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The linkage of chromatin remodeling to genome maintenance: contribution from a human disease gene BRIT1/MCPH1

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Abstract

Genomic DNA is packed into a highly condensed chromatin structure, which acts as natural barrier preventing accessibility of DNA. In various processes to maintain genomic integrity such as DNA replication, DNA repair, telomere regulation, proteins need to overcome the barrier of condensed chromatin to gain access to DNA. ATP-dependent chromatin remodeling is one of the fundamental mechanisms used by cells to relax chromatin. However, the chromatin remodeling complex does not contain intrinsic specificity for particular nuclear process, and the mechanism mediating its recruitment to DNA lesions remains to be an outstanding question. To address this question, in this review, we will discuss our current findings and future perspectives about how BRIT1/MCPH1, a human disease gene, specifies the function of chromatin remodelers and links chromatin remodeling to genome maintenance.

Keywords

ATP-dependent chromatin remodeling; SWI/SNF; BRIT1/MCPH1; genome integrity; DNA damage response

Specificity: a question raised by multiple-functions of ATP-dependent chromatin remodeling in genome maintenance

Genomic DNA in cells is packed into highly condensed chromatin structures, where the repeating nucleosomes form the basic unit. The nucleosome is composed of 146 base pairs of DNA wrapped around an octamer of the four core histones (H3, H4, H2A and H2B). These nucleosomes are further folded with linker histones and other proteins to form a higher-order chromatin architecture. The condensed nature of chromatin provides the cells with the means to store its genetic information in a compact format in the nucleus. However, it also creates a significant barrier for the access of proteins to chromatin during all cellular processes involving DNA such as transcriptional regulation and DNA replication. Cells have evolved two fundamental mechanisms to counterbalance the condensed chromatin that in turn alter DNA accessibility, including covalent histone modifications and ATP-dependent chromatin remodeling.[1,2]

ATP-dependent chromatin remodeling complexes are evolutionarily conserved from yeast to humans. They use ATP hydrolysis to increase the accessibility of nucleosomal DNA by altering nucleosome composition or repositioning nucleosomes along DNA.[3,4] There are four well-characterized families of mammalian chromatin-remodeling ATPases: the SWI/

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SNF (switching defective/sucrose non-fermenting) family, the ISWI (imitation SWI) family, the NuRD (nucleosome remodeling and deacetylation)/Mi-2/CHD (chromodomain, hlicase, DNA binding) family and the INO80 (inositol requiring 80) family.[1,3] The function of ATP-dependent chromatin remodeling complexes in transcriptional regulation has been extensively studied. Recently accumulating evidence has revealed multiple roles of chromatin remodeling complexes in genome maintenance, including cell cycle checkpoint activation, DNA repair, DNA replication, telomere regulation, centromere stability and chromosome segregation.[5,6] However, the chromatin remodeling complexes do not contain intrinsic specificity for particular nuclear process.[1,7,8] How can chromatin remodeling complexes carry out specialized roles in a variety of processes in genome maintenance?

Firstly, the specificity can be achieved by the presence of distinct chromatin-interacting domains. ATPase subunits of different families have homology only within the ATPase domain and contain different additional domains.[3,5] For example, both members of the SWI/SNF family of ATPase, BRM (homologue of Drosophila protein 'brahma') and BRG1 (BRM/SWI2-related gene 1) contain a C-terminal bromodomain that binds to acetylated histone tails.[9] ISWI family members, SNF2H and SNF2L, have a SANT ('SWI3, ADA2, NCOR and TFIIIB' DNA-binding domains) domain that mediates interaction with unmodified histone tails and linker DNA.[10] CHDs contain tandem chromodomains that recognize methylated histone tails.[11,12] The unique chromatin-interacting domains present in the ATP-dependent remodeling complexes can selectively target ATPase remodelers to chromatin regions with distinct modification patterns.

DNA damage signaling can alter the landscape of post-translational modifications on histone by phosphorylation, methylation, acetylation and ubiquitination.[13,14] Such modifications in response to DNA damage assist chromatin remodelers in the recognition and access to damaged DNA sites. For example, phosphorylation of the histone variant H2AX (γ-H2AX) provides an early chromatin marker for DNA lesions. It has been shown that γ-H2AX interacts with chromatin remodeling complex INO80 and recruits it to the DSB sites in the DNA repairing process.[15,16]

Secondly, in each family, ATPase subunits function with various additional proteins, which form multi-subunit complexes.[1,3] Both the composition of the subunits and the biological consequences of various post-translational modifications on subunits can regulate their involvement in distinct genome maintenance processes. For example, the les4 subunit of the INO80 complex is phosphorylated by the Mec1/Tel1 kinases in yeast (ATM/ATR in mammals) in response to DNA damage. This phosphorylation is not required for DNA repair process, but specifically affects DNA damage checkpoint responses.[17] Our recent study further demonstrated a previously unknown mechanism for the recruitment of chromatin remodeling complexes in response to DNA damage; we found that chromatin remodeling complex SWI/SNF is targeted to DNA damage sites via interacting with an early DNA damage responsive protein BRIT1/MCPH1.

BRIT1/MCPH1 safeguards genomic integrity

BRIT1 (BRCT-repeat inhibitor of hTERT expression) is a gene previously identified as a novel repressor of hTERT (human telomere reverse transcriptase) by a functional genomic screen.[18] The amino acid sequence of BRIT1 was later matched to a putative disease gene called microcephalin (MCPH1). Mutations of BRIT1/MCPH1 (hereafter BRIT1) in humans lead to a genetic disease primary microcephaly (MCPH), which is characterized by the reduction of brain size to one third of normal.[19] Aberrations of BRIT1 have also been found in a variety of cancers including breast, ovarian and prostate cancer[20,21]. BRIT1 contains three BRCT (breast cancer carboxyl-terminal) domains, one in its N-terminus and two in its

C-terminus.[22] BRCT domains are peptide- and phosphopeptide-binding modules present in a range of proteins involved in DNA damage response.[23] Indeed, studies from our group and others indicate the multiple functions of BRIT1 as a guardian of genomic integrity against the development of human diseases[21].

BRIT1 is an early DNA damage responsive protein. DNA damage response (DDR) is a complex process that involves the sensing of DNA damage followed by transduction of the damage signal to cellular response pathways, including cell cycle checkpoints, DNA repair, transcription and the apoptotic pathway. It is an essential cellular mechanism to cope with various exogenous and endogenous genotoxic insults and thereby to maintain genomic integrity.[24,25] BRIT1 functions in the control of the DNA damage response not only through regulating the expression levels of key checkpoint regulators such as BRCA1 and Chk1, but also through affecting DNA damage response signaling cascades and regulating the activity of the components inside this signaling network.[22,26,27] BRIT1 regulates both the ATM and ATR pathways and functions as a proximal factor in DNA damage response controlling the recruitment of multiple sensors and early mediators to the DNA damage sites such as NBS1, 53BP1, RPA and Rad17. (Ref. 20, 24) BRIT1 is potentially recruited to DNA damage site via its interaction with γ-H2AX through its C-terminal domain.[24] Results from these studies place BRIT1 at the early steps in the DNA damage response pathways.

In addition to its functions in DDR, BRIT has been found to play a significant role as a mitotic regulator. The function of BRIT1 is required to coordinate centrosome and nuclear division cycles in multiple model systems including Drosophila and chicken.[28–30] In the mammalian cells, BRIT1 is localize at the centrosomes and functions to maintain integrity and normal function of centrosome.[31,32] Besides its direct function in centrosome regulation, BRIT1 has an additional role in regulating the cell cycle entry into mitosis.[33–35]

In order to gain mechanistic insights into a wide range effect of BRIT1 in genome maintenance, we undertook a proteomic approach to systematically identify BRIT1 interaction proteins. Among many binding partners of BRIT1, we discovered that BRIT1 interacts with ATP-dependent chromatin remodeling complex SWI/SNF and coordinates chromatin remodeling in DNA damage response.[36]

BRIT1-SWI/SNF interaction mediates DNA repair-associated chromatin remodeling activity

Five subunits of human SWI/SNF complex were co-purified with BRIT1 including BRG1/BRM, BAF170, BAF155 and SNF5. Notably, these five subunits have been found to be the functional core of SWI/SNF as their *in vitro* remodeling activity was identical to the activity of whole complex.[37] By depletion of individual subunits, we found that BRIT1 interacts with SWI/SNF complex via its core subunits BAF170 and BAF155. These interactions are enhanced in response to DNA damage signaling, and the enhanced binding affinity of BRIT1-SWI/SNF is mediated through an ATM/ATR-dependent phosphorylation of BAF170.

To elucidate the functional significance of BRIT1-SWI/SNF interaction, we systematically investigated how BRIT1-mediated DNA damage response was impaired when BRIT1-SWI/SNF interaction was disrupted. Notably, we found that BRIT1 is required for two conserved repairing pathways for double strand breaks (DSBs), homologous recombination (HR) and nonhomologous end joining (NHEJ). Via interaction with BRIT1, SWI/SNF can be specifically recruited to and maintained at DNA lesions. Thereby, BRIT1 promotes chromatin relaxation at DNA damage sites that, in turn, facilitates the recruitment of DNA repair proteins to DNA damage sites for efficient repair. As a consequence, depletion of

BRIT1 leads to impaired chromatin relaxation and DNA DSB repair, which may contribute to the development of cancer and MCPH.[36] The functions of BRIT1 and SWI/SNF in regulating DNA repair found from our studies were highly consistent and supported by the studies from many other research groups.[38–40]

Our studies reveal a novel mechanism by which SWI/SNF complex is targeted to DNA lesions via an interaction with an early DNA damage responsive protein BRIT1. DNA damage response proteins, such as BRIT1, may themselves directly regulate the function of chromatin remodeling complexes both spatially and temporally to facilitate the detection and repair of DNA lesions. By interacting and recruiting chromatin remodeling complexes to DNA damage sites, early DNA damage responsive proteins can coordinate detection and repairing DNA lesions at the chromatin level. Furthermore, our studies reveal that post-translational modifications such as phosphorylation may serve as critical mechanisms to regulate the functions of SWI/SNF. In response to DNA damage signaling, unique modifications, such as phosphorylation, can occur in various subunits of chromatin remodeling complexes. These modifications may provide remodeling complexes with the means of interacting with distinct cofactors in various cellular processes to maintain genomic integrity.

BRIT1-SWI/SNF interaction: functions go beyond DNA repair

Having determined the function of BRIT1-SWI/SNF interaction in DNA repair, the next question is what the potential roles of BRIT1-SWI/SNF may play in other aspects of genome maintenance.

Telomeres are unique nucleoprotein structures at the ends of chromosomes. A minimal length of telomeric DNA repeats and proper binding of specialized proteins are required for the maintenance of telomere structure, protecting the end of the chromosomes from degradation and preventing their recognition as DSB by the DNA repair machinery.[41] TRF2 is one of essential binding components of telomeres that plays a critical role in regulating telomere length, the accessibility of telomerase and telomere integrity.[42] Our proteomic study and a recent report both showed that BRIT1 is a binding partner of TRF2.[43] Therefore, it is an intriguing question to ask whether BRIT1 also targets chromatin remodeling complex SWI/SNF to alter telomeric chromatin architecture, which accompanies or contributes to the maintenance of telomere function. Indeed, recent studies have identified both chromatin remodeling complexes INO80 and SWR1 being enriched at telomeres.[44,45] These observations raise interesting possibilities that BRIT1 may target SWI/SNF-mediated chromatin remodeling activity to telomeres and regulate telomere homeostasis at various levels including the lengthening of telomere, the recruitment of telomerase, the association and stabilization of telomere capping proteins, and the recognition of a telomere end as a DSB when it progressively loses the protection.

From our proteomic study, we also observed that BRIT1 interacts with multiple proteins involved in DNA replication such as PCNA. It has been known that coordinated chromatin remodeling activity provided by multiple remodeling complexes is a crucial step in DNA replication.[46] Alterations of local chromatin structure are involved in both the initiation of DNA replication and DNA damage responses during replication stress.[5] When cells are challenged with replication stress-inducing agents, the progression of the replication fork is stalled, which activates intra-S checkpoint activation and recruits repair proteins to remove DNA lesions. If DNA lesions are successfully resolved, the replication will resume. Otherwise, replication folks lose stability and collapse, which results in accumulation of DNA damage. It is of our research interest to understand whether BRIT1-SWI/SNF interaction functions in the formation of replication complex and the initiation of replication

process. It is also possible that BRIT1-SWI/SNF mediated chromatin remodeling activity may participate in the response to replication stress. Their biological functions may occur at multiple steps including the stabilization of stalled replication fork, recruiting intra-S checkpoint activation factors, resolving DNA lesions via facilitating DNA repair or resuming of replication after the removal of replication stress.

Post-translational modifications: the secret of fine-tuned regulatory mechanisms

In order to coordinate potential multiple functions of BRIT1-SWI/SNF interaction in various processes of genome maintenance, a fine-tuned regulatory mechanism has to be in place. Post-translational modifications on different subunits of SWI/SNF may provide an important layer of targeting of ATP-dependent chromatin remodeling to a specific cellular process. In addition to our finding of BAF170 being phosphorylated by ATM/ATR, a recent screen also identified BRG1, BRM and SNF5 as the potential ATM/ATR substrates.[47] Therefore, it is tempting to suspect that phosphorylation on the different subunits of SWI/SNF may serve as a regulatory mechanism to modulate its functions in various processes to maintain genomic integrity such as DNA repair, DNA replication and telomere maintenance. For example, here we identified BAF170 phosphorylation being involved in BRIT1-SWI/SNF interaction in DNA repair. Phosphorylation on other subunit such as SNF5 may facilitate its functions in checkpoint activation or transcriptional regulation. Moreover, phosphorylation may also directly affect the remodeling activity of SWI/SNF by modulating its catalytic subunits such as BRG1 or BRM. Therefore it will be of our future interests to illustrate the additional roles of phosphorylation on SWI/SNF subunits in genome maintenance. In addition to phosphorylation, ubiquitylation and sumoylation have been shown to be extensively involved in DNA damage response. They provide important transient and reversible modifications that regulate the processes of DNA replication, DNA repair and DNA damaging signaling.[13,48–50] To identify additional types of modifications on SWI/SNF subunits may better our understandings on its distinct functions in genome maintenance.

Conclusion

In summary, by interacting with an early DNA damage responsive protein BRIT1, SWI/SNF may target its ATP-dependent chromatin remodeling activity in multiple processes of genome maintenance via the regulatory mechanisms provided by post-translational modifications on various subunits. BRIT1 is a human disease gene. Its dysfunction leads to the two important pathological processes, cancer and neuro-developmental disorder.[19,21,51] Dysfunction of SWI/SNF has been shown to contribute to the process of tumorigenesis.[3,52–54] Mutations of a SWI/SNF-related ATPase, ATRX, also have been shown to cause several inherited mental retardation disorders with manifestations of microcephaly.[2] Thereby, to further understand the functions of BRIT1-SWI/SNF in genome maintenance will provide the mechanistic insights into chromatin remodeling activity in the fundamental cellular processes as well as pathogenesis of human diseases.

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Abbreviations

SWI/SNF	switching defective/sucrose non-fermenting
INO80	inositol requiring 80
BRIT1	BRCT-repeat inhibitor of hTERT expression
BRCT	breast cancer carboxyl-terminal
DDR	DNA damage response
DSB	double strand breaks
HR	homologous recombination
NHEJ	nonhomologous end joining

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