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Nuclear organization mediates cancer-compromised genetic and epigenetic control

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Abstract

Nuclear organization is functionally linked to genetic and epigenetic regulation of gene expression for biological control and is modified in cancer. Nuclear organization supports cell growth and phenotypic properties of normal and cancer cells by facilitating physiologically responsive interactions of chromosomes, genes and regulatory complexes at dynamic three-dimensional microenvironments. We will review nuclear structure/function relationships that include: 1. Epigenetic bookmarking of genes by phenotypic transcription factors to control fidelity and plasticity of gene expression as cells enter and exit mitosis; 2. Contributions of chromatin remodeling to breast cancer nuclear morphology, metabolism and effectiveness of chemotherapy; 3. Relationships between fidelity of nuclear organization and metastasis of breast cancer to bone; 4. Dynamic modifications of higher-order inter- and intra-chromosomal interactions in breast cancer cells; 5. Coordinate control of cell growth and phenotype by tissue-specific transcription factors; 6. Oncofetal epigenetic control by bivalent histone modifications that are functionally related to sustaining the stem cell phenotype; and 7. Noncoding RNA-mediated regulation in the onset and progression of breast cancer. The discovery of components to nuclear organization that are functionally related to cancer death and compromise gene expression have the potential for translation to innovative cancer diagnosis and targeted therapy.

1. Introduction

Functional interrelationships of nuclear organization with fidelity of genetic and epigenetic regulation are compromised in cancer cells (Pappas et al., 2017). Evidence is accruing that multiple components of nuclear organization influence gene expression and epigenetic

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regulation in biological control and cancer (Dey, 2010; Drohic et al., 2006; Hancock, 2014; He et al., 2008; Lever and Sheer, 2010; Rajapakse and Groudine, 2011; Reddy and Feinberg, 2013; Shiue et al., 2010; Stein et al., 2000a, 2003a, 2008a, 2011; Zaidi et al., 2005, 2007). Aberrant nuclear size and shape have remained key indicators in cancer diagnoses for more than 150 years. Innovative strategies that leverage transformative advances in cancer biology and cutting edge technological capabilities are elucidating the molecular and biological underpinnings of this long-observed phenomenon. A guiding concept is that nuclear organization supports cell growth and phenotypic properties of normal and cancer cells by facilitating physiologically responsive interactions of chromosomes, genes and regulatory complexes at dynamic three-dimensional microenvironments.

We provide an overview of approaches to secure biological understanding of the architectural organization of regulatory machinery in nuclear microenvironments. Emphasis is on insights into subnuclear targeting of regulatory proteins, epigenetic mitotic bookmarking of phenotypic genes, contributions of chromatin-remodeling ATPases to nuclear structure, roles of noncoding RNAs in fidelity of nuclear organization and gene expression, and how these processes are compromised in cancer cells.

These strategies will provide insight into mechanisms that influence nuclear organization and gene expression in breast cancer that can be informative for cancer diagnosis and support the development innovative therapies.

A Multidisciplinary Strategy to Characterize Cancer-Compromised Nuclear Structure-Gene Expression Relationships.

Multidisciplinary approaches that combine cellular, molecular, biochemical, clinical, in vivo, microscopic and genomic strategies are providing insight into cancer-related dynamics of regulatory machinery in the nucleus, and are supporting interrogation of mechanisms that mediate nuclear structure-gene expression relationships which are compromised in cancer. There is growing appreciation for: the dynamic remodeling that is required for fidelity of gene expression, including the pivotal role of mitotic bookmarking as a novel dimension of epigenetic regulation; functional relationships between chromatin remodelers and breast cancer initiation and progression; and, contributions of RUNX2-regulated long noncoding RNAs (lncRNAs) to deregulation of nuclear organization in cancer cells. From these experimental approaches understanding for molecular mechanisms are emerging that may explain how nuclear structure ensures fidelity of biological control, and how modified parameters of nuclear architecture contribute to cancer onset and progression.

Mechanisms by which perturbations in higher order genomic organization, subnuclear targeting, chromatin remodeling, and/or epigenetic mechanisms including lncRNAs abrogate nuclear structure-function relationships are compelling questions. Use of cell models for breast cancer progression in discovery and mechanistic studies, animal models to test findings in a complex biological system, and establishing the clinical relevance of results using patient public databases and patient tumor specimens are complimentary and necessary approaches. These strategies will contribute to defining functional changes in the

nuclear regulatory machinery that contribute to cancer, and broadly impact cancer biology and pathology.

2. Progress toward mechanistically characterizing cancer-compromised nuclear structure-gene expression relationships

Focusing on obligatory interrelationships of nuclear structure with gene expression, progress is being made toward establishing a conceptual and mechanistic basis by which multiple components of nuclear organization contribute to gene regulation in biological control and cancer. Insights are being gained into key dimensions to mechanistic understanding of how structural components of the nucleus impact gene expression and facilitate competency for genetic and epigenetic responsiveness. Advances in understanding the role of nuclear organization in biological control that is compromised in cancer are becoming increasingly apparent. Novel mechanisms that direct transcription factors to defined intranuclear microenvironments to support gene expression and chromatin remodeling have been identified (Barseguian et al., 2002; Choi et al., 2001; Harrington et al., 2002; McNeil et al., 1999; Nagaich et al., 2004; Pande et al., 2009; Zaidi et al., 2001, 2005; Zeng et al., 1997, 1998). There are advances in understanding how intra- and inter-chromosomal interactions are altered in cancer cells (Barutcu et al., 2016a; Barutcu et al., 2016c; Bouwman and de Laat, 2015; de Wit and de Laat, 2012; Fritz et al., 2016; Fritz et al., 2017; Kaufmann et al., 2015; Mateos-Langerak et al., 2009; Mifsud et al., 2015). Novel consequences of mis-regulated chromatin remodeling to cancer cell structure, function and metabolic control have been determined (Bai et al., 2013; Bert et al., 2013; Cohet et al., 2010; Kim et al., 2015; Kumar et al., 2016b; Saladi et al., 2010; Sentani et al., 2001; Shi et al., 2013; Wu et al., 2015, 2016a, 2016b, 2017). Mitotic bookmarking and oncofetal epigenetic control as novel parameters of regulation have been established (Ali et al., 2008, 2010, 2012; Arora et al., 2016; Bakshi et al., 2008; Blobel et al., 2009; Caravaca et al., 2013; John and Workman, 1998; Kadauke and Blobel, 2013; Kadauke et al., 2012; Liu et al., 2017; Lodhi et al., 2016; Lopez-Camacho et al., 2014; Pockwinse et al., 2011; Sarge and Park-Sarge, 2009; Teves et al., 2016; Wong et al., 2014; Xing et al., 2005; Young et al., 2007a, 2007b; Zaidi et al., 2003, 2010b, 2011b, 2014; Zaret, 2014; Zhao et al., 2011). The recent discovery of oncofetal epigenetic control in breast cancer cells provides a novel dimension to control that partially recapitulates mechanisms operative in embryonic stem cells (Messier et al., 2016; Stein et al., 2016; Zaidi et al., 2017a). Noncoding RNAs have revealed their importance in tumor growth and progression and provided proof-of-concept for therapeutic applications (Anastasia et al., 2012; Balatti et al., 2017; Di Leva et al., 2014; Garitano-Trojaola et al., 2013; Gutschner and Diederichs, 2012; Hafner et al., 2017; Huarte, 2015; Tracy et al., 2018a, 2018b; Yu et al., 2017).

3. Gene expression in biological control and cancer in the context of nuclear architecture

3.1. Perturbed nuclear organization in cancer

Genetic and epigenetic regulatory mechanisms that operate in vivo must be understood within the three-dimensional context of nuclear organization, because physiological

transcriptional control occurs in association with structural components of the nucleus (Deng et al., 2013; Malyavantham et al., 2010; Meldi and Brickner, 2011; Zaidi et al., 2005). Parameters of nuclear architecture link and integrate regulatory information in a manner that permits functionally important selective expression (Gasser, 2002; Lamond and Earnshaw, 1998; Ma et al., 1999; McNeil et al., 1998; Misteli, 2000; Stein and Berezney, 1996; Stein et al., 2000b; Zeng et al., 1997, 1998). For example, chromatin folding reduces distances between regulatory sequences, facilitating cross-talk between promoter and enhancer elements (Peterson and Workman, 2000; Spencer and Davie, 2001). The “histone code” defines chromatin-mediated epigenetic control through posttranslational modifications of the highly conserved N-terminal tails of histones (Chi et al., 2010; Huang et al., 2014; Pepenella et al., 2014; Ruthenburg et al., 2007). In addition, CpG methylation of specific promoters selectively silences the expression of tissue-specific genes (Fischle et al., 2003; He et al., 2008). And mitotic bookmarking, the retention of transcription factors at gene loci on chromosomes during cell division, epigenetically sustains RNA polymerase I and II control of cell growth and phenotype in normal and cancer cells (Ali et al., 2008; Arampatzi et al., 2013; Arora et al., 2016; Bakshi et al., 2008; Caravaca et al., 2013; Festuccia et al., 2016; John and Workman, 1998; Kadauke and Blobel, 2013; Kadauke et al., 2012; Kelly and Jones, 2011; Lake et al., 2014; Lerner et al., 2016; Liu et al., 2017; Lodhi et al., 2014, 2016; Lopez-Camacho et al., 2014; Pockwinse et al., 2011; Sarge and Park-Sarge, 2009; Teves et al., 2016; Verdeguer et al., 2010; Young et al., 2007a, 2007b; Zaidi et al., 2010a, 2010b, 2011b, 2014b, 2017a, 2017b; Zaret, 2014; Zhao et al., 2011). The significance of mitotic bookmarking is reinforced by a recent report from the Tjian laboratory that most transcription factors are significantly enriched on mitotic chromosomes (Teves et al., 2016). Studies in the past few years have characterized intra- and inter-chromosomal interactions that impact gene activation and repression (Barutcu et al., 2015, 2016a, 2016b, 2017; Dekker and Mirny, 2016; Fritz et al., 2016, 2017; Gibcus and Dekker, 2013; Hnisz et al., 2016; Hou and Corces, 2012; Naumova et al., 2013; Nora et al., 2017). Recent mapping of higher order chromatin organization in mammary epithelial and breast-cancer cell lines by our group has revealed remodeling of genomic organization during transition from a tissue specific to a cancer phenotype (Barutcu et al., 2014, 2015, 2016a, 2016b, 2016c, 2017; Dobson et al., 2017; Fritz et al., 2016, 2017). Despite the compelling evidence for linkage of nuclear organization with genetic and epigenetic control there is a requirement to define cellular and molecular mechanisms that connect the regulated and regulatory aspects of nuclear organization to gene expression.

4. The regulatory landscape of the cancer cell nucleus

Nucleic acids and gene regulatory machinery are focally compartmentalized into specialized regions, designated nuclear microenvironments, for combinatorial control of nuclear functions. The dynamic assembly and organization of these microenvironments is mediated by scaffolding proteins binding at sites in enhancers and target gene promoters, as well as in subnuclear domains (Carrozza et al., 2003; Handwerger and Gall, 2006; Kosak and Groudine, 2004; Misteli, 2004; Taatjes et al., 2004; Tai et al., 2014; Zaidi et al., 2005, 2007, 2010a, 2013a, 2014). The association of regulatory proteins with gene loci, modifications in chromatin remodeling complexes, and epigenetic changes modulate genome accessibility to

regulatory factors for the physiological control of cell fate and lineage commitment. Cancer cells show striking alterations in nuclear morphology, as well as in the nuclear organization of genes, transcripts and regulatory complexes. Mechanistically, these cancer-related changes disrupt levels of nuclear organization that include gene sequences, chromatin organization, higher-level genomic configurations, and subnuclear domains (Belton et al., 2012; Cremer et al., 2015; Drohic et al., 2006; Fraser and Bickmore, 2007; Leonhardt and Cardoso, 2000; Naumova et al., 2013; Singh et al., 2000; Stein et al., 2000a). Similarly, there are cancer-related alterations in the organization and localization of macromolecular complexes at intranuclear sites where regulatory signals are assembled and integrated. Significantly, solid tumors, leukemias, and lymphomas exhibit modified nuclear architecture that can facilitate tumor diagnosis and perhaps relate to therapeutic responsiveness. The recent finding that chromatin remodeling is linked with therapeutic responsiveness of breast cancer cells provides insight into parameters of genomic organization that have fundamental regulatory and clinical relevance (Wu et al., 2015, 2016a, 2016b).

The punctate architectural association of AML/RUNX transcription factors that mediate tissue-specific transcription has enabled examination of mechanisms that localize these regulatory proteins to transcriptionally active subnuclear domains (Harrington et al., 2002; Stein et al., 2007; Zaidi et al., 2001; Zeng et al., 1997, 1998). Mutational analysis has established that association of RUNX transcription factors with the nuclear matrix is independent of DNA binding and requires a protein segment designated the nuclear-matrix targeting signal (NMTS). Subnuclear targeting signals are unique in sequence and structure, establishing a novel architectural and mechanistic dimension of nuclear structure and function that confers specificity to intranuclear localization of regulatory proteins. Examples include RUNX factors, YY1, SATB1 and DNA polymerase, as well as glucocorticoid, vitamin D, androgen and estrogen receptors (DeFranco and Guerrero, 2000; Maczys et al., 2016; Mancini et al., 1999; Seo et al., 2005; Stenoien et al., 2000; Zaidi et al., 2001; Zeng et al., 1997). Altered subnuclear targeting of RUNX1 occurs in leukemia, where it is a frequent target of chromosomal translocations in patients with acute myeloid leukemia (AML) (Speck and Gilliland, 2002). The modified subnuclear targeting signal of the resulting fusion protein organizes it into nuclear microenvironments that are distinct from those in which wildtype RUNX1 resides (Barseguian et al., 2002; McNeil et al., 1999). Thus, the pathology of AML is, at least in part, related to compromised RUNX1 subnuclear targeting and protein interactions. Consistent with these findings is the demonstration that subnuclear targeting of RUNX2 proteins in BrCa cells is required for generation of metastasis-associated osteolytic disease. These findings show that the essential functions of RUNX factors require fidelity of subnuclear organization (Barnes et al., 2004; Javed et al., 2005; Pratap et al., 2005, 2006, 2008, 2009). It will be informative to explore the involvement of RUNX1 and its subnuclear targeting to maintaining the epithelial phenotype and in transformation to mesenchymal phenotype (94, 95), and the pivotal role of RUNX2-regulated lncRNAs in nuclear organization in metastatic breast cancer (Barnes et al., 2004; Javed et al., 2005; Pratap et al., 2006).

4.1. Mitotic chromosomal retention of AML/RUNX transcription factors to sustain phenotype

Persistence of cell identity requires post-mitotic restoration of nuclear organization and assembly of regulatory complexes. It has been conclusively demonstrated that RUNX proteins, as well as myogenic and adipogenic transcription factors that determine lineage commitment, remain bound to their target genes, including rRNA genes, on mitotic chromosomes (Ali et al., 2010; Young et al., 2007a, 2007b; Zaidi et al., 2003, 2010b, 2017b). It has been established that RUNX2 remains associated with both RNA polymerase I and II-transcribed genes during mitosis (Young et al., 2007a, 2007b). Other investigators have demonstrated that many regulatory factors remain associated with mitotic chromosomes (Arampatzi et al., 2013; Arora et al., 2016; Blobel et al., 2009; Caravaca et al., 2013; Festuccia et al., 2016; Grob et al., 2014; John and Workman, 1998; Kadauke and Blobel, 2013; Kadauke et al., 2012; Kelly and Jones, 2011; Lake et al., 2014; Lerner et al., 2016; Liu et al., 2017; Lodhi et al., 2014, 2016; Sarge and Park-Sarge, 2009; Teves et al., 2016; Verdeguer et al., 2010; Wong et al., 2014; Xing et al., 2005; Zaret, 2014; Zhao et al., 2011). Furthermore, the Tjian laboratory recently reported that the apparent exclusion of transcription factors from chromosomes is “largely a fixation artifact” (Teves et al., 2016). Retention of RUNX proteins is required for post-translational modifications of histones and post-mitotic gene expression, indicating that the architectural function of mitotically-associated transcription factors has heritable consequences (Ali et al., 2008; Bakshi et al., 2008; Young et al., 2007a, 2007b; Zaidi et al., 2003, 2010b, 2011). Epigenetic mitotic bookmarking not only retains phenotype but is also implicated in mechanisms that drive coordinate control of cell growth and tissue-specific gene expression. These findings by provide a foundation for the novel biological paradigm that mitotic bookmarking by phenotypic transcription factors represents a heritable dimension to gene regulation. However, there is a requirement to better understand the regulatory activities of RUNX1, and a necessity to characterize specific genes that are bookmarked by RUNX1 during mitosis and contribute to functional plasticity in the G1 nucleus.

4.2. Chromatin remodeling: linkage with transformation and tumorigenesis

Chromatin formation, the mechanism for packaging the eukaryotic genome, is dynamically regulated by enzymes that post-translationally modify histones and alter chromatin structure in an ATP-dependent manner. Chromatin structure changes in response to extracellular signaling during development and differentiation, and in response to growth, stress, or other signals. Not unexpectedly, global and local chromatin structural changes are associated with cellular transformation and cancer, and it has been documented that irregular nuclear shapes correlate with altered spatial organization of chromatin (Zink et al., 2004).

The mammalian SWI/SNF complexes are a family of chromatin-remodeling enzymes that regulate gene expression by disrupting histone-DNA contacts in an ATP-dependent manner (Kwon et al., 1994). The complexes are evolutionarily conserved in eukaryotes and contain either BRM (Brahma) or BRG1 (Brahma-related gene 1) as the central ATPase subunit (Khavari et al., 1993; Muchardt and Yaniv, 1993; Wang et al., 1996). The BRM and BRG1 proteins display similar enzymatic properties (Phelan et al., 1999; Sif et al., 2001), but can serve different regulatory functions (Bultman et al., 2000; Kadam and Emerson, 2003;

Muchardt et al., 1998). BRG1 was initially proposed to be a weak tumor suppressor in mammary gland because about 10% of Brg1±mice eventually developed mammary tumors (Bultman et al., 2000, 2008). Subsequent work showed that BRG1 is a tumor suppressor in some cancers but is a cancer driver in others. We have recently reviewed this subject in depth (Wu et al., 2017). The evidence shows that the assignment of BRG1 as a mammary tumor suppressor is inconsistent with many observations. Supporting data of note: (i) The conditional knockout of Brg1 in the mouse mammary gland did not cause mammary tumors (Serber et al., 2012). (ii) Fewer than 2% of sequences in the TCGA BrCa database contain BRG1 or BRM mutations (our analysis); other reports put the mutation rate at <3% (Kadoch et al., 2013). (iii) We and others showed that BRG1 and BRM protein levels are up-regulated in most human breast tumors (Bai et al., 2013; Do et al., 2016; Wu et al., 2015) and that BRG1 and BRM are required to maintain high rates of breast tumor cell proliferation in culture and in orthotopic xenografts (Wu et al., 2015). (iv) From a cohort of ~3000 BrCa patients, it has been demonstrated that high BRG1 levels correlate with poor clinical outcome (Wu et al., 2016a). (v) BRG1 is expressed at elevated levels relative to normal tissue in primary melanoma, in prostate, gastric, and colorectal carcinomas, and in other tumors (Cohet et al., 2010; Lin et al., 2010; Saladi et al., 2010; Sentani et al., 2001; Sun et al., 2007; Watanabe et al., 2011). (vi) Four recent publications show that BRG1 is a BrCa driver and a promising therapeutic target (Wu et al., 2015, 2016a, 2016b, 2017). The challenge is now to characterize how chromatin remodeling epigenetically influences breast cancer progression.

4.3. Epithelial to mesenchymal transition: RUNX1 and the cancer genome

Recent studies from our group and others have shown that RUNX1, an established phenotypic transcription factor required for definitive hematopoiesis and mutated in hematological malignancies, is expressed in breast epithelial cells (Browne et al., 2015; Hong et al., 2017; Janes, 2011; Speck and Gilliland, 2002; van Bragt et al., 2014). Genome-wide analyses of breast tumors have identified inactivating mutations in RUNX1, indicating a tumor suppressive role in BrCa (Pereira et al., 2016; Yates et al., 2017). Mechanistically, RUNX1 regulates an epithelial to mesenchymal transition (EMT) and its high expression is linked with favorable patient outcome (Hong et al., 2017). Importantly and from a higher order nuclear organization standpoint, RUNX1 is distributed throughout the breast cell genome and regulates higher order chromosome interactions (Barutcu et al., 2016b). Chromosome conformation capture in RUNX1-depleted breast epithelial cells shows alterations in chromosomal interactions in the absence of RUNX1 (Barutcu et al., 2016a, 2016b). Functionally, absence of RUNX1 results in modified gene expression and leads to epithelial to mesenchymal transition (Hong et al., 2017), directly linking RUNX1-mediated genomic interactions to function (Fig. 1). Together, these studies show that RUNX1 stabilizes the mammary epithelial cell phenotype, and that reduced expression of RUNX1 is an early event in BrCa. It will be informative to experimentally address how many of RUNX1-mediated genomic interactions are maintained through cell divisions, and any alterations in these interactions may relate to early events of breast cancer onset.

4.4. Noncoding RNAs, RUNX2 and cancer

RUNX2 is highly expressed in metastatic triple negative BrCa cells (Barnes et al., 2004; Javed et al., 2005; Pratap et al., 2005, 2006). It has been shown, not only that RUNX2 activity promotes tumor growth in vivo (mammary fat pad and intratibial orthotopic sites) (Pratap et al., 2005, 2009), but that the nuclear-matrix targeting signal of RUNX2 is essential for primary tumor growth and metastatic bone disease (Barnes et al., 2004; Javed et al., 2005). The subnuclear organization of RUNX2 complexes that recruit mediators of cancer-promoting pathways including TGF/BMP, IHH, MMPs and Wnt (Pratap et al., 2005, 2006, 2009, 2011) support a role for RUNX2 in the mis-regulated nuclear structure of metastatic BrCa cells. The impact of crosstalk between small noncoding RNAs (miRNAs) (Hassan et al., 2012; Taipaleenmaki et al., 2015) has been demonstrated and it has been shown that RUNX2--targeting miRNAs (miR-135 and miR-203) repress RUNX2 in normal mammary epithelial cells but are not found in BrCa cell lines. Repletion of these in metastatic cells impaired tumor growth in metastatic BrCa in xenograft mouse models (Taipaleenmaki et al., 2015, 2016). It will be important to investigate crosstalk between RUNX2 and long noncoding RNAs (lncRNAs). lncRNAs have emerged in recent years as major contributors to biological control, with demonstrated roles in virtually every area of biology. lncRNAs exert their effects via multiple mechanisms that modulate gene expression at epigenetic, transcriptional, and posttranscriptional levels. Significantly, lncRNAs mediate chromosomal interactions that contribute to the phenotype of normal and disease cells (Deng et al., 2013). Hundreds of lncRNAs are associated with BrCa, and the roles of lncRNA in dysregulation of the architectural landscape of cancer cells are now emerging. Initial studies indicate that levels of specific lncRNA differ dramatically in expression across the diverse BrCa subtypes (Kumar et al., 2016a). lncRNAs have been identified that are regulated by RUNX2 in BrCa and initiated functional characterization of one of these, Mitosis-Associated Non-Coding RNA (MANCR), a lncRNA that is retained during mitosis, mediates genome stability in triple negative BrCa cells, and is negatively correlated with patient survival (Tracy et al., 2018a). It will be important to mechanistically characterizing RUNX2-regulated lncRNAs related to progression of breast cancer to the metastatic stage within the context of higher order nuclear organization, with the goal of demonstrating in vivo that inhibition of aberrantly expressed lncRNAs can inhibit tumor progression.

5. Conclusion

Novel discoveries have been made of bidirectional relationships between transcriptional regulators and nuclear organization and how these contribute to epigenetic control of breast cancer phenotypes. These findings provide a paradigm for understanding compromised regulatory mechanisms in breast cancer, within the context of higher-order nuclear architecture.

Moving forward, there is a requirement to experimentally determining how perturbations of architecturally organized regulatory complexes and chromatin remodelers deregulate the expression during interphase as well as to examine epigenetic mechanisms operating on mitotic chromosomes. It will be biologically and clinically informative to interrogate mechanisms that relate components of nuclear architecture with parameters of gene

expression. Addressing the functional activity of proteins and/or noncoding RNAs that are linked to transcriptional control and/or higher-order chromatin organization will expand insight into the integration of nuclear structure and function. Combining complimentary expertise and experience, unique contributions are emerging for understanding novel dimensions of gene expression in nuclear microenvironments and defining how changes in the organization and assembly of gene regulatory machinery can contribute to the onset and progression of cancer.

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Fig. 1. RUNX1 regulates higher order genome organization and epithelial to mesenchymal transition in breast cancer cells

Schematic representation of key properties and activities of RUNX1 in breast epithelial cells. RUNX1 is highly expressed and punctately organized (green circles) in normal breast epithelial cells (red cuboidal cell) and its levels decrease—depicted by the green arrow—as breast epithelial cells transition into mesenchymal phenotype (yellow spindle-shaped cell), a key initial event at the onset of breast cancer. Conversely, downregulation of RUNX1 in breast epithelial cells leads to EMT, indicating that RUNX1 stabilizes the epithelial phenotype. Importantly, RUNX1 depletion in normal breast epithelial cells lead to localized disruption of higher order genome organization that corresponds to changes in gene expression necessary for EMT. Insets at the bottom show schematic of a RUNX1 domain, where RUNX1 protein organizes several coordinately regulated target genes to ensure stable epithelial phenotype (left panel). Upon RUNX1 depletion, the RUNX1 nuclear microenvironment is disrupted, resulting in deregulation of target genes (right panel). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)