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BAF Complexes and the Glucocorticoid Receptor in Breast Cancers

Nicholas Dietrich[1,*], **Jackson A. Hoffman**[1,*], **Trevor K. Archer**[1,#]

[1]Epigenetics and Stem Cell Biology Laboratory, National Institute of Environmental Health Sciences, National Institutes of Health, North Carolina, United States

Abstract

Breast cancers are a diverse group of diseases and are often characterized by their expression of receptors for hormones such as estrogen and progesterone. Recently another steroid hormone receptor, the glucocorticoid receptor (GR) has been shown to be a key player in breast cancer progression, metastasis, and treatment. These receptors bind to chromatin to elicit transcriptional changes within cells, which are often inhibited by the structure of chromatin itself. Chromatin remodeling proteins, such as Brahma-related gene 1 (BRG1), function to overcome this physical inhibition of transcription factor function and have been linked to many cancers including breast cancer. Recent efforts to understand the interactions of BRG1 and GR, including genomic and single cell analyses, within breast cancers may give insight into personalized medicine and other potential treatments.

Introduction:

Genetic information is packaged in cells as chromatin, a hierarchically condensed structure of DNA and histone proteins in the nucleus. The condensation of DNA into chromatin creates a structural barrier that may inhibit DNA binding proteins from accomplishing their functions. ATP-dependent chromatin remodeling complexes such as the SWItch/Sucrose Non-Fermentable (SWI/SNF) complex alter the contacts between DNA and histones to allow for critical processes such as DNA repair, recombination, and gene expression [1,2]. This alteration in chromatin structure permits transcription factors including nuclear receptors (NRs) to bind and mediate a variety of biological processes [1,3]. The SWI/SNF complex regulates NR mediated transcription, often by direct interaction with NRs. The MMTV promoter model in breast cancer cells was utilized to characterize the requirement for SWI/SNF chromatin remodeling in glucocorticoid (GR), progesterone (PR), and androgen receptor (AR) mediated activation [4,5]. While the mechanisms of NR and SWI/SNF interactions have been extensively reviewed [6–9], recent work utilizing next-generation sequencing technology has characterized the combinatorial roles that SWI/SNF

Corresponding author: archer1@niehs.nih.gov.
*These authors contributed equally to this review

and NRs play in mediating gene expression changes. As the SWI/SNF complex may function as a shared protein complex for nuclear receptors, studies directed towards this platform may be informative for the function of multiple nuclear receptors. This review will highlight the recent advances of work relevant to understanding the roles of the SWI/SNF complex and GR in breast cancer and provide insight into the promising future of studying these proteins within the context of this disease.

BRG1, BAF complex, and Cancer:

SWI/SNF is a large, multiprotein complex with diverse and variable subunit composition [10,11]. Initially, two distinct SWI/SNF complexes were identified in mammalian cells, BAF and PBAF. These complexes both contain a central ATPase (BRG1 or BRM) and several common BRG1-BRM associated factor (BAF) subunits, and the particular complex compositions can be seen in Table 1. While the BAF and PBAF complexes perform similar biochemical functions, different biological roles have been described for each. PBAF-specific subunits are often associated with cell differentiation and cell-type identity regulation, while BAF complex specific roles have been characterized in development, self-renewal, and pluripotency [12]. The recent description of two additional complexes (embryonic stem cell-specific BAF and non-canonical BAF) have emphasized the importance for correct assembly of unique complexes for specific biological processes [13–15].

Advances in cryo-electron microscopy have allowed for determination of the structure of the SWI/SNF complex. A 3.7 angstrom structure of an *in vitro* assembled BAF complex revealed that the ATPase domain of BRG1 is engaged with nucleosomal DNA, with some subunits modeled into the structure rather than *de novo* determined. This interaction is guided in place by the ARP (actin-related protein) module and the HSA (helicase/SANT associated) domain of BRG1. This HSA-ARP module bridges the ATPase to the base module, which contains the N-terminal region of BRG1 and the other auxiliary subunits. This base module serves several functions, including nucleosome binding by BAF47, stabilization of the core by ARID1A, scaffolding by BAF155 and BAF170, and organizational support by BAF60 and BAF57 [16]. Recent studies on the structure of yeast remodelers including SWI/SNF and RSC have revealed similar structures [17–19]. These efforts have allowed preliminary hypotheses for the mechanisms of chromatin remodeling, which require further testing to confirm.

Determination of the composition, assembly and structure of SWI/SNF complexes is critical for human health as human SWI/SNF subunits and associated proteins are mutated in nearly 20% of human cancers [20]. Recent efforts have characterized the organization of human SWI/SNF complexes, which are assembled in modular fashion [21]. Cancer-relevant deleterious mutations of SWI/SNF proteins have provided additional insight into complex assembly and chromatin interaction [22]. Cancer-relevant truncations or mutations of ARID1A also disrupted complex formation [21] and loss of BAF47 altered the genomic distribution of the BAF complex [23]. Catalytically inactivating mutations of BRG1 and BRM are also found in human cancers [24]. BAF complexes containing catalytically inactive BRG1 protein did not bind to all chromatin sites bound by complexes containing WT BRG1.

Rather, the binding of complexes with catalytically inactive BRG1 was biased toward sites bound by PBAF complexes. Furthermore, sites of SWI/SNF chromatin interaction were linked to gene expression profiles associated with tumor-suppressor pathways [22], providing insight into how SWI/SNF mutations result in cancer and suggesting that SWI/SNF chromatin interactions could be targeted for cancer treatment. More systematic investigations of individual subunit losses have also demonstrated how losses of these subunits can lead to cancers and highlights novel synthetic lethalities [25]. Extensive efforts have also demonstrated that elevated levels of complex members such as BRG1 are found in cancers of the breast, brain, colon, and pancreas. TGCA analysis demonstrates very low BRG1 mutation frequency in invasive breast cancers, but elevated expression occurred much more frequently [24,26–30]. BRG1 has been demonstrated to bind at promoters of genes that are overexpressed in primary breast tumors and invasive breast cancer cell lines and activate their transcription directly. The BRG1 complexes formed at these locations work in concert with EP300 and often PARP1 to direct the transcription of proliferation and DNA repair genes in breast cancer cells [31,32]. Direct studies have shown that knockdown of BRG1 decreased breast cancer cell proliferation. The additional observation that BRG1 knockdown also sensitizes triple negative breast cancer cells to chemotherapeutics suggests BRG1 may be a valuable target in breast cancers where the normal frontline treatment has been focused on nuclear receptors. These observations highlight the fact that BRG1 plays critical roles in breast cancer biology independent nuclear receptors, and more focus should be placed on understanding these functions in future studies [33].

Glucocorticoid Receptor Function and Breast Cancer:

Nuclear hormone receptors elicit the transcriptional response to hormones and have well-established roles in many hormone-dependent and hormone-regulated cancer types. Breast cancers are commonly stratified by the expression status of Estrogen Receptor (ER) and PR, and the expression of AR and GR have also been demonstrated to play a role in the prognosis of breast cancers. Furthermore, ER, GR, and PR are heterogeneously expressed within individual tumors indicating that treatments targeting hormone receptors will have non-uniform effects on breast cancer cells [34–36]. As such, crosstalk between receptors has become the focus of many recent studies [37]. In breast cancer cells, antagonists of ER and PR are commonly used treatments, and activation of GR through glucocorticoid treatment is widely utilized as a co-treatment to alleviate side effects of chemotherapy. GR was also recently described to negatively modulate PR in breast cancer and this crosstalk may also be a key focus for therapeutics [38]. However, recent work has suggested that activation of GR promotes breast cancer metastasis, underscoring the need for more research into the function of GR in breast cancer progression [39].

GR expression is nearly ubiquitous in humans, however the transcriptional responses to glucocorticoids in different cells types are diverse and distinct. GR elicits a robust transcriptional response in both human and mouse breast cancer cell lines which has been broadly studied to elucidate mechanisms of GR activity. Mapping GR chromatin interactions in breast cancer cells has revealed that GR largely interacts with regions of chromatin that are at least partially accessible prior to hormone treatment [40–42]. This suggested that GR chromatin interactions are prefigured by other factors and/or epigenetic

features of chromatin. Indeed, many GR binding sites are occupied by the BAF complex, pioneer factors such as FOXA1, and the enhancer-associated histone variant H2A.Z prior to hormone treatment [42–44]. These pre-patterning events were not independent, as GR preferentially bound to pioneer factor binding sites or to H2A.Z containing nucleosomes that were also enriched for the presence of BRG1 [42,44]. GR also interacted with other transcription factors including ER and PR, suggesting the transcriptional response to glucocorticoids in breast cancer is directed, in part, via the pre-patterning of GR chromatin interactions by many factors [45,46].

Intriguingly, GR binding also resulted in the recruitment of transcription factors and chromatin remodelers upon hormone treatment. Sites bound by GR exhibited increased enrichment of BRG1, pioneer factors, H2A.Z, and chromatin accessibility after hormone treatment. Thus, while GR bound to pre-patterned regions of chromatin, it also induced further chromatin remodeling and transcription factor recruitment [42–44]. GR also appeared to be capable of acting as a pioneer factor at some binding sites, as hormone treatment and GR binding resulted in new FOXA1 and ER binding sites, an indication of pioneer factor activity [40,43,45]. Furthermore, GR was also able to bind to some regions of the genome that did not appear to be pre-patterned by chromatin accessibility or the binding of other factors [47]. As such, there are multiple mechanisms of GR interaction with chromatin that can be classified by the chromatin and transcription factor environment in both untreated and hormone-treated breast cancer cells [42,44]. Understanding the mechanisms by which GR regulates transcription and its subsequent influences on ER and PR activity, is critical for enhancing the efficient clinical targeting of hormone signaling for breast cancer treatment.

Technological Advances toward Precision Medicine

Single cell genomic experiments such as single cell RNAseq (scRNA-seq) represent a new frontier in cancer and molecular genetics. During the last decade, single cell gene expression analysis has been widely used to interrogate gene expression signatures, tumor and cellular heterogeneity, and cell type compositions in many disease models [48]. In breast cancer models, these analyses have provided insights that may impact prognosis and treatment. For instance, scRNA-seq studies have demonstrated that heterogeneity in immune cell populations within tumors have expanded the diversity of breast cancer, demonstrating the contribution of immune cells to breast cancer phenotypes [49,50]. Indeed, scRNA-seq in primary triple negative breast cancer cells and single cell QRT-PCR in the luminal MCF7 cell line revealed that each population contained a subpopulation of stem-like cells with signatures associated with treatment/drug resistance and metastasis [51,52]. The transcriptional response to drug treatments in breast cancer cells was also demonstrated to be heterogeneous, as scRNA-seq in luminal T47D breast cancer cells treated with the synthetic glucocorticoid Dexamethasone revealed striking levels of heterogeneity [53]. Taken together, these single cell transcriptomic experiments demonstrated the importance in understanding how the heterogeneity of breast cancer cells contributes to disease progression and prognosis (Figure 1).

Beyond scRNA-seq, other single cell assays have provided critical insight into the interplay between tumor and immune cell populations. Single cell proteomics using mass cytometry has generated an atlas of the relationship between tumor and immune cells in breast cancer [54]. This experiment revealed that the phenotypes of tumor and immune cells within breast cancers and the relationships between these cell types stratified patients and underscored the importance of characterization of the tumor ecosystem. Such advances in the understanding of the patient-specific heterogeneity in the tumor ecosystem are critical to inform breast cancer treatments and facilitate the use of precision medicine.

Recent technological advances have also paved the way for examination of the epigenetic landscape in single cells. Single cell ChIP-seq has been used to examine the profiles of active and repressive histone modifications in breast cancer cells [55]. As with scRNA-seq, these experiments revealed a subpopulation of cells that shared a common chromatin signature with drug-resistant cells. Single cell analysis of chromatin accessibility has been performed across a variety of adult mouse tissues, in developing mouse mammary glands, and in mouse breast cancer models [56–58]. These studies demonstrate the potential for the analysis of epigenetic characteristics in single cells as a tool for interrogating the regulatory mechanisms underlying the heterogeneity observed in the transcriptomic profile of breast cancer cells. Furthermore, various “multi-omic” single cell experiments have been developed to simultaneously perform combinations of transcriptomic, epigenomic, and proteomic assays, providing great promise for future experiments [59,60]. Such interrogation of the epigenetic and transcriptomic environment in single cells has the potential to provide novel insight into the role of GR (as well as ER and PR) and the SWI/SNF complex in breast cancer. Recognizing and understanding cellular heterogeneity in breast cancer will in turn inform clinical treatments based on inter-tumor heterogeneity and provide new tools and targets for patient-specific precision medicine.

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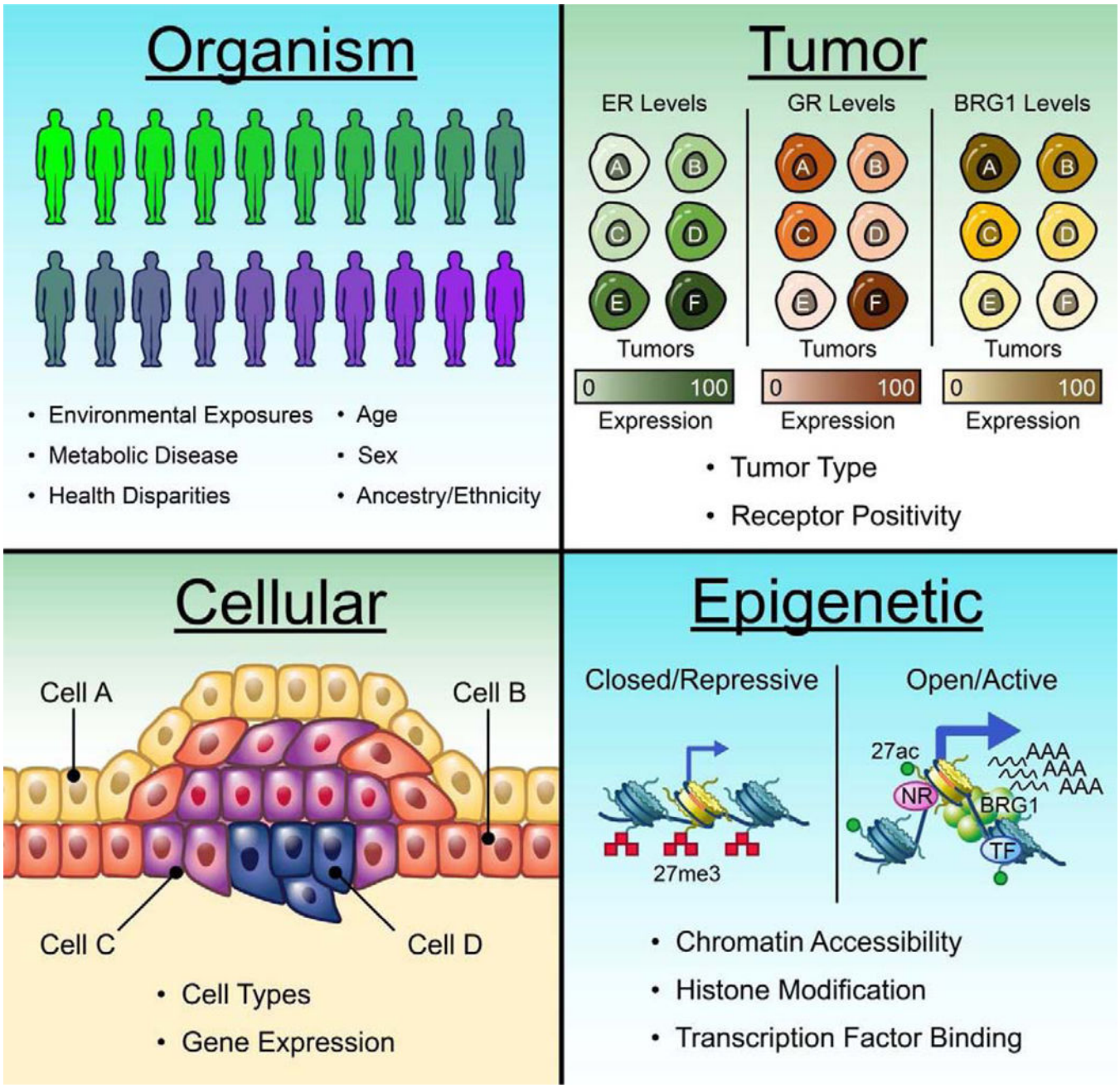

Figure 1: Levels of Heterogeneity in Human Breast Cancer.

Organisms: many factors contribute to the heterogeneity observed between individuals. Differential environmental exposures, metabolic diseases, health disparities, age, sex, and ancestry/ethnicity all have impacts on breast cancer progression, prognosis, and treatment. Tumors: distinct tumor types and grades exhibit heterogeneous characteristics including the status of hormone receptor expression/activity as well as the expression of other factors and mutation burden. Cellular: the diverse cell types of mammary tissue give rise to different types of tumors. Furthermore, heterogeneity between and within different cell types in individual tumors confound treatment strategies targeting the activity of specific

genes/proteins. Epigenetics: heterogeneity in the chromatin landscape and transcription factor interactions result in further cellular heterogeneity within tumors. These levels of heterogeneity are likely inter-related and further understanding of each level will be critical for improving breast cancer treatment strategies.

Table 1.

SWI/SNF proteins that compose mammalian BAF, PBAF, or ncBAF complexes.

The complexes that each protein has been categorized into is marked by color and column.

Subunit	BAF	PBAF	ncBAF	Complex Identity
SMARCA4/2	X	X	X	Common
SMARCC1/2	X	X	X	BAF and PBAF
SMARCD1/2/3	X	X	X	BAF specific
BCL7A/B/C	X	X	X	PBAF specific
ACTB	X	X	X	BAF and ncBAF
ACTL6A	X	X	X	ncBAF specfic
SMARCB1	X	X		
SMARCE1	X	X		
ARID1A/B	X			
DPF1/2/3	X			
SS18/1L	X		X	
PBRM1		X		
PHF10		X		
BRD7		X		
ARID2		X		
GLTSCR1/1L			X	
BRD9			X	