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# Connections between Genomic Instability and Cancer Stem Cells

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## 1. Introduction

Cancer is caused by successive gene mutations that amount to confer malignant phenotype. Genomic instability is considered a key endogenous mechanism for accumulation of mutations, and therefore, has been proposed as an engine of tumorigenesis. Recently, cancer stem cells, or tumor initiating cells, have been identified in a variety of human cancers. These cancer stem cells are believed to be responsible for the initiation of malignant growth and metastasis of some, and perhaps all cancer types. How are these two engines of tumorigenesis related to each other? Is genomic instability a driving force in the genesis of cancer stem cells? Is the genome in cancer stem cells inherently unstable? Could genomic instability in cancer stem cells be the cause of the observed cancer cell heterogeneity? In this article, we will discuss some early clues indicating that these two driving forces of tumorigenesis appear to be intimately connected.

## 2. Genomic instability

Genomic instability is a key hallmark of malignancy (Aguilera & Gómez-González, 2008; Jallepalli & Lengauer, 2001; Venkitaraman, 2007). Cancer cells bear numerous molecular changes encompassing nearly 10 years of genesis *in vivo*. The old question of whether the chicken or the egg came first comes to mind when one attempts to sort out whether a molecular change is the cause or a consequence of cancer (Venkitaraman, 2007). This question is particularly challenging since most cancer research relies on cultured cancer cells, devoid of both actual chronologic age and natural physiologic milieu. Genomic instability exemplifies the challenge of such an undertaking: is genomic instability a cause or simply a ramification of the malignant process? Many lines of evidence suggest that genomic instability is a causative factor rather than a result of cancer (Aguilera & Gómez-González, 2008; Jallepalli & Lengauer, 2001; Venkitaraman, 2007). Thus, it seems that genomic instability is intimately linked to cancer stem cells.

## 3. Cancer stem cell

Cancer stem cells also called tumor-initiating cells, are characterized by their self-renewal capacity and ability to initiate tumors (Ailles & Weissman, 2007; Clarke et al., 2006; Dick,

2008; Wicha et al., 2006). Cancer stem cell populations have been identified in a variety of human cancer types (Ailles & Weissman, 2007; Clarke et al., 2006; Dick, 2008; Wicha et al., 2006). Strictly speaking, some isolated cancer stem cells may be more accurately referred to as cancer stemoids (or stem cell-like cancer cells) (Blagosklonny, 2007). Although these cells may exist only as a minority within the cancer cell population, mounting evidence suggests that cancer stem cells contribute to tumor growth, metastasis, and resistance to therapy (Ailles & Weissman, 2007; Clarke et al., 2006; Dick, 2008; Wicha et al., 2006).

#### **4. Genomic instability as a driving force for transforming normal stem cells to cancer stem cells**

Adult normal stem cells represent one purported origin of cancer stem cells. What causes the transformation from normal stem cells to cancer stem cells? Is genomic instability involved in this transformation? Recent work casts insight into potential roles of GIN in the transformation of normal adult stem cells to cancer stem cells. Mirura et al. obtained cancer progenitor cells from bone marrow derived mesenchymal stem cells after long term culture (Miura et al., 2006). Interestingly, these cancer progenitor cells formed fibrosarcoma *in vivo*. The mechanism of transformation was found to be associated with accumulated chromosomal abnormality and increased c-Myc expression (Miura et al., 2006), suggesting an association between cancer progenitor cells and genomic instability. Such an association was also observed in non-hematopoietic stem cells. After a long term culture of human adult non-tumorigenic neural stem cells, Shiras et al. observed concurrent emergence of a high level of genomic instability and a spontaneously immortalized clone which developed into a cell line with features of cancer stem cells, including the capacity to form CD133 positive neurospheres and development into intracranial tumors (Shiras et al., 2007). Additionally, increased expression of well known developmental genes (Notch and Hes) were found both before and after cell transformation (Shiras et al., 2007). Therefore, genomic instability could be a potential driving force in the transformation of normal stem cells into cancer stem cells. How does genomic instability contribute to the transformation of normal stem cells? It has been suggested that normal stem cells and their cellular pathways may acquire stochastic malignant ability (Lagasse, 2008). Clark and colleagues generated highly metastatic cancer stem cells by implantation of murine embryonic germ cells (EGCs) into the testes of adult severe combined immune deficiency (SCID) mice (Conway et al., 2009). Karyotype analysis showed that generation of cancer stem cells is associated with acquisition of genomic rearrangements not found in the original EGCs. Microarray-based gene expression analysis revealed similarity between EGCs and cancer stem cells, and the differentially expressed transcripts are consistent with activation of oncogene pathways. This work suggests that genomic instability may induce stochastic activation of cancer gene pathways in transformation of normal stem cells to cancer stem cells (Conway et al., 2009). Alternatively, cancer stem cells may be derived from clonal selection for resistance to growth limiting conditions imposed by mutagens or carcinogens (Blagosklonny, 2002).

#### **5. Genomic instability in cancer stem cells**

Is the genome inherently unstable in stem cells? If the answer is yes, cancer stem cells may have two reasons for having an unstable genome: being a stem cell as well as a cancer cell.

Let us first look at embryonic stem (ES) cells. Human ES (hES) cells, like other stem cells, have the capacity to self-renew without differentiation, and yet can differentiate to various tissue types upon exposure to specific differentiation cues. It has been technically challenging to propagate hES cells in vitro without allowing differentiation (Bodnar et al., 2004). Cultured hES cells have been shown to have genomic instability with frequent aneuploidy of chromosomes 12, 17q and X, suggesting that the increased dosage of chromosome 17q and 12 genes may provide a selective advantage for propagation of undifferentiated hES cells (Draper et al., 2004). Additionally, long term in vitro culture can result in almost 100% cells with genomic instability, hypothesized by the authors to possibly be an adaptation to loss of ECM support (Imreh et al., 2006). By analyzing 17 hES cell lines with comparative genomic hybridization (CGH), Spits et al. identified amplification of 20q11.21 and a derivative of chromosome 18 (Spits et al., 2008). It is unclear whether hES cells are inherently genetically unstable or if genomic instability is a strong selection factor for long term viability and establishment of hES cells.

By following five human embryonic cell lines over long term cultures, Lefort et al. identified recurrent genomic instability. An amplification of 2.5–4.6 mb at 20q11.21 was recurrent in four out five cell lines. This amplification has also been associated with oncogenic transformation. This study suggests that some genomic instability changes may be selected due to growth advantage they confer to hES cells (Lefort et al., 2008).

The next question to ask is how stable is the genome of adult stem cells? Unlike hES cells, human adult stem cells by design must be maintained for an average human life span of approximately 75 years. Arguably, genomic stability is essential for the maintenance and longevity of adult stem cells (Gerson et al., 2006). Supporting of this hypothesis is the observed premature aging and high cancer incidence in medical syndromes with genetic defects in DNA repair machinery, such as ataxia telangiectasia, xeroderma pigmentosum and Bloom syndrome, to name a few.

Why do embryonic stem cells tend to have increased genomic instability? Work by Mantel et al. suggests that there is uncoupling of apoptosis from mitotic checkpoint activation in both hES and mouse embryonic stem cells (mES) cells. The group showed that mitotic spindle checkpoint activation in somatic cells or in ESC-derived early differentiated cells resulted in robust apoptosis, yet same treatment did not trigger apoptosis in ESCs. It is therefore possible that such tolerance of ploidy changes by ESCs contribute to the karyotypic instability (Mantel et al., 2007). Aoki et al. (Aoki et al., 2007) also observed a three to nine fold increase in anaphase bridge index (ABI), a measure of chromosomal instability, in polyps and mESCs with beta-catenin/Wnt pathway activation resulting from APC/beta-catenin mutations. The WNT signal-activated ES cells produced new chromosomal aberrations at higher rate.

Gene array analysis suggests that cancer stem cells resemble embryonic rather than adult stem cells (Wong et al., 2008). It may be possible that there is similar kind of uncoupling (Bao et al., 2006) between mitotic checkpoint activation and apoptosis in cancer stem cells. Another possible reason for increased genomic instability in cancer stem cells is malignant transformation of aged stem cells. Stem cells have a lifetime exposure to various tumorigenic agents and other stress, and are therefore prime targets for malignant transformation (Ju & Rudolph, 2006).

## 6. Genomic instability in cancer stem cells as a potential mechanism for cancer cell heterogeneity

If cancer stem cells are genomically unstable, it is plausible to reason that genomic instability may contribute to the heterogeneity in cancer cells forming the bulk majority of the tumor (Solé et al., 2008). Wang et al. performed karyotype analysis on a melanoma patient experiencing apparent complete remission and subsequent recurrence over a 12 year period (Grichnik, 2006). Their data point to the existence of a common progenitor cancer cell that gives rise to genomically unstable progeny. Cells karyotyped from the same culture revealed chromosomal differences suggesting ongoing chromosomal instability within the cell population isolated from each metastasis (Grichnik, 2006; Wang et al., 2006).

When cancer stem cell self-renew, numerous genetic variants can be produced. Heterogeneous cancer stem cell populations may acquire drug resistant or metastatic phenotypes. According to this model, cancer stem cells with genomic instability is considered “a powerful vehicle with a powerful engine”, a formidable force for generating heterogeneity and a daunting challenge for designing targeted therapy against one specific pathway (Jones et al., 2008). Initial success with targeted therapy, limited albeit unequivocally positive, suggests cancer heterogeneity is not a completely insurmountable phenotype for designing therapy. Cancer stem cells may present a relatively less heterogeneous cell population for targeting than their progeny.

## 7. Conclusion

Early clues have indicated that genomic instability and cancer stem cells appear to be intimately connected.

Genomic instability might be a potential driving force in the transformation of normal stem cells into cancer stem cells.

Future studies need to focus more on early detection and management of the stem cells carrying genomic instability before they undergo malignant transformation.

## 8. Acknowledgment

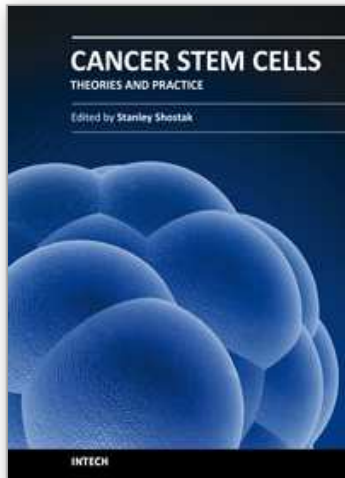
We thank Drs. Johannes Fruehauf and Shuanglin Xiang for their discussion and support.

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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

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