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# Role of Transcription Regulatory Complexes and Epigenetic Modifications in Driving the Cell Fate Decisions

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**Abstract.-** Specific transcription factors and co-regulatory proteins cooperate to regulate the expression of phenotypic genes involved in driving the specific cell lineage. Epigenetic mechanisms such as histone and DNA CpG-methylation that are controlled by regulatory complexes, also contribute in regulating cell fate decisions by regulating cellular transcription. During cancer a transformed cell faces cascade of external and internal signaling events that cause disruption of regulatory complexes and lead to failure of transcriptional machinery to run microenvironment. In general, together perturbation of transcriptional and epigenetic events in a cancer cell results in abnormal regulation of cell proliferation, growth and differentiation. These major biological mechanisms regulate tumor growth and progression during cancer. Recent findings have explored the existence of cancer "stem-like" cells in the tumor that are resistant to chemo-therapy and radio-therapy. These "stem-like" cells can be identified in the tumor due to the expression of marker genes and epigenetic modifications. Many specific post-translational epigenetic modifications such as, acetylation, methylation and phosphorylation of the histones are linked to transcriptional regulation of cancer "stem-like" phenotype. The current review briefly summarizes the importance of transcriptional regulatory complexes, epigenetic markings and molecular events involved in "stem-like" cell fate determination during cancer.

**Key words:** Transcription factors, co-regulatory proteins, epigenetic modifications, cell fate regulation.

## EPIGENETIC REGULATORY COMPLEXES, GENES TRANSCRIPTION AND CELL FATE

Cells demonstrate unique transcriptional and epigenetic (Histone and DNA) instructions in each specific lineage. These epigenetic modifications that regulate gene expression are reversible and controlled through transcriptional regulatory complexes (Boland *et al.,* 2014; Goldberg *et al.,* 2007; Hanna *et al.,* 2008; Reik, 2007). Histones post-translational modifications and gene promoters DNA CpG-methylation are the two well-studied epigenetic mechanisms that control gene transcription and influence the cell phenotype without altering the DNA sequence (Aithal and Rajeswari *et al.,* 2013; Cedar and Bergman, 2009; Miranda and Jones, 2007; Ruthenburg *et al*., 2007; Shilatifard, 2006).

Association of epigenetic modifications and cellular phenotype are well addressed (Goldberg *et al.,* 2007; Hanna *et al.,* 2008; Reik, 2007; Roy and Kundu 2014). For example, specific epigenetic modifications on the amino-terminal tails of histones are linked to gene activation and depression or heterochromatin formation that results in irreversible silencing (Ruthenburg *et al*., 2007; Shilatifard, 2006). These epigenetic codes also reflect and provide information about the transcriptional regulatory complexes involved in dictating cell fate (Eguchi *et al.,* 2014; Hanna *et al.,* 2008; Cedar and Bergman, 2009; Miranda and

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Jones, 2007; Jenuwein and Allis, 2001). In addition, epigenetic gene bookmarking plays a key role in sustaining a transformed cell phenotype to assist tumor progression and more interestingly, subsets of epigenetic modifications are inheritable to maintain cellular identity during lineage progression of transformed cells (Esteller, 2008; Sarge and Park-Sarge, 2005; Jones and Baylin, 2007; Martin and Zhang, 2007; Ng and Gurdon, 2008; Probst *et al.*, 2009). Recent key observations demonstrate that some phenotypic transcription factors with co-regulatory proteins are retained on loci that are important for cell fate decisions (Rando and Verstrepen, 2007; Ali *et al.*, 2008; Xing *et al.*, 2005 Young *et al.*, 2007a), and constitutes a novel concept of "architectural epigenetics" (Young *et al.*, 2007b). Together, regulatory factors and epigenetic modifications determine the fate of cell in specific lineage by regulating the expression of genes specific to cell phenotype, we termed as "fate specific or phenotypic genes". For extensive studies, we refer to in-depth reviews elaborating multiple dimensions of epigenetic control (Goldberg *et al.*, 2007; Jenuwein and Allis, 2001; Zaidi *et al.*, 2010, 2014; Filipowicz *et al.*, 2008; Goodrich and Kugel, 2006).

Bookmarking of target genes regulates key cellular events of growth, proliferation, and cell differentiation (Moazed, 2009; Groudine and Weiuntraub, 1982; John and Workman, 1998; Michelotti *et al.*, 1997; Smith *et al.*, 2002; Tang *et al.*, 2003). For example, in the mammals multiple repeat copies of the rRNA are tandemly organized in a head to tail fashion on acrocentric chromosomes and are transcribed by RNA polymerase I (Pol I). In interphase, rRNA regulatory machinery is configured as round conspicuous body termed as nucleolus (Fig. 1), where ribosome biogenesis and the demand for protein synthesis are accommodated to regulate cell growth (Boisvert *et al.*, 2007; Mayer and Grummt, 2006; White, 2005). During mitosis, RNA Pol I transcription ceases and rRNA genes specifically reside at the short arm of the acrocentric chromosomes to form a structure called Nucleolar Organizer Regions (NORs, Fig. 1) (Klein and Grummt, 1999; Spence and Luthardt, 1975). However, NORs carry interphase transcription regulatory machinery *i.e.*, upstream binding factor (UBF), selectivity factor (SL1) and components of RNA Pol I factor that are key to facilitate rRNA gene transcription as cells come out of mitosis (Roussel *et al.*, 1993). The retention of transcriptional regulatory proteins at the promoters of the "phenotypic" genes through mitosis demonstrates a unique component of epigenetic control to support cell growth and proliferation following cell division. For more information on gene bookmarking by phenotypic factors and regulation of biological events readers are referred to classical research articles (Roussel *et al.*, 1993; Lian *et al.*, 2004; Ali *et al.*, 2010; Berkes and Tapscot, 2005; Kitzmann and Fernandez, 2001; Mohun, 1992).

## STEM CELLS AND CANCER "STEM" CELLS FATE REGULATION

Stem cells are defined by their ability to self-renew and generate population of cells that are different from the parent phenotype. Stem cells can divide by either asymmetric or symmetric modes of division, and that the balance between these two modes is controlled by developmental and environmental signals to produce appropriate numbers of stem cells and differentiated daughters. Available data, suggests that most stem cells have the ability to switch between asymmetric (ACD) and symmetric (SCD) modes of division, depending on the cellular context and that the balance between these two modes of division is compromised during disease states that may cause stem cells to switch between symmetric and asymmetric cell divisions (Berika *et al.*, 2014; Marjanovic *et al.*, 2012). For example, both neural and epidermal progenitors change from primarily symmetric divisions that expand stem-cell pools during embryonic development to asymmetric divisions that expand differentiated cell numbers in mid to late gestation. For these cells, divisions are classified as symmetric or asymmetric depending on whether one or both daughter cells retain the position and morphology associated with stem cells. As layers of differentiated cells arise in the forebrain, progenitors increasingly undergo apparently asymmetric divisions: one cell remains in the ventricular zone

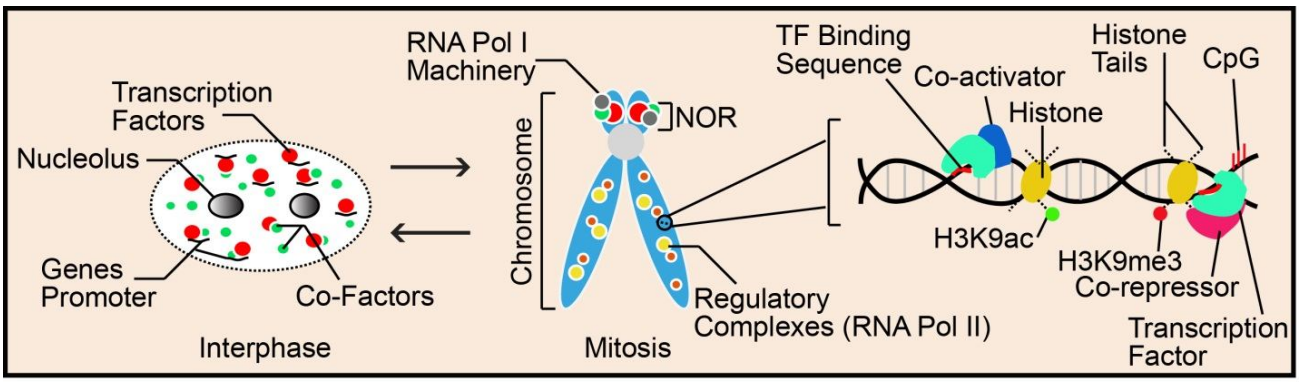


**Fig. 1. Transcriptional regulatory complexes marking phenotypic genes.** Sketch diagram representing interphase cell showing the round nucleolus (grey) where ribosomal gene biosynthesis occurs, transcription factors (red) and other regulatory proteins (green) acting separately or form a complex to regulate target genes expression (black solid lines). Interphase cell, when enters the mitosis, retains transcription factors and co-factors involved in regulating the RNA Polymerase I and II transcription of phenotypic genes. Nucleolar organizing regions (NORs) at acrocentric short arm of chromosome showing the organization of RNA Pol I transcription machinery for the regulation of ribosomal genes. Representative of DNA sequence (black) showing the transcription factor binding sites (red), histone and histone tails bearing active and inactive modifications. Transcription factors associate with co-activators or co-repressor proteins to regulate gene expression. These architectural complexes either positively regulate (H3K9ac) or suppress (CpG, H3K9me3) the promoters of phenotypic genes in context dependent manner during interphase.

(where stem cells are located) and the other cell migrates into overlying layers of differentiated neurons (Chenn and McConnell, 1995; Noctor *et al.*, 2004).

Consequently, the concept of cancer stem cells has been emerging and focus is shifting towards cancer stem cell therapeutics (Le *et al.*, 2014; Sherley *et al.*, 2014). Cancer stem cells use symmetric divisions to self-renew and to generate differentiated progeny that are destined to acquire the same fate (Fig. 2, upper panel). A hallmark of all symmetric divisions is to increase the number of stem or differentiated cells. Symmetric stem-cell divisions are common during wound healing, regeneration and have also been observed during the development of both vertebrates and invertebrates. The capacity for symmetric stem cell self-renewal may confer developmental plasticity, increased growth and enhanced regenerative capacity; however, it may also confer an inherent risk of cancer. Stem cells can rely either completely on symmetric divisions for tumor progression or on a combination of symmetric and asymmetric divisions. Asymmetric cell division is unique aspect of stem cells in which a cell gives rise to two genetically identical cells but functionally different cells. One of the cells is destined for lineage progression, while the other attains the characteristics of parent cell. Studies in yeast, *C. elegans* and *Drosophila* have provided us a mechanistic process of asymmetric cell division (Armakolas *et al.*, 2010; Cowan and Hyman, 2004; Sousa-Nunes and Somers *et al.*, 2013; Thorpe *et al.*, 2008; Colman-Lerner *et al.*, 2001) and furthermore in neurogenesis ACD also has been ascribed to cell fate decisions (Colman-Lerner *et al.*, 2001; Januschke and Gonzalez, 2008). One strategy by which cancer stem cells can accomplish these two tasks is asymmetric cell division, whereby each stem cell divides to generate one daughter with a stem-cell fate (self-renewal) and one daughter that differentiate thus adding to the tumor heterogeneity (Chenn and McConnell, 1995; Betschinger and Knoblich, 2004; Clevers, 2005; Doe and Bowerman, 2001; Yamashita *et al.*, 2005; Lobo *et al.*, 2007). Therefore, asymmetric division is a particularly attractive strategy because it manages both tasks (tumor expansion and heterogeneity) with a single division (Fig. 2, upper panel). It is also possible that mammalian cells utilize ACD mechanisms to ensure

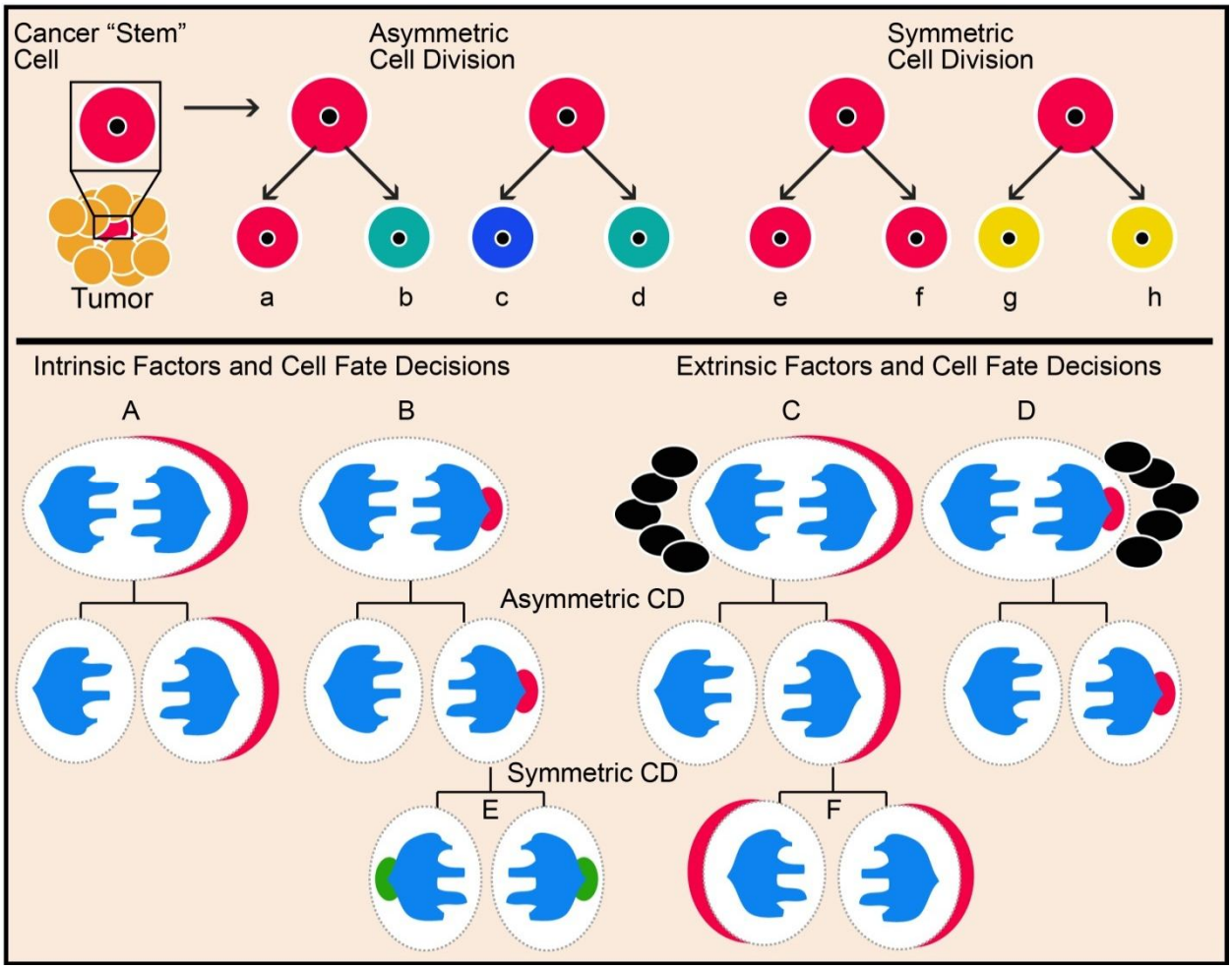


Fig. 2. Cancer "stem" cell fate regulation through symmetric and asymmetric cell divisions. Tumor bulk showing the small population of tumor-propagating cells that self-renew (a) and produce differentiating cells (b). Tumor-initiating cells divide asymmetrically to give rise two cells each showing different phenotype (c) and (d). Cancer "stem" cells also show symmetric cell divisions to give rise two "stem-like" cells (e and f) or divide to give rise two cells showing same phenotype (g) and (h). Lower panel showing tumor-propagating cells dividing asymmetrically (A and B), due to polar distribution of intrinsic factors (surface markers, cytoplasmic proteins and/or nuclear factors) that results in the formation of two daughter cells. Also lower panel demonstrating asymmetric cell division under the influence of extrinsic signals that results in polar distribution of surface and nuclear molecules (C and D) involved in regulating cell fate. Asymmetrically dividing cell gives rise to two cells, one cell exhibiting the properties of parent cell while the other gives rise to different type of cell (asymmetric cell division) or both the cells demonstrate different characteristics due to difference in phenotype (asymmetric cell division). Cell divisions involving intrinsic and extrinsic signals also regulate symmetric cell divisions. Both cells can be cancer "stem" cells (symmetric cell division) or representing one lineage (symmetric cell division) as shown in the lower panel E and F.

the maintenance of cancer stem cells while giving rise to distinct lineages from common ancestor cell.

The role of asymmetric cell division in stem-cell and cancer stem cell, coupled with the mechanisms that regulate this process, have been extensively reviewed (Betschinger and Knoblich, 2004; Clevers, 2005; Doe and Bowerman, 2001; Yamashita *et al.*, 2005; Lobo *et al.*, 2007; Gómez-López *et al.*, 2014). In brief, two types of signaling cues govern cell fate decisions. The first relies on the asymmetric partitioning of cell components that determine cell fate; we refer to such mechanisms as

'intrinsic' (Fig. 2, lower panel). The second involves the asymmetric placement of daughter cells relative to external cues; we refer to these mechanisms as 'extrinsic' (Fig. 2, lower panel). Intrinsic mechanisms include regulated assembly of cell polarity factors and regulated segregation of cell fate determinants. In situations in which the only difference between the daughter cells is their position relative to the stem-cell niche, the daughter cells may initially have equivalent developmental potential, but they may acquire different fates owing to exposure to varying external signals. In this way, the division is asymmetric with respect to the ultimate fate of the daughter cells even though the division is intrinsically symmetric, initially yielding two daughter cells with equivalent developmental potential. Recent findings suggest that the unequal distribution of non-genomic regulatory proteins is a defining factor for driving the specific lineage of a cell. Together, recent findings highlight the fundamental role of symmetric and asymmetric distribution of transcription regulatory factors and epigenetic modifications in driving cell fate through target genes expression.

## PERSPECTIVE

The ability of cancer initiating cells to switch back and forth between symmetric and asymmetric modes of division, depending on developmental and environmental cues, is a key adaptation that increases the capacity of tumor propagating cell to survive. A potential cost of the increased use of symmetric divisions by normal stem cells may be a higher incidence of cancer, particularly the evidence that cancer frequently arises from the transformation of somatic stem cells. Moreover, if tumor growth and progression are driven by cancer "stem" cells then this process may remain biologically dependent on modes of division that permit the geometric expansion of stem cells. The idea that symmetric divisions are required for neoplastic proliferation remains hypothetical, but raises the possibility that studies of the asymmetric division machinery could identify important new tumor suppressor mechanisms. A key issue for the future is to explore how normal and cancer "stem" cells are regulated to switch between asymmetric and symmetric divisions. A molecular understanding, of this regulatory switch for cell division, is not only relevant to basic stem-cell biology, but also has tremendous clinical importance for controlling stem cells therapeutically.

In addition to that, the mitotic association of regulatory proteins, combined with the global, genome-wide assessment of histone-DNA modifications, provides an epigenetic profile of the signatures involved in cancer prognosis as well as monitoring chemo and radio based therapies. As a result of the extensive efforts to define transcriptional and epigenetic signatures, patterns with both diagnostic and therapeutic value are emerging. Some of these will prove to be important for the cancer patients. The strategy of personalized medicine, that is, obtaining comprehensive genetic, epigenetic and expression data from individuals patients and identifying the trends that correlate to disease onset and remission, can be helpful for treatment based on patient's personal characteristics. It is important that physician and scientists combine their efforts to improve clinical trial by translating cancer bio-marker research.

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