-Caro, M., Cobaleda, C., Gonzalez-Herrero, I., Vicente-Duenas, C., Bermejo-Rodriguez, C., Sanchez-Beato, M., Orfao, A., Pintado, B., Flores, T., Sanchez-Martin, M., et al. (2009). Cancer induction by restriction of oncogene expression to the stem cell compartment. EMBO J. *28*, 8–20.

Perez-Losada, J. and Balmain, A. (2003). Stem-cell hierarchy in skin cancer. Nat. Rev. Cancer *3*, 434–443.

Reya, T., Morrison, S.J., Clarke, M.F., and Weissman, I.L. (2001). Stem cells, cancer, and cancer stem cells. Nature *414*, 105–111.

Romero-Camarero, I., Jiang, X., Natkunam, Y., Lu, X., Vicente-Duenas, C., Gonzalez-Herrero, I., Flores, T., Luis Garcia, J., McNamara, G., Kunder, C., et al. (2013). Germinal centre protein HGAL promotes lymphoid hyperplasia and amyloidosis via BCR-mediated Syk activation. Nature Commun. *4*, 1338.

Utikal, J., Polo, J.M., Stadtfeld, M., Maherali, N., Kulalert, W., Walsh, R.M., Khalil, A., Rheinwald, J.G., and Hochedlinger, K. (2009). Immortalization eliminates a roadblock during cellular reprogramming into iPS cells. Nature *460*, 1145–1148.

Velasco-Hernandez, T., Vicente-Duenas, C., Sanchez-Garcia, I., and Martin-Zanca, D. (2012). p53 restoration kills primitive leukemia cells *in vivo* and increases survival of leukemic mice. Cell Cycle *12*, 122–132.

Vicente-Duenas, C., Fontan, L., Gonzalez-Herrero, I., Romero-Camarero, I., Segura, V., Aznar, M.A., Alonso-Escudero, E., Campos-Sanchez, E., Ruiz-Roca, L., Barajas-Diego, M., et al. (2012a). Expression of MALT1 oncogene in hematopoietic stem/progenitor cells recapitulates the pathogenesis of human lymphoma in mice. Proc. Natl. Acad. Sci. USA *109*, 10534–10539.

Vicente-Duenas, C., Gonzalez-Herrero, I., Cenador, M.B., Criado, F.J., and Sanchez-Garcia, I. (2012b). Loss of p53 exacerbates multiple myeloma phenotype by facilitating the reprogramming of hematopoietic stem/progenitor cells to malignant plasma cells by MafB. Cell Cycle *11*, 3896–3900.

Vicente-Duenas, C., Romero-Camarero, I., Cobaleda, C., and Sanchez-Garcia, I. (2013). Function of oncogenes in cancer development: a changing paradigm. EMBO J. *32*, 1502–1513.

Vicente-Duenas, C., Hauer, J., Ruiz-Roca, L., Ingenhag, D., Rodriguez-Meira, A., Auer, F., Borkhardt, A., and Sanchez-Garcia, I. (2014). Tumoral stem cell reprogramming as a driver of cancer: Theory, biological models, implications in cancer therapy. Semin Cancer Biol.

Vicente-Duenas, C., Romero-Camarero, I., Gonzalez-Herrero, I., Alonso-Escudero, E., Abollo-Jimenez, F., Jiang, X., Gutierrez, N.C., Orfao, A., Marin, N., Villar, L.M., et al. (2012c). A novel molecular mechanism involved in multiple myeloma development revealed by targeting MafB to haematopoietic progenitors. EMBO J. *31*, 3704–3717.

Weinstein, I.B. (2002). Cancer. Addiction to oncogenes – the Achilles heel of cancer. Science *297*, 63–64.

Zhao, Y., Yin, X., Qin, H., Zhu, F., Liu, H., Yang, W., Zhang, Q., Xiang, C., Hou, P., Song, Z., et al. (2008). Two supporting factors greatly improve the efficiency of human iPSC generation. Cell Stem Cell *3*, 475–479.