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Higher order genomic organization and epigenetic control maintain cellular identity and prevent breast cancer

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Abstract

Cells establish and sustain structural and functional integrity of the genome to support cellular identity and prevent malignant transformation. In this review, we present a strategic overview of epigenetic regulatory mechanisms including histone modifications and higher order chromatin organization (HCO) that are perturbed in breast cancer onset and progression. Implications for dysfunctions that occur in hormone regulation, cell cycle control and mitotic bookmarking in breast cancer are considered, with an emphasis on epithelial-to-mesenchymal transition and cancer stem cell activities. The architectural organization of regulatory machinery is addressed within the contexts of translating cancer-compromised genomic organization to advances in breast cancer

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risk assessment, diagnosis, prognosis, and identification of novel therapeutic targets with high specificity and minimal off target effects.

Keywords

Higher order chromatin organization; breast cancer; epithelial to mesenchymal transition; cancer stem cells; hormone regulation; mitotic bookmarking; RUNX

Introduction.

Physiological control of gene expression is dependent on chromatin context and requires timely and dynamic interactions between transcription factors and coregulatory machinery that reside in specialized sub-nuclear microenvironments [1–5]. Multiple levels of nuclear organization functionally contribute to biological control and are perturbed in cancer[1–47]. Morphologically, cancer nuclei are generally larger, more irregularly shaped and have altered sub-nuclear structures [23,31,48]. These changes in nuclear structure have long been used by pathologists as a major diagnostic tool to detect tumor cells [23,31]. While it is well-known that nuclear morphology is disrupted in cancer cells, emerging evidence supports significant contributions by concomitant changes in higher order chromatin organization (HCO). There is increasing understanding for mechanisms utilized to maintain HCO in normal cells, and the functional consequences of modifications in HCO in cancer onset and progression. Technological advances including high-throughput next generation sequencing[49–53] and sophisticated microscopic techniques[5,54,55] have revolutionized investigation into genomic organization within the contexts of biological control and pathology.

Cells must maintain genomic structural integrity and functional identity throughout successive generations to prevent malignant transformation[56,57]. The retention of cell type specific transcription factors and epigenetic histone modifications at target gene loci, designated bookmarking, has been posited to be critical to sustain cellular phenotypes[58–60]. Bookmarking of chromatin domains has been proposed to play a significant role in re-establishing fidelity for HCO of the genome[61]. Upon exit from mitosis, the biogenesis of nuclear bodies, that include nucleoli (where ribosomal RNA is transcribed) and histone locus bodies (HLB; where histone mRNA is transcribed), contribute to HCO mediated biological control[62,63]. These physiologically important examples of regulatory compartmentalization are obligatory for the balance between proliferation and cell lineage specificity. Reprogramming of lineage-committed cells during the initial stages of cancer is associated with loss of critical parameters of normal cellular identity. A cogent hypothesis is that cancer cells hijack an epithelial-to-mesenchymal transition (EMT) in which cells reliquish their epithelial tight junctions and polarity while acquiring mesenchymal characteristics that include migration and invasiveness (Figure 1). Many of the signaling cascades associated with this process are well known[64]. Signaling pathways that include TGFβ, SNAIL, ZEB, and WNT have been implicated in control that is operative in cancer stem cells (CSCs) [65–67]. The cancer stem cell hypothesis postulates that a sub-fraction of

tumor cells designated CSCs are competent to proliferate, self-renew, ‘differentiate’, and drive tumor initiation, growth, and recurrence[68].

In this review, we will present a strategic overview of the principles underlying epigenetics and HCO with consideration for their role(s) in EMT and CSCs during breast cancer initation and progression. The significance of hormone regulation for these pivotal regulatory processes, and the importance of the cell cycle and bookmarking in establishing and maintaining normal breast epithelial cellular identity will be discussed. The implications for these crucial regulatory dimensions of cancer underscore the need for a deeper understanding of mechanisms driving cancer-compromised organization of genome regulatory machinery to inform novel therapeutic strategies.

Higher order chromatin organization is integral to fidelity of genome regulation.

The genome is hierarchically organized at multiple, complex and interdependent levels. At the molecular level, ~146 base pairs of DNA are wrapped around an octameric core of histones (H2A, H2B, H3, H4) termed the nucleosome[69]. These repeated nucleosomes are configured as a ‘beads-on-a-string’ 10nm chromatin fiber[57,70]. Repressed chromatin has been posited to form a helical 30nm solenoid-like structure[57,70]. However, recent studies using small-angle X-ray scattering, cryo-EM, or super-resolution microscopy have not observed these solenoids *in vivo*[71]. These studies instead found that the beads-on-a-string structures in nuclei are not uniform, but heterogeneous varying in diameter. The advances in sophisticated microscopic and sequencing techniques have revealed fundamental principles governing higher order levels of chromatin organization that is relevant for cell structure and function. These studies have identified that the chromatin fiber is folded into globular domains designated topologically associating domains (TADs)[72–75]. TADs then coalesce into two main compartments that are either euchromatic, termed A co-partments, or heterochromatic, termed B compartments[76,77]. These are in turn comprised of six computationally distinct subcompartments, two that are euchromatic and four that are heterochromatic[78]. More recently, it has been demonstrated that these subcompartments exist as a spectrum of compartments wherein some TADs associate with both A and B compartments[79]. As expected, compartments present at the extremes of the spectrum are more indicative of euchromatic or heterochromatic states, respectively. The euchromatic A compartments are noticeably more gene rich, transcriptionally active, marked by active epigenetic signatures, and preferentially accessible to DNaseI than heterochromatic B compartments[37,80]. At the highest level of organization, chromosomes occupy discrete territories within the nucleus[81,82].

The vast majority of the human genome does not encode proteins. Consequently, there has been speculation that these non-coding regions are so-called “junk DNA”[83]. While there is still no discernable function readily apparent for a portion of what was considered “junk”, increasing evidence has established that many non-coding regions provide regulatory control over gene expression and genome integrity [84]. Key to fidelity of regulation, regions of the genome either activate (enhancers) or suppress (silencers) expression of their cognate genes.

These elements can be located distal (even up to 1mb) from the genes they regulate. The requirement for long-range interactions of enhancers looping back to interact with their correct promoters is integral and coincident with gene expression. Disruption of physiologically responsive enhancer-promoter interactions has been shown to contribute to cancer onset and progression [85–88]. For example, regulatory elements within regions several kb in length that lack protein-coding genes exhibit long-range interactions with both protein and non-protein-coding genes[89]. These genes include MYC, IGFBP5, KLF4, CCDC26, and DIRC3 and have critical roles in breast cancer[90–93].

Enhancers are precluded from interacting with inappropriate promoters by insulator elements bound by chromatin organizer proteins that mediate long-range intra- and interchromosomal interactions[94–96]. Additionally, these insulators provide barriers against the aberrant spreading of heterochromatin from silencers. In performing these essential functions, insulators organize the genome into the TADs that serve as subnuclear microenvironments[94–96]. Regions within individual TAD microenvironments are epigenetically marked largely consistently throughout[74,75] and contain genes that are expressed at relatively similar levels [97,98]. These genes within the same TADs are generally co-regulated and responsive to the same transcriptional stimuli[97,99]. TADs also function as structural domains to constrain long-range contacts between enhancers and promoters such that they occur almost exclusively within TADs[72,100]. Given the inextricable link between structure and function within the context of the cell nucleus, it is important to consider the role of HCO in maintaining genomic stability and fidelity[101–103], and the resulting disruptions that occur in these TAD microenvironments introduced by translocations, deletions, inversions, and mutations during cancer progression[88].

CTCF and/or epigenetic dependent mechanisms contribute to higher order chromatin organization.

CTCF is a major protein involved in insulator function and mediates intra- and interchromosomal looping interactions in vertebrates[104]. Through interactions with chromatin remodeling proteins, histone modifying enzymes, and transcription factors, CTCF is implicated in a broad spectrum of critical regulatory functions including imprinting[105], X chromosome inactivation[106], and organizing the major histone locus[41]. CTCF and its binding sites are mutated in many cancers, including breast cancer, suggesting its functions are perturbed upon malignant transformation[107–110].

While the mechanism of how chromatin loops and TADs are established is not fully elucidated, CTCF as well as its interaction with the structural maintenance of chromosome (SMC) cohesin complex are key components of HCO. The best-accepted model to explain TAD formation and maintenance involves a *loop-extrusion model*[111,112]. This model proposes that a cohesin ring holds two strands of DNA together and creates loops by actively extruding the DNA. Once cohesin encounters a CTCF motif that is in a convergent orientation, a loop is formed[112] (Figure 1). Because CTCF is essential[113], investigations have focused on its depletion using the auxin inducible degron (AID) or siRNA methods. Using an RNAi method, it was found that CTCF knockdown slightly decreased intra-TAD contacts while increasing inter-TAD interactions[114]. Depletion of CTCF using the AID

system[115] resulted in greater reduction of CTCF and led to a loss in TAD insulation, but does not alter intra-TAD contacts[116]. In this study, ~20% of TAD boundaries were unaffected by CTCF-independent upon auxin mediated CTCF degradation. In contrast, another study found that while CTCF knockdown reduced genomic occupancy of the cohesin complex, its loss only slightly weakened TAD boundaries and the vast majority of TADs remained unaltered[117]. Although the segregation of A and B compartments generally occurs at TAD boundaries, knockdown of cohesin and/or CTCF did not affect A and B compartmentalization[116,118].

While CTCF plays a major role in chromatin organization, its absence at many TAD boundaries suggests alternative mechanisms, including epigenetic modifications, for delineation of TAD structures. The fact that TADs are found in species that do not have orthologues of CTCF including *Caenorhabditis elegans*, *Arabidopsis thaliana, Schizosaccharomyces pombe*, or *Caulobacter crescentus* and *Escherichia coli* provides definitive evidence for CTCF-independent mediation of TAD partitioning, particularly in ancestral genomes[119–123]. In these species, other insulators, may play an important role in defining TAD boundaries. Alternatively, evidence suggests that the folding of nucleosomes from beads-on-a-string into chromatin domains may be directly related to the differential compaction of chromatin induced by active versus inactive epigenetic states. High levels of acetylation on histone tails results in destabilization of chromatin domains[124]. This destabilization of chromatin domains could explain the enrichment of epigenetic marks indicative of actively transcribed genes (e.g. housekeeping genes) at TAD boundaries[74]. In fact, expression data is capable of predicting the three-dimensional folding of the genome[125,126]. The partitioning of TAD boundaries based upon active expression independently of CTCF binding appears to be more frequent in drosophila melanogaster[125,127]. TAD boundaries in drosophila are indicative of transitions between open and closed compartmentalization to an even greater extent than in human nuclei[125]. In fact, the differential packing ability of active and inactive genes was shown to predict TAD boundaries in drosophila based upon polymer simulations[127]. TADs in drosophila are therefore responsive to transcriptional stimuli (e.g. recovery from heat-shock[128] or zygotic genome activation, or transcriptional inhibition[129]). The fact that the HCO of genomes from lower organisms are more specified by epigenetic states than HCO in the human genome suggests that human cells have more tight control over HCO. Loss of this tight control over epigenetic regulation and HCO are fundamental alterations that occur during breast cancer progression.

Parameters of breast cancer genome topography: Epithelial to mesenchymal transition, cancer stem cells, epigenetics and higher order chromain organization.

Breast cancer is the most common cancer in women, encompassing a diverse array of subtypes with different cellular origins (luminal versus basal) and distinct molecular alterations (e.g., hormonal status including ER, PR, and HER2) that relate to malignancy [130]. Gross morphologic alterations in nuclei in breast cancer are indicative of poor prognosis[131] and can be used to predict ER status suggesting putative differences in nuclear morphology between these breast cancer subtypes[132]. Despite considerable advancements

deciphering critical genes and pathways driving the various subtypes of breast cancer, the initial molecular events transforming normal cells require more investigation.

During cancer progression, cells lose epithelial-like polarity and acquire mesenchymal-like phenotypes that include increased migration, invasiveness, resistance to chemotherapy, and immune-response in a process termed Epithelial to Mesenchymal Transition (EMT)[133]. The hallmark of EMT is decreased expression of tight junction proteins including cytokeratin and E-cadherin, and the activation of the mesenchymal genes such as N-cadherin, Vimentin (a cytoskeletal intermediate filament), and Fibronectin[64]. Due to the importance of EMT in normal development, EMT is precisely regulated by coordinated crosstalk between transcription factors and signaling cascades. For example, E-cadherin expression is downregulated by EMT-inducing transcription factors that are stimulated by Wnt and Notch pathways[134]. EMT can be activated by extracellular signals, such as cytokines (e.g. TGFβ, BMP, and TNFβ), growth factors (eg. FGF, EGF), and certain extracellular matrix (ECM) proteins[135]. In turn, the EMT process induces a dynamic reorganization of the cytoskeleton to form membrane protrusions necessary for migration and invasion[134]. Recent evidence has demonstrated an interaction between cytoskeletal structure, nuclear morphology, and higher order chromatin organization ([136–139]). For example, the cytoskeletal arrangement of vimentin or actin correlate with nuclear morphology, and depolymerization of vimentin using withaferin A perturbs nuclear morphology[140]. Proteins that link the cytoskeleton to the nuclear envelope can transfer cytoplasmic forces into the nucleus. Although it is known that actin shuttles into and out of the nucleus, the function of nuclear actin in mediating HCO is unclear. In one study, it was found that cells overexpressing an NLS-containing actin demonstrated decreased expression of adhesive genes, and exhibited altered cytoskeletal and focal adhesion organization and inhibited cell motility relative to cells overexpressing wild type actin[141]. Moreover, actin or actin related proteins (ARPs) can function in association with chromatin remodelers and/or act as cofactors with other nuclear complexes[142,143]. Moreover, TGFβ-induced EMT results in genomic instability associated with the suppression of several nuclear envelope proteins that are implicated in the regulation of mitosis[144]. Together, this evidence suggests a complex interplay between the signaling cascades, cytoskeletal rearrangement, and genome instability induced by EMT and HCO in breast cancer (Figure 1).

Efforts have been made to prevent or revert EMT or CSC properties which can restrain invasion, metastasis, and chemo-resistance. A promising therapeutic strategy is to target the epigenetic properties of cancer cells. For example, 5-azacytidine was shown to block DNA methyltransferase (DNMT) activity leading to hypomethylation and gene de-repression, thereby preventing EMT *in vitro*[145]. ZLD1039, an EZH2 inhibitor, also demonstrated a strong anti-cancer effect by inhibiting breast tumor growth and metastasis[146]. Restoration of factors which function epigenetically is another promising avenue for breast cancer treatment. For example, reduced levels of BRMS1L (breast cancer metastasis suppressor 1 like) is associated with breast cancer metastasis and poor patient survival[147]. BRMS1L was shown to epigenetically silence the expression of FZD10, a receptor for the Wnt/β-catenin pathway. Therefore, restoring BRMS1L levels can potentially be used to inhibit aberrant Wnt signaling in breast cancer patients.

Although the requirement for EMT to support cancer metastasis has been challenged[148,149], it is well acknowledged that EMT is in fact a major driving force in cancer stem cell formation[65,150]. CSCs are a subpopulation of tumor cells which are capable to form new tumors, self-renew, and "differentiate" into non-stem like cancer cells[151]. When injected into immunocompromised mice, the CSCs can form tumors with much higher efficiency compared with non-CSC tumor cells[152]. Multiple lines of evidence have demonstrated that activation of EMT signaling pathways increases the mesenchymal-like CSC population[65,150]. For example, the E-cadherin promoter is hypermethylated by the EMT-inducing transcription factors Yap, Snail, and Zeb[153–155].

RUNX-mediated control of Epithelial-to-Mesenchymal transition and breast cancer stem cells.

Our laboratory has demonstrated that the RUNX1 transciption factor has a key role in supporting the normal breast epithelial phenotype[156–158]. Depletion of RUNX1, not only initiated EMT [156], but also increased the CSC population in breast cancer cells[157], through TGFβ and TGFβ independent mechanisms. This suppression of breast CSCs is regulated through multiple signaling cascades including ZEB1[157] and YAP[159]. The regulation of RUNX1 in suppressing ZEB1 is of particular interest considering that the poised epigenetic state of the ZEB1 promoter has been shown to be crucial for generation of CSCs[160]. This is even more intriguing considering RUNX1 and ZEB1 are both downstream of TGFβ[161]. In contrast to RUNX1, RUNX2 (a driver of metastatic bone disease) induces EMT in breast and other cancers[162] by upregulating the expression of SNAI2[163,164].

RUNX transcription factors directly contribute to chromatin looping by recruiting mediators, chromatin remodelers, and chromatin organizing proteins to regulatory elements of target genes[158,165]. For example, in hematopoietic stem cells, RUNX1 contributes to the interaction of the CD34 promoter to its distal enhancer [4]. Likewise, RUNX2 was shown to bind the promoter of Supt3h and facilitate long-range interactions between the Supt3h and the RUNX2 promoters[166]. Similar to other transcription factors, RUNX1 has also been shown to be enriched at TAD boundaries and facilitate HCO that is functionally relevant in early stage luminal ER+ BrCa [167]. Another level of HCO, that involves all RUNX factors, is their unique protein domain that targets RUNX to subnuclear sites via a nuclear matrix targeting signal (NMTS). This NMTS is essential for assembling multimeric complexes containing KATs, HDACs, and coregulatory factors for signaling pathways critical to cancer progression (e.g. SMADs, WWD, and P53)[158]. Together these studies suggest RUNX factors are regulators of EMT and can potentially influence HCO in breast cancer.

Hormone signaling and its impact on higher order chromatin organization.

Nuclear hormone receptor (NR) signaling is a major contributor to altered epigenetic and gene expression profiles during breast cancer progression. NRs are ligand-activated transcription factors that drive the development and maintenance of normal cellular phenotypes[168], and their dysregulation can result in the loss of key aspects of cellular identity in cancer. Despite the important role these signaling cascades have in modifying the epigenetic landscape in breast cancer cells, the contribution of higher order chromatin

organization to these events is less well understood. Open questions remain regarding the contribution of individual NRs to epigenetic signatures and higher order chromatin structures that drive EMT during early and late stage tumor development.

The importance of the biological activity of hormones in breast cancer was indicated by the removal of the ovaries in women, which greatly reduced further metastasis of breast cancer in these patients[169]. Additionally, it is well appreciated that the active metabolite of estrogen, 17β-estradiol, is required for the development of normal breast tissue and contributes an oncogenic role in breast cancers [170]. The invention and application of microarray and next generation sequencing technologies has expanded our understanding and classification of breast cancers [171] and to this end, the intrinsic molecular subtypes of breast cancer are determined by the expression of different genes including hormone receptors [172]. Luminal A or B and unclassified/normal-like breast cancers are characterized by the presence of estrogen receptor (ER, Reviewed in [173]) and/or progesterone receptor (PR), while triple-negative or basal-like and HER2-enriched subtypes are hormone-receptor negative (Reviewed in [174]). Other critical hormone receptors that have been identified in breast cancer are the androgen receptor (AR), glucocorticoid receptor (GR) and thyroid receptor (TR) [175,176].

Hormone signaling is a critical regulator of EMT.

The lack of proper hormone regulation may be one of the key requirements altering cellular identity during breast cancer EMT. The best-studied and arguably most critical hormone in EMT and breast cancer progression is estrogen. Estrogen promotes an epithelial phenotype by suppressing TGFβ, MTA3, and NF-kB. Indicative of EMT, loss of ERα results in altered expression of EGFR, HER2, matrix metalloproteinases and their endogenous inhibitors. Both Snail1 and ZEB1, which are elevated in EMT and in breast CSCs, in turn suppress ERα expression. ERβ has also similarly been shown to suppress EMT. Other hormones also play critical and opposing roles in EMT. For example, growth hormone induces EMT[177] whereas prolactin inhibits EMT[178]. While several EMT inducing genes were increased by PR during mammary alveologenesis[179–181], progesterone reversed EMT phenotypes in basal-like breast cancer via a membrane bound PRα mediated pathway [182]. Therefore, these studies indicate a complex role for progesterone in normal breast development where it induces EMT versus basal breast cancer where it reverses EMT.

In addition to their roles in EMT and CSCs (discussed above), RUNX factors have been implicated in ER signaling. Loss of function mutations in the DNA binding-Runt homology domain of RUNX1 were detected with a particular frequency in the luminal A ER+ subtype of breast cancer[183–186] (Figure 2). Mechanistically, RUNX1 has been shown to recruit and tether ERα to the genome in breast cancer[187]. A conditional knockout of *Runx1* in mice resulted in a significant reduction in ER-positive mature luminal cells. This phenotype can be reversed by *Trp53* or *Rb1* mutation, suggesting a role for RUNX1 in ER+ luminal breast cancer with background mutations in P53 or RB1[188]. Loss of RUNX1 in the luminal A subtype of breast cancer was also shown to facilitate estrogen-induced WNT signaling by suppressing AXIN1[189]. In contrast, the oncogenic activities of RUNX2 were antagonized by estradiol stimulation[190].

Estrogen receptor α coordinates long-range chromatin interactions to drive aberrant transcription in breast cancer.

Estrogen-dependent breast cancer is characterized by abnormally high levels of ERα expression[191]. ERα acts as a driver of tumorigenesis in about 80% of human breast cancers[191]. Therefore, endocrine therapies that target ERα are the cornerstone of breast cancer treatment. The tumor-promoting activity of ERα depends on dynamic interaction with dozens of other factors, including pioneer factors and chromatin remodeling complexes, to regulate chromatin structure and gene expression. ERα's most reliable cofactor, FOXA1, was discovered through the observation that forkhead motifs are heavily enriched within ERα binding sites[192]. FOXA1 is a pioneer factor, meaning it is able to interact with compacted DNA and unravel it to facilitate the subsequent binding of other transcription factors[193]. It has been shown to be required for ERα binding in breast cancer cells, and its knockdown slows the growth of the MCF7 cell line[194]. The transcription factor GATA3 has also been shown to be a key player in estrogen-dependent gene regulation[195]. Interestingly, GATA3 is required development of normal mammary glands[196], suggesting an important role in promoting cellular differentiation, yet silencing of GATA3 inhibits estrogen-dependent breast cancer cell proliferation[197]. Both FOXA1 and GATA3 are required for establishment of a stable estrogen-responsive transcriptional complex, and they both serve as prognostic indicators for response to antiestrogen therapy[192,198].

The organization of the estrogen-dependent breast cancer cell genome is defined by ERα activity. ERα transcriptional activation is mediated through a complex network of ER binding sites located both proximal and distal to transcriptional start sites of target genes[199]. Many of the distal binding sites have been shown to act as transcriptional enhancers that are involved in long range chromosomal interaction, transcription complex formation, and wide-spanned chromatin rearrangement[200,201]. Studies of this phenomenon indicate that ERα can regulate a number of its target genes in a relatively confined space, which requires the arrangement of different regulatory regions into a single transcriptional hub. For example, ERα was not only recruited to bind a known target in MCF7 ER-positive breast cancer upon estrogen stimulation, but also resulted in the regulation of enhancer-promoter interactions mediating transcription[193]. Genes that were contacted by enhancers upon estrogen stimulation contained increased transcriptional activity. With the development of ChIA-PET (a method for determining protein mediated intra-and inter-chromosomal contacts), global ER-mediated chromatin interactions were detected[201]. This comprehensive chromatin map of ER-alpha revealed that long-range chromatin interactions loop distal promoters together for coordinated transcriptional control. Furthermore, distant estrogen response elements localized in regions frequently amplified in ER positive breast cancers form long-range interactions that support estrogen mediated signaling. These gene clusters potentially predict poor clinical outcomes and drug resistance in breast cancer [202]. Estradiol stimulation of MCF7 further demonstrated that hormone-stimulation can function through 3D chromatin organization, its core receptor (ER in this case), epigenetics and gene expression[203]. Further dissection of this multi-step process (hormone stimulation > receptor activation > recruitment of chromatin remodeling factors > changes in HCO and gene expression) will allow a deeper understanding of the extent to which estrogen-dependent transcriptional dysregulation in breast cancer is influenced by defects in chromatin organization.

In addition to the characterization of estrogen signaling in ER positive breast cancer others have begun to study the effects of other types of hormone-signaling on HCO. Progestin and estradiol influence topologically associated domains (TADs) in the human breast cancer cell-line T47D, that expresses ER and PR[97]. While the majority of TAD boundaries remain unaltered after 1 hour of progestin stimulation, genes within 20% of TAD regions display differential expression. Regions that were responsive to progestin showed some coincidence with estradiol altered regions, however, elements unique to estradiol stimulation are also detected. Hormone-induced alterations in gene expression and chromatin remodeling, result in simultaneous changes in intra-TAD interactions within TADs that are hormone responsive. Furthermore, stimulation with glucocorticoids, which activate the glucocorticoid receptor also alter long-range chromatin interactions, DNAseI hypersensitivity, and corresponding gene expression programs in murine breast cancer cells[204].

Progesterone receptor enhances and blunts estrogen receptor signaling through epigenetic modifications in breast cancer.

The progesterone receptor (PR) is a critical player in progression, therapeutic responsivity and eventual outcome of breast cancers. These receptors when bound to DNA induce assembly of chromatin remodeling complexes and cofactors to induce changes in gene transcription. PR amplifies ER expression in breast cancer cells through direct binding to low-methylated *ESR1* promoter. Loss of PR expression results in an increased methylation of the *ESR1* promoter and re-expression of PR did not restore ER expression or decrease methylation[205]. Not surprisingly, methylation of PR-responsive promoters genome-wide impedes PR binding to consensus response elements and subsequent changes in gene expression[205]. Demethylation of *ESR1* in ER negative breast cancer cells can reactivate ERα expression and restore sensitivity[206].

In addition to directly increasing ER expression in breast cancer, unliganded PR increases breast cancer cell proliferative response to estrogen and enhances antiestrogens effectiveness through inducing changes in chromatin organization via a scaffolding complex that includes ERα and PELP1 transcriptional co-regulator[207]. This unliganded PR binds genomic sites and targets a repressive complex containing HP1γ (heterochromatin protein 1 gamma), LSD1 (lysine-specific demethylase 1) among other co-repressors to induce a closed chromatin conformation that precludes gene expression. This includes approximately 20% of hormone-inducible genes in breast cancer cells, keeping these genes silenced prior to hormone treatment. Upon hormone treatment, the liganded PR induces displacement of the repressor complex and allows the recruitment of coactivators needed for chromatin remodeling and increased gene expression[207].

Addition of hormone can magnify these nuclear events and also trigger a kinase signaling cascade through activation of cell membrane receptors to amplify these events [208,209]. Phosphorylated and under-SUMOylated unliganded PR recruits steroid receptor coactivator 1 (SRC1) to regulate the expression of growth-promoting genes and SUMOylated PR recruits histone deacetylase 3 (HDAC3) to reduce chromatin accessibility and decrease expression of the same genes[209]. Of note, the liganded PR also can recruit the chromatin remodeling enzyme BRG1 associated with the demethylase repressor complex HPYγ-LSD1

anchored by the histone methyltransferase SUV39H2 to induce heterochromatin. This hormone-dependent transcriptional repression is mediated through BRG1 recruitment to repressed genes involved in cell proliferation and apoptosis. The pioneer factor FOXA1 marks the hormone-repressive promoters enabling BRG1, and not additional associated factors (BAFs), to mediate heterochromatinization[210]. Knockdown of BRG1 in normal-like mammary epithelial ER-low MCF10A resulted in altered HCO and expression of key extracellular matrix genes that can exert mechanical forces and affect nuclear structure{Barutcu, 2016 #536}. Distinguishing the effects of perturbed BRG1 signaling on HCO in ER positive breast cancers will be of particular interest.

Androgen Receptor signaling in breast cancer is context-dependent.

The androgen receptor (AR) is a well-characterized clinical target in male prostate cancer, however its diagnostic and therapeutic potential in female breast cancer has recently emerged in the literature. AR has clinical implications in both ER-positive and ER-negative breast tumors[211]. In ER-positive tumors, AR expression was associated with positive clinical outcomes. Higher AR expression was predictive of a more favorable response to ER-targeted therapies, such as tamoxifen and aromatase inhibitors[212]. There is also preclinical evidence that breast cancers that have become resistant to tamoxifen can be effectively treated with AR-targeted endocrine therapies such as bicalutamide and enzalutamide[213].

Triple negative breast cancer (TNBC) has recently been re-organized into several subcategories[214]. One of these subsets of triple negative breast tumors, termed luminal androgen receptor (LAR) tumors, in which AR has been shown to be a driver of EMT and tumor progression. LAR breast cancer cells are sensitive to androgen therapies, such as bicalutamide and enzalutamide, *in vitro* and *in vivo* [215–217]. Other molecular subtypes have also exhibited sensitivity to enzalutamide *in vivo*[216]. The underlying mechanisms for growth suppression by anti-androgens in these cancers has yet to be fully delineated. However, it has been demonstrated that AR plays a role in promoting growth-factor receptor, PI3K/AKT, and WNT/β-catenin signaling in TNBC cells[216,217]. While AR is a driver of EMT through these signaling cascades, and HCO may be a critical component of EMT during breast cancer progression (discussed above), the potential for AR to alter HCO during EMT is unexplored.

Thyroid hormone signaling in breast cancer.

The actions of non-steroidal NRs in breast cancers are not well characterized[218]. Both thyroid hormone receptor alpha (TRα) and thyroid hormone receptor beta (TRβ) are expressed in breast tissue. In BRCA-positive breast cancer TRα and TRβ exhibit opposing roles in prognostic survival; greater expression of TRα strongly correlates with a decrease in overall survival whereas expression of TRβ is associated with improved survival[219]. Additionally, the isoform of TRα has been observed to be critical as expression of TRα2, a splice variant without a triiodothyronine (T_3) binding site, is associated with improved survival[220]. TRα2 acts antagonistically to TRα1, which exhibits a functional LBD, by binding to TREs and blocking TRα1 from interacting with the chromatin. This blocks thyroid hormone mediated actions arising from TRα1.

Notably, there is compelling evidence that loss of TRβ, a member of the thyroid hormone receptor (TR) family, through genomic modifications and epigenetic silencing is characteristic of breast and other solid tumors[221–227]. TRβ is silenced or mutated in nearly 60% of invasive breast cancers[219,228–231]. Of clinical significance, expression of wild-type TRβ is associated with a good prognosis in BRCA-positive breast cancer[219] as well as early breast cancer[232] and indicates a positive responsivity to chemotherapy[230,233]. TRβ, both unliganded and liganded, regulates gene expression via interaction with co-regulators and chromatin remodeling complexes[234–240]. Disruption of TRβ in breast cancer is therefore expected to alter the assembly of co-factors needed for transcriptional programming. In xenograft studies, loss of TRβ in malignant breast cells results in tumor growth and progression whereas restoration of TRβ function reverses these effects and critically blocks estrogen-induced breast cell tumor growth[241–245]. These observations indicate that not only does TRβ repress tumorigenic signaling, but TRβ may specifically counter ERα tumorigenic signaling in ER+ breast cells. Remarkably, the mechanisms by which TRβ blunts breast tumor growth and protects normal breast epithelial cell function are currently unknown. TRβ, both unliganded and liganded, regulates gene expression via interaction with hormone response elements and recruitment of co-regulators and chromatin remodeling complexes[237,239,246–248]. The impact that the recruitment of these chromatin remodelers has on HCO requires further investigation. It will be of particular interest to determine whether TRβ signaling counters the estrogen-mediated alterations in HCO discussed above and whether maintainence of the normal mammary epithelial cellular identity requires the long range enhancer-promoter contacts mediated by TRβ.

Nuclear receptor crosstalk has implications for breast cancer outcomes and treatment.

In early stage, hormone receptor positive, and dedifferentiated breast cancers, the dynamic gene expression programs are framed by an array of NRs and their cofactors. The studies that have defined NR-regulated transcription and NR-binding events have largely been studied as isolated events using single hormones. This over-simplified approach to understanding nuclear receptor function has become inadequate as it becomes increasingly clear that hormones and NRs do not act alone. Emerging evidence shows that co-expressed NRs exhibit extensive crosstalk with each other in normal tissue and in hormone-driven cancers.

The role of steroid hormone receptor crosstalk in breast cancer has been recently reviewed; specifically interactions between ER and PR, ER and AR, and crosstalk from glucocorticoid receptor[249]. Briefly, ER and PR have been demonstrated to form protein-protein interactions and PR expression can drive ER-mediated upregulation of over 200 genes *in vitro*[207]. Progesterone treatment aids in the recruitment of ER to over 14,000 EREs in T47D cells through a progesterone-dependent protein-protein interaction[172]. However, progesterone treatment repressed the oncogenic properties of E2 in a xenograft of these cells[172,192].

TR/ER interaction at common DNA motifs with opposite transcriptional effects has been described[250] and an overlap in estrogen and T_3 responsive genes has been noted in breast cancer[251]. As with PR, TRβ, both unliganded and liganded, regulates gene expression via interaction with co-regulators and chromatin remodeling complexes [234–239]. Disruption of

TRβ in breast cancer is therefore expected to alter the assembly of co-factors needed for transcriptional programming. Addition of T_4 stimulates breast cancer cell proliferation although the effect is likely non-genomic mediated through T_4 -αvβ3 integrin and kinase signaling[252]. In the presence of ER, T_3 blunts cell proliferation[253]. The role of ligand, T_3 or T_4, has yielded controversial results revealing the complexity of NR cross-talk and interactions that are context dependent.

It is well-established that BRG1 facilitates gene expression control by steroid NRs [210,254,255] and is recruited to ER-responsive promoters [256–257]. PR directly interacts with BRG1 in the absence of additional accessory factors to suppress gene expression in breast cancer [210] and thus may inhibit ER activity to diminish resistance to estrogen-based therapy [172]. Our recent studies established that TRβ interacts with BRG1[258] to synergistically induce changes in chromatin accessibility resulting in decreased expression of an oncogene, RUNX2, in opposition to ERα action. As TRβ and ERα can differentially regulate gene expression mediated through the same DNA binding site and BRG1 cooperatively enhances gene suppression and activation respectively, overlapping genome occupancy by these factors should reveal a subset of coordinately regulated genes central to maintain a normal breast phenotype or tumor suppression program. Our findings point to a convergence of TRβ and ERα signaling whereby TRβ counters ERα genomic occupancy, nuclear organization and transcriptional programs in hormone-dependent cancers. The BRG1 dependent crosstalk between ER and PR as well as TR and ER may be a generalizable mechanism of epigenomic crosstalk between members of the NR superfamily of genes. Given the importance of hormone signaling in regulating the epigenome and gene expression in breast cancer, a deeper understanding of how these signaling cascades impact cellular phenotypes will inform therapeutic strategies. Understanding the role(s) that HCO has in mediating these processes is still in its infancy.

The challenge of cellular division and implications for genomic organization.

Mitosis represents a major reconfiguration of the interphase genome organization every cell cycle. This raises a fundamental question of biological and clinical importance: what mechanisms control reacquisition and preservation of cellular identity during proliferation and growth? As cells prepare for mitosis their chromosomes are packaged into rod-like structures. During prophase TAD structures are lost in a condensin (structural maintenance of chromosomes complex) dependent manner. In early prometaphase a helical arrangement of consecutive 400kb outer loops containing 80kb inner loops emanate from a central spiral-staircase on a condensin scaffold. These loops progressively increase in size to ~12kb during prometaphase, while secondary loops are formed[259]. During this process, while many protein factors are excluded from the condensing mitotic chromosome, a fraction of transcription factors and chromatin remodelers are retained. This retention of binding during mitosis is termed bookmarking[260].

Mitotic Gene Bookmarking in Biological Control.

The first evidence of mitotic bookmarking by a transcription factor was reported in 2003 by our group [261]. RUNX2 was shown to remain associated with chromatin throughout mitosis occupying both cell growth-related ribosomal RNA (rRNA) genes that are transcribed by RNA Pol I, as well as cell proliferation and phenotype-related genes regulated by RNA Pol II [262]. Consistent with these findings, components of RNA Pol I and II machineries are retained on mitotic chromosomes[263–265]. Subsequently, our group provided evidence that, during differentiation of multipotent mesenchymal stem cells (MSCs) into myoblasts, osteoblasts or adipocytes, mitotic bookmarking of the ribosomal RNA (rRNA) genes by Myc was replaced by respective lineage-specifying factors MyoD, myogenin, RUNX2, and C/EBPβ. Myc is an activator of rRNA genes during proliferative stage of MSCs. The replacement of Myc by these factors suppresses RNA Pol I-mediated transcriptional control of rRNA genes through an interaction with the upstream binding factor 1 (UBF1; [262,264,266]. Concomitantly, these lineage-specifying factors occupy RNA Pol-II regulated genes involved in cell proliferation and fate determination.

Mitotic bookmarking of RNA Pol-II genes by various transcription factors has been demonstrated to be a key component regulating cellular identity in a host of physiological conditions. These include GATA1 in hematopoeisis [267] components of the MHC Class II enhanceosome in B lymphoblastoids [268]; FOXA1 in liver development [269], and hepatocyte nuclear factor 1 β (HNF1β) in the early steps of pancreas, kidney, and liver development [270]. Clinically relevant mutations found in HNF1β of patients suffering from renal multicystic dysplasia and diabetes; these mutations prevented HNF1β to mitotically bookmark DNA, highlighting clinical relevance of mitotic gene bookmarking [271]. Together, these findings identified mitotic gene bookmarking as a wide-spread epigenetic mechanism for coordinate control of cell growth, proliferation and phenotype maintenance.

In pluripotent or totipotent cells or breast cancer cells that have lost aspects of their cellular identity, the presence of both activating and suppressing histone marks at a single genomic locus, designated bivalency, has been posited to be critical for a poised plastic state of chromatin[160,272–274]. Interestingly, in pluripotent cells bivalent control of a large subset of genes is confined to mitosis, while histone mediated epigenetic suppression is constitutive throughout the cell cycle[275]. Mitosis restricted presence of activating histone modifications poises phenotypic genes for the potential to subsequently be expressed at lineage commitment. At that time, histone specific repression is relinquished. It has recently been observed that bivalency may be recapitulated when phenotype-specific genes are downregulated in early-stage cancer[276]. Such oncofetal epigenetic control may reflect loss of cell type specificity and reemergence of progenitor-like properties.

Mitotic bookmarking and nuclear organization.—The retention of factors on mitotic chromatin has been implicated in higher order chromatin organization. For example, it has been posited that the chromatin organizer proteins, CTCF and SMC3, have been shown to be retained on mitotic chromosomes[277–279]. Analysis of drosophila CTCF (dCTCF) occupancy identified sites that are bound throughout the cell cycle and those that are bound only in interphase or mitosis. dCTCF binding sites that fell within the same class (ie. Throughout

the cell cycle versus only in interphase or mitosis) were highly enriched at TAD boundaries[280]. In contrast, a more recent study demonstrated that CTCF binding is lost in prometaphase. ATAC-seq determined that while CTCF sites became closed during metaphase, transcription start sites were accessible, consistent with the view that transcription factors bookmark. Dekker and colleagues, along with other investigators [37,279,281–284] have found that the histone variants and modifications are maintained during mitosis suggesting a major role for epigenetics in bookmarking. In addition, epigenetic modifying complexes are also maintained on mitotic chromosomes. For example, the polycomb protein PSC is partially retained during mitosis, and its occupancy is enriched at TAD boundaries[285]. Given the potential role for the segregation of active versus inactive chromatin in delineating TAD structures, bookmarking by epigenetic histone modifications may provide the basis for maintaining cellular identity and HCO.

Mitotic Gene Bookmarking in Cancer.

Given the documented examples of mitotic gene bookmarking thus far, it comes as no surprise that this epigenetic mechanism has significant roles in promoting a cancerous phenotype. For example, in acute myeloid leukemia, bookmarking by RUNX1-ETO (an oncogenic fusion protein between the DNA binding domain of RUNX1 and the entire ETO protein including its NHR domain) has been demonstrated at growth-related rRNA genes, as well as RNA Pol-II genes involved in myeloid cell differentiation. In comparison to normal RUNX1, RUNX1-ETO results in the opposing regulatory effects on mitotically bookmarked genes [286] regulating vital cellular processes such as differentiation, proliferation, apoptosis, and self-renewal to promote leukemogenesis[287]. Given the roles of RUNX1 in estrogen signaling, and in suppressing EMT and CSC phenotypes in breast cancer, bookmarking by RUNX1 could be a fundamental mechanism maintaining the normal mammary epithelial phenotype.

Reestablishing chromatin domains and nuclear bodies upon exit from mitosis.

—The rod-like chromosomes found in mitosis rapidly decondense into chromosome territories (CTs) following completion of cell division and initiation of G1. Within CTs, TADs are decondensed during G1 corresponding with their level of activity[79]. These TADs are then replicated as units with more active TADs being replicated earlier than those that are less active[288]. This is consistent with the longstanding evidence that highly transcribed genes tend to replicate earlier in S phase[289]. This correlation is not absolute and reflect the presence of genes that are minimally expressed within TADs that are predominantly more active and vice versa. TAD structures may therefore be more determinative for replication timing than expression of individual genes.

The differential acetylation of genomic regions of mitotic chromatin may be the primary mechanism by which nuclear bodies are re-established from mitosis into G1 and S phase. Nucleolar organizer regions (NORs) contain the rRNA genes discussed above are present on five different acrocentric chromosomes are bookmarked during mitosis[262,264,266]. This bookmarking provides a basis for the reassembly of these NOR-bearing chromosomes and biogenesis of nucleoli[63,290] (Figure 3). Interestingly, it was discovered that there is a dominant nucleolus that associates with more of these acrocentric chromosomes.

Furthermore, particular subsets of these NOR-bearing chromosomes preferentially associated with the same nucleolus[291]. Epigenetic bookmarking of the histone genes may also be critical for the HCO of the histone locus body wherein the regulation of the histone genes occurs during S phase[62,292]. The HLB that contains the major histone gene locus is contained within a TAD. In this TAD, three subclusters of histone genes form an active chromatin hub, while two inactive histone genes are excluded. Other regions loop back into this hub suggesting additional potential regulatory roles for HCO in histone gene expression. As expected with the increased proliferative state of breast cancer cells, this region is the most upregulated cluster of genes in breast cancer *in vitro* and in tumor samples relative to matched controls. In addition, CTCF is present within the HLB and occupies the TAD boundaries around the major histone gene locus, and therefore may play a critical role in the determination of the HCO of this nuclear body[41].

Conclusions.

Cells establish and retain structural and functional integrity of the genome to support cellular identity and prevent malignant transformation. Mitotic bookmarking sustains competency for normal biological control, and propetuates gene expression associated with transformed and tumor phenotypes. Regulatory cascades that include RUNX and hormone signaling are altered in EMT and breast CSCs, thereby contributing to breast cancer onset and progression. And downstream, epigenetic mechanisms including histone modifications and higher order chromatin organization are perturbed. In turn, higher order chromatin organization provides a blueprint for control of gene expression within the three dimensional context of nuclear architecture. Elucidation of mechanisms that mediate the genomic organization of regulatory machinery will provide novel insight into control of cancer-compromised gene expression. This understanding can translate to enhanced capabilities for tumor diagnosis, prognosis, and provide options for targeted therapy.

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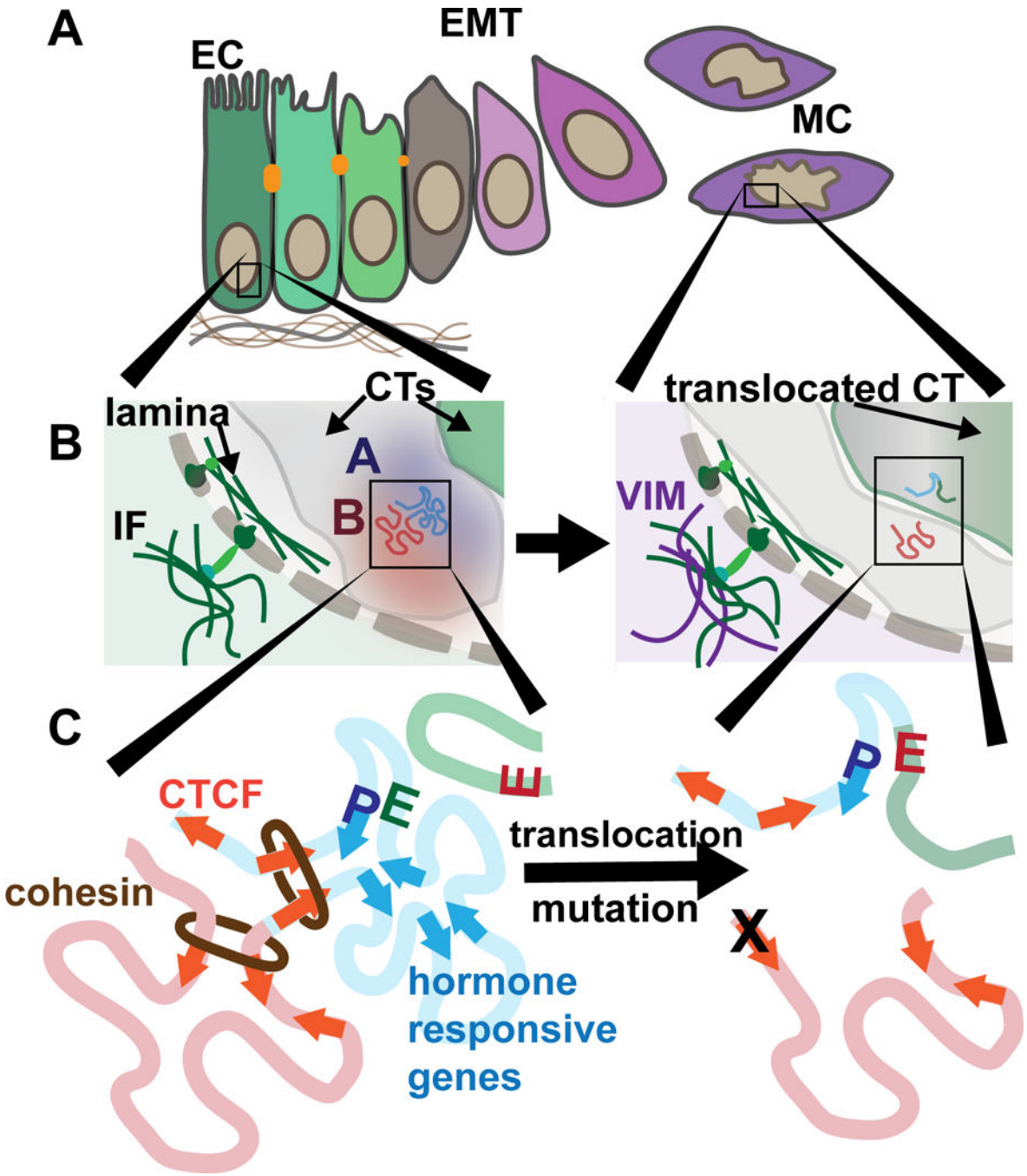

Figure 1. Cancer-compromised higher order chromatin organization.

A.) An epithelial-to-mesenchymal transition (EMT) occurs during breast cancer progression during which cells relinquish their epithelial cell (EC) tight junctions and polarity while acquiring mesenchymal cell (MC) characteristics that include migration and invasiveness. B.) An inset of a portion of the nucleus is shown. The nucleo-cytoplasmic link is illustrated wherein forces from within the cytoplasm can be transferred into the nucleus. The intermediate filament (IF) protein, vimentin (VIM), is increased in expression during EMT. Portions of two chromosome territories (CTs) are shown (grey and green). Compartments

within one CT are shown. An open, euchromatic, A compartment is blue and closed, heterochromatic, B compartment is red. C) In the loop extrusion model, cohesin extrudes DNA until two convergent CTCF motifs are encountered. Genes that are responsive to a stimulus (e.g. hormones) are enriched to reside within the same TADs. Alterations in the genome that occur within cancer nuclei such as translocations, deletions, and inversions may result in the disruption of proper enhancer (E)- promoter (P) interactions and result in aberrant regulation. Mutation of CTCF binding sites are frequent in cancers and mutation of these sites has been shown to disrupt looping.

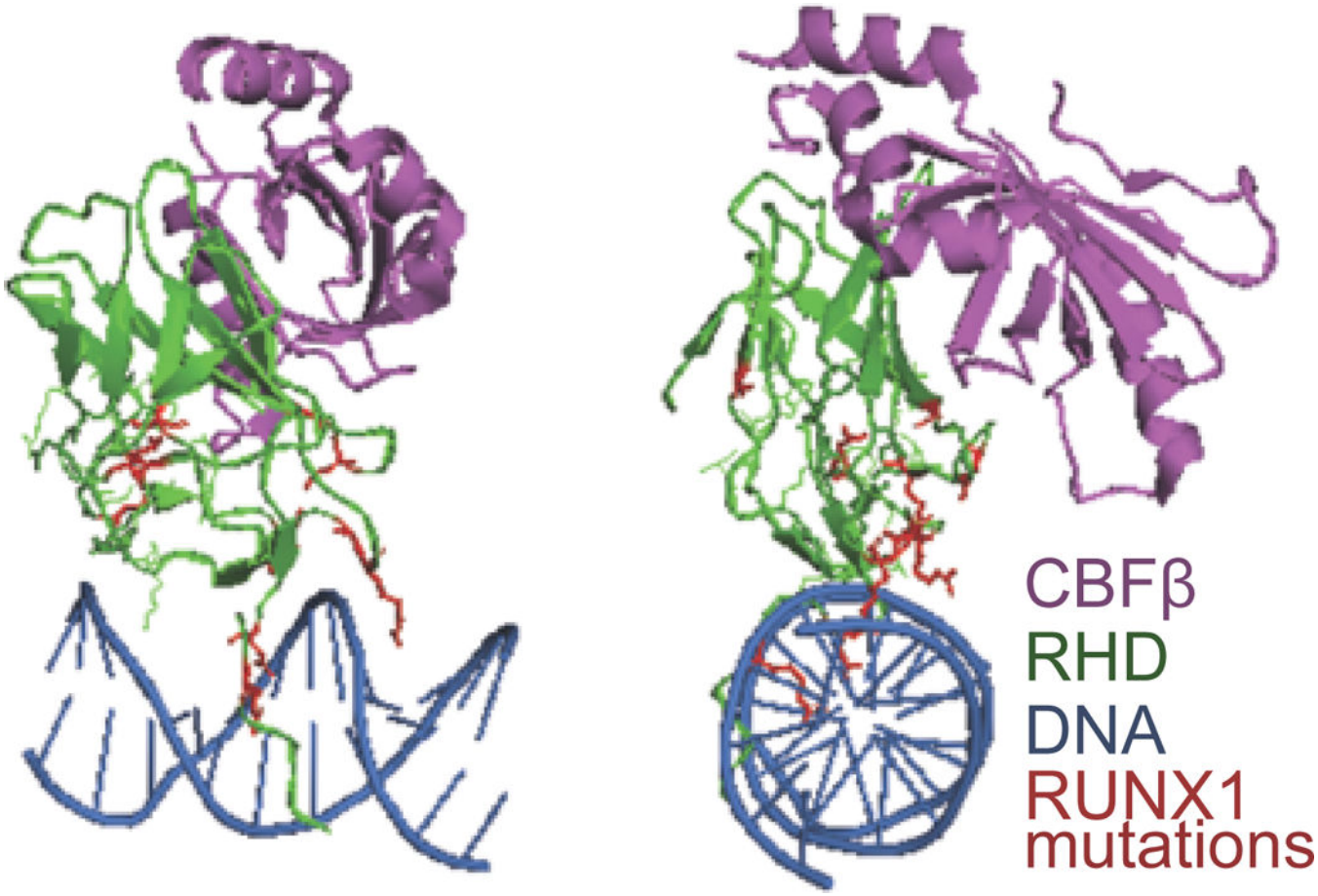

Figure 2. Mutations in the DNA binding- Runt homology domain of RUNX1 in breast cancer.

The structure of RUNX1's Runt homology domain (RHD; rendered based on the Protein Data Bank code 1H9D[293] is shown in two orientations rotated 90 degrees relative to each other (front and side). CBF-β is shown in purple, DNA binding-RHD is in green, and DNA is in blue. Mutations found in the RHD in breast tumor patient samples (red) suggests a loss of RUNX1 function in breast cancer.

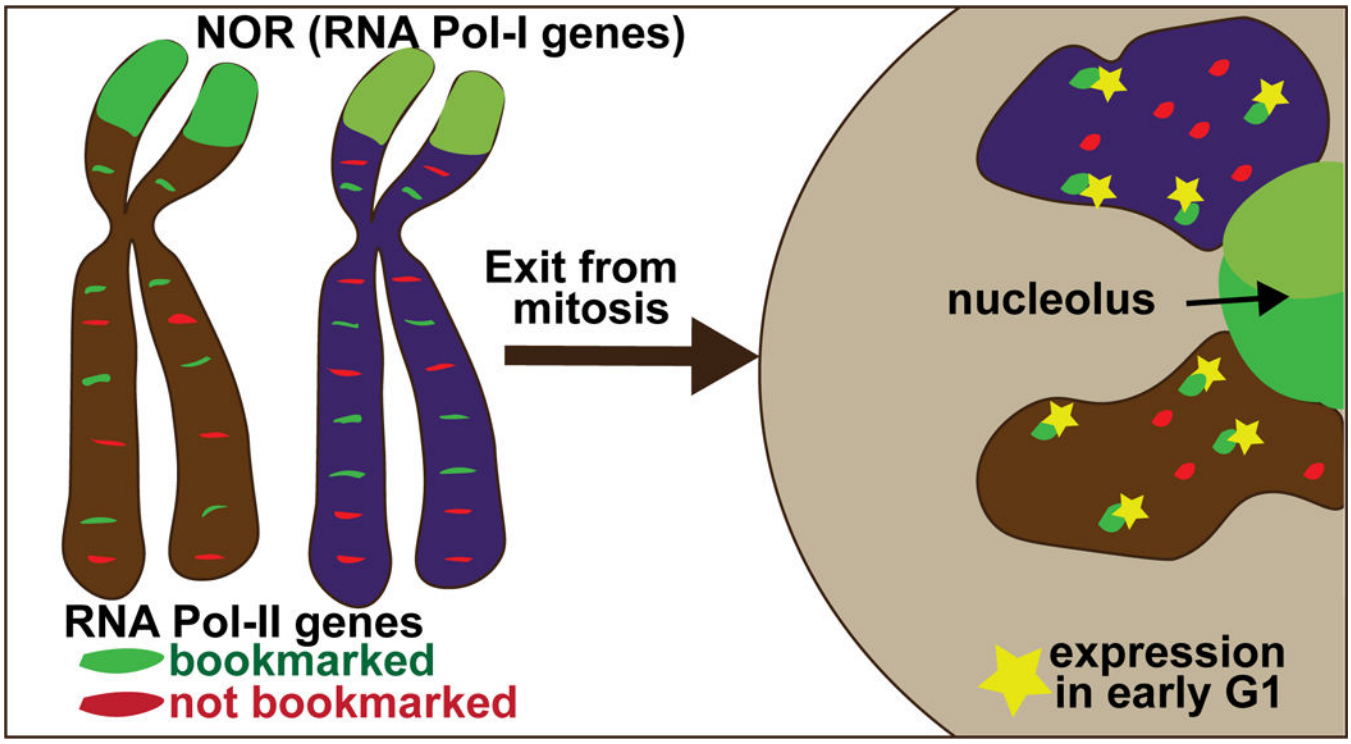

Figure 3. Mitotic bookmarking maintains nuclear organization, cellular identity and genome regulation in daughter cells.

Bookmarking is the retention of transcription factors and epigenetic modifications on mitotic chromosomes. Genes that are bookmarked (green) are active in early G1 compared with genes that are not bookmarked during mitosis (red). Bookmarking of the nucleolar organizer regions (NORs) is key to the biogenesis of nucleoli upon exit from mitosis.