Biochemical and Biophysical Research Communications 418 (2012) 512–517

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

SRG3/mBAF155 stabilizes the SWI/SNF-like BAF complex by blocking CHFR mediated ubiquitination and degradation of its major components

Inkyung Jung [a,1], Dong H. Sohn [a,1,2], Jinwook Choi [a], Joo Mi Kim [b], Shin Jeon [a], Jae Hong Seol [b], Rho Hyun Seong [a,*]

[a] Research Center for Functional Cellulomics, Department of Biological Sciences, Institute for Molecular Biology and Genetics, Seoul National University, Seoul 151-742, Republic of Korea
[b] Research Center for Functional Cellulomics, Department of Biological Sciences, Seoul National University, Seoul 151-742, Republic of Korea

ARTICLE INFO

Article history:
Received 24 December 2011
Available online 20 January 2012

Keywords:
Chromatin remodeling
E3 ubiquitin ligase
Protein degradation
Ubiquitination

ABSTRACT

The murine SWI/SNF-like BAF complex is an ATP-dependent chromatin remodeling complex that functions as a transcriptional regulator in cell proliferation, differentiation and development. The SWI/SNF-like BAF complex consists of several components including core subunits such as BRG1, BAF155/SRG3, BAF47/SNF5/INI1, and BAF170. We have previously shown that the interaction between SRG3/mBAF155 and other components of the complex stabilizes them by attenuating their proteasomal degradation. However, it has not been known how the major components of the SWI/SNF-like BAF complex such as BRG1, SNF5, and BAF60a are targeted for the ubiquitination and degradation, and how SRG3/mBAF155 protects them from the degradation process. Here we report that CHFR interacts with BRG1, SNF5, and BAF60a of the SWI/SNF-like BAF complex and ubiquitinates them to target for degradation through a proteasome-mediated pathway, and that SRG3/mBAF155 stabilizes these components by blocking their interaction with CHFR.

1. Introduction

The SWI/SNF-like BAF complex is an evolutionarily conserved multisubunit complex that uses the energy of adenosine triphosphate (ATP) hydrolysis to mobilize nucleosomes and remodel the structure of chromatin for transcriptional regulation [1,2]. The complex is essential for early embryogenesis, development, cell cycle control, thymocyte development, and tumorigenesis [1,3,4].

Srg3 (*Swi3-related gene*)/*mBAF155* is a murine homolog of yeast *Swi3*, Drosophila *Moira*, and human *Baf155* [5]. Previous studies have shown that SRG3/mBAF155 has a scaffold function in stabilizing the SWI/SNF-like BAF complex by interacting directly with the core subunits BRG1, SNF5, and BAF60a [6]. SRG3/mBAF155 interacts with BRG1 through its highly conserved SANT (SWI3, ADA2, N-CoR, and TFIIIB) domain [7]. It also interacts with SNF5 and BAF60a through its conserved SWIRM (SWI3, RSC8, and MOIRA) domain. SRG3/mBAF155 also interacts with other components of the SWI/SNF-like BAF complex and stabilizes them by attenuating or blocking their proteasomal degradation [6]. It has also been reported that MOIRA and BAF155 interact with BRM and BAF57, respectively [8,9]. These results suggest that SRG3/mBAF155 is a scaffold that interacts physically with other components of the SWI/SNF complex and stabilizes them. Although control of the stability the SWI/SNF-like BAF complex is important for diverse cellular processes, its mechanism is poorly understood.

The proteasome-mediated degradation is induced by ubiquitination of the target protein [10,11]. Protein ubiquitination is a central regulatory process for proteolytic degradation [12–14]. The stability of the SWI/SNF-like BAF complex is reported to be regulated by ubiquitination. Unkempt, a RING finger protein, binds to BAF60b and induces its ubiquitination and proteosomal degradation [15]. BAF57 is also ubiquitinated and degraded by the E3 ubiquitin ligase, thyroid hormone receptor interacting protein 12 (TRIP12). BAF155 blocks the interaction between BAF57 and TRIP12 and, thus, protects BAF57 from degradation [9]. These results suggest that protein degradation by the ubiquitination pathway regulates the quality and functional fidelity of the SWI/SNF-like BAF complex. However, it is not clear how the stability of major components of the SWI/SNF-like BAF complex, such as BRG1, SNF5, or BAF60a, is controlled.

Abbreviations: BRM, brahma; BRG1, BRM-related gene-1; BAF, BRG1-associated factor; HA, hemagglutinin; DTT, dithiothreitol; SDS–PAGE, sodium dodecyl sulfate–polyacrylamide gel electrophoresis; Rb, retinoblastoma tumor suppressor protein.

* Corresponding author. Address: Research Center for Functional Cellulomics, Department of Biological Sciences, Institute for Molecular Biology and Genetics (Bldg. 105), Seoul National University, Kwanak-gu, Kwanak-ro 599, Seoul 151-742, Republic of Korea. Fax: +82 2 878 9380.
E-mail address: rhseong@snu.ac.kr (R.H. Seong).

[1] They contributed to this work equally.

[2] Present address: Division of Immunology and Rheumatology, Stanford University School of Medicine, VA Palo Alto Health Care System, USA.

0006-291X/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbrc.2012.01.057

CHFR (Checkpoint with FHA and RING finger domains) is one of the E3 ligases, which is known to be a tumor suppressor and play an essential role in cell cycle control and tumorigenesis [16,17]. In addition, CHFR interacts with helicase-like transcription factor (HLTF), which belongs to the SWI/SNF family, and regulates its stability and functions by ubiquitination [18]. Thus, it appears that CHFR affects chromatin structure via interaction with chromatin remodeling factors. Here, we report that CHFR interacts with the BRG1, SNF5, and BAF60a components of the SWI/SNF-like BAF complex and ubiquitinates them to mark them for degradation through a proteasome-mediated pathway. We also report that SRG3/mBAF155 stabilizes these components by blocking their interaction with CHFR.

2. Materials and methods

2.1. Plasmid constructs

For cloning of plasmids used in transfection, the cDNAs for murine SRG3, BRG1, SNF5, and BAF60a were inserted into the pCAGGS or pCAGGSBS vector with N-terminal FLAG or Myc tag. The mutants of SNF5 were PCR-amplified with appropriate primers for FLAG-SNF5 (1–319), -SNF5 (1–245), and -SNF5 (1–185 + Rpt2) and inserted into the pCAGGSBS vector. Each construct was tagged with N-terminal FLAG epitope. The pCDNA3-Myc-CHFR plasmid construct [19] and HA-Ubiquitin plasmid construct were generously provided by JH, Seol (Seoul National University, Seoul, Korea) and CH, Chung (Seoul National University, Seoul, Korea), respectively.

2.2. Cell culture and transient transfection

COS-1 cells and 293T cells were cultured in Dulbecco's modified Eagle's medium (DMEM, WelGENE) containing 10% fetal bovine serum (FBS, WelGENE). NIH3T3-U6 and NIH3T3-U6-shSRG3 stable cell lines were maintained in DMEM containing 10% bovine calf serum (BCS, HyClone). All the transfection experiments were performed with Lipofectamine 2000 (Invitrogen), $CaPO_4$-method or polyethyleneimine (PEI) according to the manufacturer's instructions. All cells were split into 60 mm dishes to 70–80% confluency at 24 h before transfection. Appropriate control empty vectors were supplemented to adjust the total amounts of DNA in each experiment. Cells were harvested after 48 h of incubation. Before the harvesting, the cells were treated with 20 μM of MG132 (A.G. Scientific, INC.) for 6 h.

2.3. Antibodies, immunoprecipitation, and immunoblotting

For immunoprecipitation experiments, cells were lysed in buffer X (100 mM Tris–Cl pH 8.5, 250 mM Nacl, 1% NP-40, 1 mM EDTA, 2 mg/ml BSA) and the proteins were immunoprecipitated with specific antibodies as previously described [20]. For immunoblot analysis, proteins were subjected to SDS–PAGE and transferred to immobilon-P membrane (Millipore). Antibodies of anti-FLAG (M2, Sigma), anti-Myc (9E10, Roche Applied Science), anti-HA (HA-7, Sigma), and anti-β-actin (AC-15, Sigma) were purchased commercially. Antisera against SRG3 were raised from rabbits in our laboratory [20].

2.4. In vitro ubiquitination assay

For *in vitro* ubiquitination assay, FLAG-BRG1, FLAG-SNF5 or FLAG-BAF60a translated *in vitro* by using TNT T7 quick coupled system (Promega, L1170) was incubated at 37 °C for 0 or 30 min with E1 (0.5 μg), E2 (UBCH5a, 0.5 μg), ubiquitin (10 μg), 1 mM DTT, and 5 mM ATP in the presence or absence of E3 (His-CHFR, 7 μg) as previously described [19]. After the indicated times, each sample was analyzed by immunoblotting with anti-SNF5, -BAF60a, or -BRG1 antibodies.

3. Results

3.1. Major components of the SWI/SNF-like BAF complex interact with CHFR

BRG1, SNF5, and BAF60a are degraded by a proteasome-mediated degradation pathway [6]. The degradation of BRG1, SNF5, and BAF60a was inhibited by treatment with the potent proteasome inhibitor MG132, and SNF5 protein was poly-ubiquitinated [6]. We tested whether BAF60a and BRG1 are also poly-ubiquitinated in the presence of MG132 (Fig. 1A and B). Significant increases in BAF60a-ubiquitin and BRG1-ubiquitin conjugates were detected in the presence of MG132. These results show that BAF60a and BRG1, as well as SNF5, are ubiquitinated and regulated by a proteasome-mediated degradation pathway.

CHFR is known to function as a mitotic checkpoint protein and as an ubiquitin ligase for HLTF [18,21]. These results suggested the possibility that CHFR may function as an E3 ubiquitin ligase for the components of the SWI/SNF-like BAF complex. Therefore, we analyzed the interaction between the components of the mammalian SWI/SNF-like BAF complex and CHFR by immunoprecipitation. The expression vectors of FLAG-tagged BRG1, SNF5, BAF60a, or SRG3/mBAF155 (hereafter referred to as SRG3) were co-transfected with Myc-CHFR expression vector into COS-1 cells, and cell lysates were immunoprecipitated with anti-FLAG or anti-Myc antibodies. As shown in Fig. 1C–F, BRG1, SNF5, and BAF60a were co-immunoprecipitated with CHFR, whereas SRG3 did not interact with CHFR at all. These results suggest that BRG1, SNF5, and BAF60a, but not SRG3, are the substrates of CHFR for ubiquitination.

3.2. CHFR induces ubiquitination of major components of the SWI/SNF-like BAF complex

We further examined whether CHFR actually induces ubiquitination of the components of the SWI/SNF-like BAF complex, both *in vitro* and *in vivo*. For the *in vitro* ubiquitination assay, we incubated FLAG-tagged BRG1, SNF5, or BAF60a, which were translated *in vitro*, with or without CHFR for the indicated times. As shown in Fig. 2A–C, the ubiquitination of BRG1, SNF5, or BAF60a increased when these proteins were incubated with CHFR for 30 min. To confirm that CHFR induces ubiquitination *in vivo*, 293T cells were co-transfected with FLAG-SNF5 and HA-Ubiquitin expression vectors, with or without Myc-CHFR expression vector, and cell lysates were immunoprecipitated with anti-FLAG antibody (Fig. 2D). In the presence of CHFR, the SNF5-ubiquitin conjugates significantly increased, indicating that CHFR induces the ubiquitination of SNF5 *in vivo*.

Next, we investigated whether CHFR can increase the degradation of its substrates, BRG1, SNF5, and BAF60a. 293T cells were co-transfected with FLAG-BRG1, -SNF5, or -BAF60a expression vector together with the Myc-CHFR expression vector (Fig. 2E–H). CHFR down regulated the stability of these components in a dose-dependent manner. In the presence of MG132, the protein levels were restored to those at which CHFR was not overexpressed. These findings indicate that CHFR increases the degradation of BRG1, SNF5, and BAF60a through the ubiquitination-proteasome-mediated degradation pathway. However, SRG3 protein was not affected by CHFR overexpression at all. As described previously, unlike other components, SRG3 did not interact with CHFR. Thus, CHFR regulates the stability of the components of the SWI/SNF-like BAF complex by inducing ubiquitination but does not affect SRG3 level. In addition, the SNF5-ubiquitin conjugates significantly increased in the

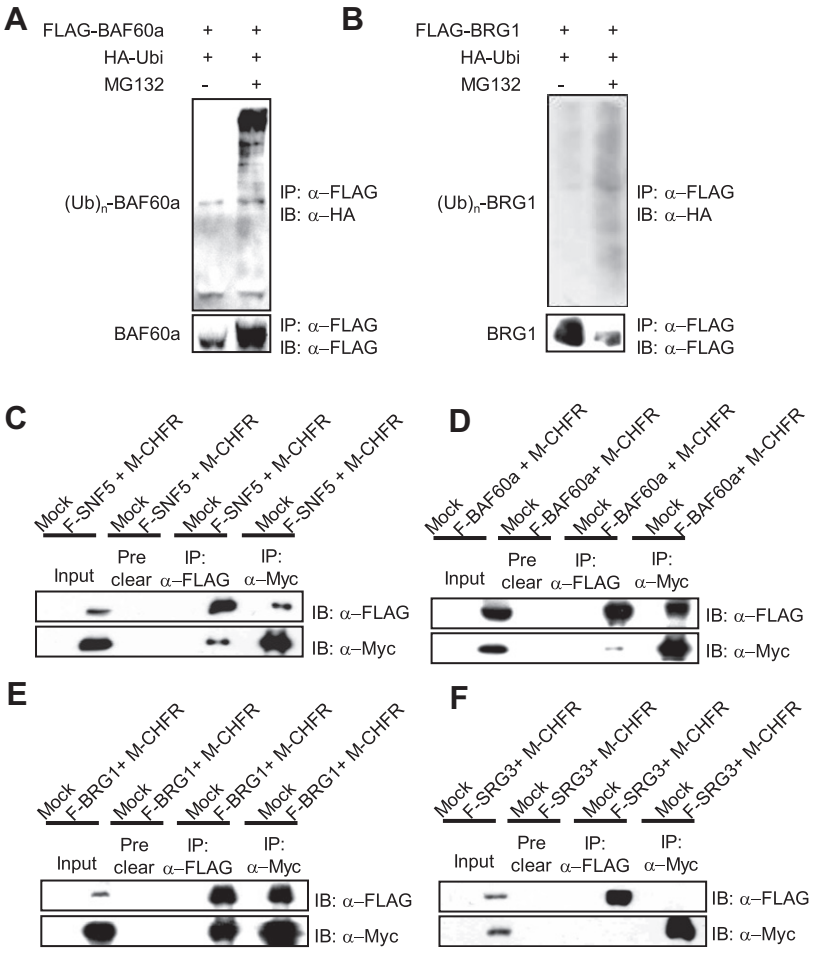

Fig. 1. The components of the SWI/SNF-like BAF complex are ubiquitinated and interact with CHFR. (A and B) COS-1 cells were co-transfected with FLAG-BAF60a (A) or FLAG-BRG1 (B) expression vectors along with HA-Ubiquitin expression vector. After 42 h of incubation, cells were treated with MG132 (20 μM) for 6 h. Whole cell lysates were immunoprecipitated with anti-FLAG antibody and subjected to immunoblot analysis with anti-HA antibody (upper panel). The membranes were stripped after analysis and immunoblotted again with anti-FLAG antibody (lower panel). (C–F) FLAG-SNF5 (C), FLAG-BAF60a (D), FLAG-BRG1 (E) or FLAG-SRG3 (F) expression vectors were co-transfected into COS-1 cells with Myc-CHFR expression vectors. Whole cell lysates were immunoprecipitated with anti-FLAG or anti-Myc antibodies and subjected to immunoblot analysis with anti-Myc or anti-FLAG antibodies, respectively. The cells transfected with an empty vector were used as control (labeled as 'Mock').

presence of MG132 with CHFR *in vivo*. These results suggest that CHFR enhances the degradation of the components of the SWI/SNF-like BAF complex by inducing their poly-ubiquitination.

3.3. SRG3 can stabilize the SWI/SNF-like BAF complex by interfering with CHFR

Since SRG3 and CHFR have opposite roles in stabilizing the subunits of the SWI/SNF-like BAF complex, it is likely that SRG3 inhibits the activity of CHFR for regulation of protein stability of those components. To verify this, we co-transfected BRG1, SNF5, or BAF60a expression vectors together with increasing amounts of CHFR expression vector and a fixed amount of SRG3 expression vector into 293T cells and analyzed the protein levels of each component by immunoblot analysis. As shown in Fig. 3A–C, the protein levels of BRG1, SNF5, and BAF60a were downregulated by CHFR expression but were maintained in the presence of SRG3, although the level of CHFR was not significantly changed. These results suggest that the degradation of the components of the SWI/SNF-like BAF complex induced by CHFR is inhibited by SRG3 expression. We further examined whether the protein stability and ubiquitination of BAF60a is affected by *Srg3* knockdown. The established NIH3T3 cell line stably expressing small hairpin RNA against *Srg3* and its control cell line [22] were co-transfected with FLAG-BAF60a expression vector and HA-Ubiquitin expression vector (Fig. 3D). BAF60a level was decreased by knockdown of *Srg3* and restored by MG132 treatment. Cell lysates were immunoprecipitated with anti-FLAG antibody and then immunoblotted with anti-HA antibody for detecting ubiquitinated BAF60a proteins. In the presence of MG132, the ubiquitination of BAF60a was increased by *Srg3* knockdown. Thus, SRG3 stabilizes BAF60a by inhibiting the ubiquitination of BAF60a, which is induced by CHFR.

3.4. Rpt2 region of SNF5 is the CHFR-interacting region

Alignment analysis of SNF5 and its homologs revealed that SNF5 has 2 highly conserved domains, namely, repeat 1 (Rpt1) and repeat 2 (Rpt2), and 1 moderately conserved domain, namely, homology region 3 (HR3) [23,24]. To identify which regions of SNF5 are important for the interaction with CHFR, we generated several deletion mutants of SNF5 (Fig. 4A). FLAG-tagged wild-type SNF5 and its mutants were co-expressed with Myc-CHFR in COS-1 cells, and cell lysates were immunoprecipitated with anti-FLAG antibody and immunoblotted with anti-FLAG and anti-Myc antibodies (Fig. 4B). The HR3 deletion mutant of SNF5 [SNF5 (1–319)] interacted with CHFR, but the Rpt2 and HR3 deletion mutant of SNF5 [SNF5 (1–245)] did not. In addition, when the Rpt1 region was replaced by the Rpt2 region [SNF5

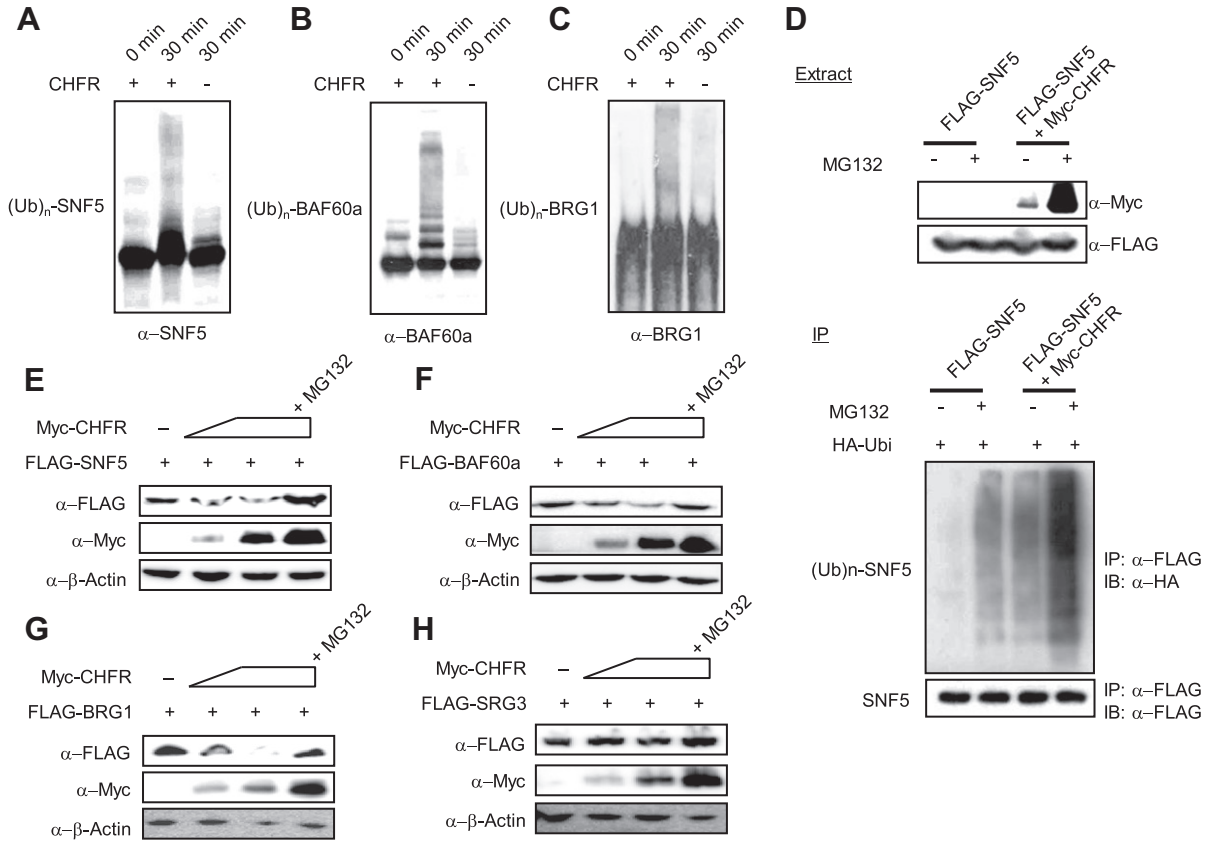

Fig. 2. CHFR enhances the degradation of the SWI/SNF-like BAF complex *in vitro* and *in vivo* by inducing its ubiquitination. (A–C) For *in vitro* ubiquitination assay, *in vitro* translated FLAG-SNF5 (A), FLAG-BAF60a (B) or FLAG-BRG1 (C) were incubated with E1, E2 (UBC-5Q), ubiquitin, ATP, DTT, protease inhibitor, and His-CHFR for the indicated times at 37 °C. After incubation, the samples were immunoblotted with anti-SNF5, -BAF60a, or -BRG1 antibodies. (D) 293T cells were co-transfected with FLAG-SNF5 and HA-Ubiquitin expression vectors, and treated with MG132 (20 μM) or vehicle for 6 h. After 48 h of incubation, whole cell lysates were subjected to SDS–PAGE and immunoblotted with anti-Myc or anti-FLAG antibodies (left panel). Also, the cell lysates were immunoprecipitated with anti-FLAG antibody and subjected to SDS–PAGE, and immunoblotted with anti-HA antibody (right, upper panel) or anti-FLAG antibody (right, lower panel). (E–H) 293T cells were co-transfected with FLAG-SNF5 (E), FLAG-BAF60a (F), FLAG-BRG1 (G), or FLAG-SRG3 (H) expression vectors along with increasing amount of Myc-CHFR expression vector. Cells were treated with MG132 (20 μM) for 6 h and whole cell lysates were analyzed by immunoblot analysis with anti-Myc and anti-FLAG antibodies.

(1–185 + Rpt2)], the deletion mutant interacted with CHFR. Taken together, these results suggest that SNF5 interacts with CHFR through the Rpt2 region of SNF5.

4. Discussion

Post-translational modification of proteins by ubiquitin ligase is a central regulator in a variety of cellular processes. The SWI/SNF-like BAF complex is a major transcriptional regulator, and therefore it needs to be carefully regulated. SRG3/mBAF155 has been found to play a role as a scaffold for other components of the complex [6], enabling the complex to function efficiently when required. We demonstrated that the major components of the complex BRG1, SNF5, and BAF60a were stabilized by ectopic expression of SRG3 *in vitro*. Furthermore, BAF155, a human homolog of SRG3, has been reported to mediate the stabilization of BAF57 expression [9]. From our results, we concluded that BRG1, SNF5, and BAF60a were ubiquitinated and degraded via the 26S proteasome-mediated pathway [6]. However, the identity of the ubiquitin ligases involved in this process has been unknown. Recent studies have shown that E3 ligases are important for the regulation of the SWI/SNF-like BAF complex. TRIP12 interacts with BAF57 and ubiquitinates it [9]. Unkempt, another ubiquitin ligase, is involved in BAF60b ubiquitination in a Rac1-dependent manner, which increases the degradation of BAF60b but not of BAF60a or BAF60c [15]. Here, we show that CHFR, an E3 ubiquitin ligase, ubiquitinates and directs BRG1, SNF5, and BAF60a to a proteosomal degradation pathway.

CHFR was found to associate with several chromatin remodeling factors, which control chromosome stability, and to function as a tumor suppressor. CHFR ubiquitinates and negatively regulates histone deacetylase 1 (HDAC1), promoting *p21* gene expression to induce *p21*-dependent cell cycle arrest [19]. It also synergistically maintains genomic stability with another E3 ubiquitin ligase, ring finger protein 8 (RNF8), and inhibits tumorigenesis by modulation of histone modifications and suppression of ataxia telangiectasia mutated (ATM) kinase activation [25]. CHFR and RNF8 double-knockout mice showed low H2A and H2B ubiquitination, H4K16 acetylation in thymocytes and suppressed ATM activation in response to DNA damage response, thereby causing T-cell lymphoma to develop. CHFR functions as a regulator controlling the stability of HLTF, which belongs to the SWI/SNF chromatin remodeling complex family [18]. All these results indicate that CHFR is involved in the regulation of chromatin structure by modulating histone modifications and/or ubiquitinating several different chromatin remodeling proteins.

The SWI/SNF-like BAF complex has been shown to have the activity of a tumor suppressor. It physically interacts with Rb and mediates Rb-mediated cell cycle arrest [26]. In addition, SNF5 represses cyclin D1 expression by recruiting the HDAC complex to its promoter [27,28]. The SWI/SNF-like BAF complex also associates with BRCA1 orc-Myc [29,30] and controls p53-mediated transcrip-

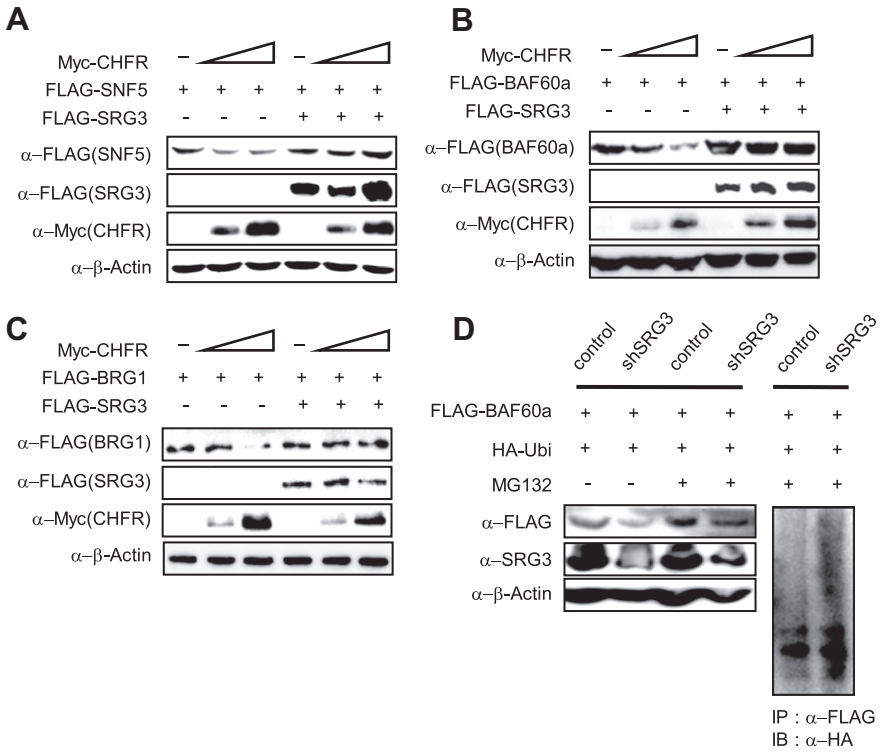

Fig. 3. SRG3 can stabilize the SWI/SNF-like BAF complex by interfering with CHFR. (A–C) FLAG-SNF5 (A), FLAG-BAF60a (B), or FLAG-BRG1 (C) expression vectors were co-transfected into 293T cells along with increasing amount of Myc-CHFR expression vector in the absence or presence of FLAG-SRG3 expression. After 48 h of incubation, whole cell lysates were analyzed by immunoblot analysis with anti-FLAG and anti-Myc antibodies. (D) NIH3T3-U6 control and NIH3T3-U6-shSRG3 stable cell lines were co-transfected with FLAG-BAF60a and HA-Ubiquitin expression vectors. After 42 h of incubation, cells were treated with MG132 (20 μM) or vehicle for 6 h. Whole cell lysates were immunoblotted with anti-FLAG or anti-SRG3 antibodies (left panel). Also, the cell lysates were immunoprecipitated with anti-FLAG antibody and subjected to SDS–PAGE, and immunoblotted with anti-HA antibody (right panel).

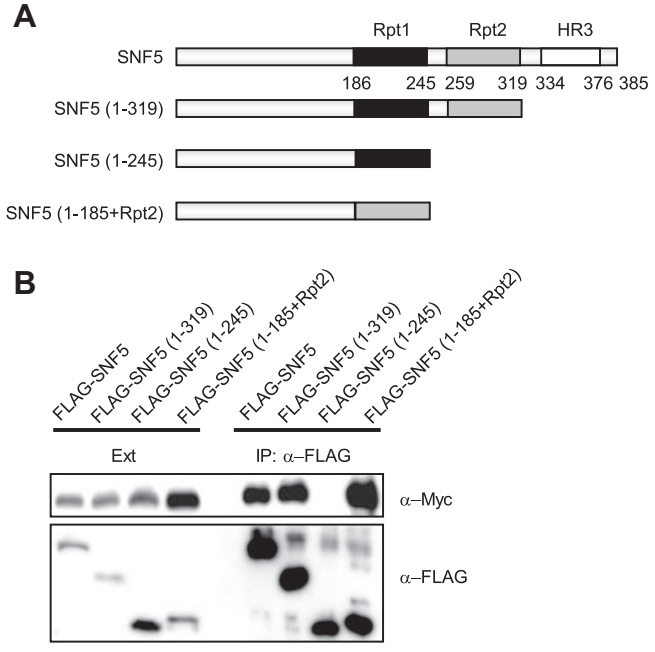

Fig. 4. Rpt2 region of SNF5 is CHFR-interacting region and responsible for the degradation of SNF5 by CHFR. (A) The schematic representation of deletion mutants of SNF5 is depicted. The Rpt1, Rpt2, and HR3 regions are indicated with solid black box, gray box, and white box, respectively. Each SNF5 mutant was tagged with FLAG epitope (not shown). (B) The interactions between deletion mutants of SNF5 and CHFR were analyzed by immunoprecipitation. COS-1 cells were co-transfected with FLAG-tagged wild type or mutant SNF5 expression vectors with Myc-CHFR expression vector. After 48 h of incubation, whole cell lysates were immunoprecipitated with anti-FLAG antibody and subjected to SDS–PAGE, and immunoblotted with anti-Myc and anti-FLAG antibodies.

tional activity, which regulates cell cycle arrest [22,31]. Some studies have shown that inactivation of SNF5 result in a failure of cell cycle arrest caused by p53 defects [32,33]. SRG3 was also shown to function as a tumor suppressor by modulating $p21^{WAF1/CIP1}$ expression [22].

In contrast, other studies have shown that the expression of the SWI/SNF subunits is maintained in human tumor cells. The increase in BRG1 level is associated with enhanced tumor cell growth and invasion in human gastric and prostate cancer [34,35]. BAF57 activity is maintained in prostate cancer while supporting androgen receptor (AR) activity; BAF57 inhibitory peptide sufficiently blocks androgen-dependent prostate cancer cell proliferation in AR-positive cells [36,37]. These results make it clear that the robust expression of subunits of the SWI/SNF-like BAF complex can induce cancer cell growth and invasion in a cell context-dependent manner. The pathway involved in the maintenance of expression of the SWI/SNF-like BAF complex in several cancer cells remains unknown. Therefore, it is crucial to find the mechanism by which the protein level of the SWI/SNF-like BAF complex is regulated. Thus, it is notable that CHFR, a tumor suppressor, regulates the ubiquitination and degradation of the SWI/SNF chromatin remodeling proteins. It is conceivable that CHFR functions as a tumor suppressor also by reducing the expression level of the components of the SWI/SNF-like BAF complex in a context-dependent manner with implications for the understanding of epigenetics of cell cycle control and potentially, cancer pathogenesis. This hypothesis needs to be investigated further.

Acknowledgments

This work was supported by the National Research Foundation (NRF) of Korea in part through the Research Center for Functional

Cellulomics and in part through NRF Grant (2009-0081789) to R.H.S. I.J., J.C., S.J. are supported by the BK21 Program from MEST, Korea. I.J., J.C. and J.K. are supported by Seoul Science Fellowship.

References

[1] C. Muchardt, M. Yaniv, ATP-dependent chromatin remodelling: SWI/SNF and Co. are on the job, J. Mol. Biol. 293 (1999) 187–198.
[2] R.E. Kingston, G.J. Narlikar, ATP-dependent remodeling and acetylation as regulators of chromatin fluidity, Genes Dev. 13 (1999) 2339–2352.
[3] S. Bultman, T. Gebuhr, D. Yee, C. La Mantia, J. Nicholson, A. Gilliam, F. Randazzo, D. Metzger, P. Chambon, G. Crabtree, T. Magnuson, A Brg1 null mutation in the mouse reveals functional differences among mammalian SWI/SNF complexes, Mol. Cell 6 (2000) 1287–1295.
[4] J.K. Kim, S.O. Huh, H. Choi, K.S. Lee, D. Shin, C. Lee, J.S. Nam, H. Kim, H. Chung, H.W. Lee, S.D. Park, R.H. Seong, Srg3, a mouse homolog of yeast SWI3, is essential for early embryogenesis and involved in brain development, Mol. Cell. Biol. 21 (2001) 7787–7795.
[5] P. Sudarsanam, F. Winston, The SWI/SNF family: nucleosome-remodeling complexes and transcriptional control, Trends Genet. 16 (2000) 345–351.
[6] D.H. Sohn, K.Y. Lee, C. Lee, J. Oh, H. Chung, S.H. Jeon, R.H. Seong, SRG3 interacts directly with the major components of the SWI/SNF chromatin remodeling complex and protects them from proteosomal degradation, J. Biol. Chem. 282 (2007) 10614–10624.
[7] R. Aasland, A.F. Stewart, T. Gibson, The SANT domain: a putative DNA-binding domain in the SWI–SNF and ADA complexes, the transcriptional co-repressor N-CoR and TFIIIB, Trends Biochem. Sci. 21 (1996) 87–88.
[8] M.A. Crosby, C. Miller, T. Alon, K.L. Watson, C.P. Verrijzer, R. Goldman-Levi, N.B. Zak, The trithorax group gene moira encodes a brahma-associated putative chromatin-remodeling factor in *Drosophila melanogaster*, Mol. Cell. Biol. 19 (1999) 1159–1170.
[9] B.R. Keppler, T.K. Archer, Ubiquitin-dependent and ubiquitin-independent control of subunit stoichiometry in the SWI/SNF complex, J. Biol. Chem. 285 (2010) 35665–35674.
[10] R.L. Welchman, C. Gordon, R.J. Mayer, Ubiquitin and ubiquitin-like proteins as multifunctional signals, Nat. Rev. Mol. Cell Biol. 6 (2005) 599–609.
[11] J. Herrmann, L.O. Lerman, A. Lerman, Ubiquitin and ubiquitin-like proteins in protein regulation, Circ. Res. 100 (2007) 1276–1291.
[12] D.-Q. Li, K. Ohshiro, S.D.N. Reddy, S.B. Pakala, M.-H. Lee, Y. Zhang, S.K. Rayala, R. Kumar, E3 ubiquitin ligase COP1 regulates the stability and functions of MTA1, Proc. Natl. Acad. Sci. 106 (2009) 17493–17498.
[13] D. Mukhopadhyay, H. Riezman, Proteasome-independent functions of ubiquitin in endocytosis and signaling, Science 315 (2007) 201–205.
[14] T.T. Huang, A.D. D'Andrea, Regulation of DNA repair by ubiquitylation, Nat. Rev. Mol. Cell Biol. 7 (2006) 323–334.
[15] P. Lorès, O. Visvikis, R. Luna, E. Lemichez, G. Gacon, The SWI/SNF protein BAF60b is ubiquitinated through a signalling process involving Rac GTPase and the RING finger protein Unkempt, FEBS J. 277 (2010) 1453–1464.
[16] D. Kang, J. Chen, J. Wong, G. Fang, The checkpoint protein Chfr is a ligase that ubiquitinates Plk1 and inhibits Cdc2 at the G2 to M transition, J. Cell Biol. 156 (2002) 249–259.
[17] X. Yu, K. Minter-Dykhouse, L. Malureanu, W.M. Zhao, D. Zhang, C.J. Merkle, I.M. Ward, H. Saya, G. Fang, J. van Deursen, J. Chen, Chfr is required for tumor suppression and Aurora A regulation, Nat. Genet. 37 (2005) 401–406.
[18] J.M. Kim, E.N. Cho, Y.E. Kwon, S.J. Bae, M. Kim, J.H. Seol, CHFR functions as a ubiquitin ligase for HLTF to regulate its stability and functions, Biochem. Biophys. Res. Commun. 395 (2010) 515–520.
[19] Y.M. Oh, Y.E. Kwon, J.M. Kim, S.J. Bae, B.K. Lee, S.J. Yoo, C.H. Chung, R.J. Deshaies, J.H. Seol, Chfr is linked to tumour metastasis through the downregulation of HDAC1, Nat. Cell Biol. 11 (2009) 295–302.
[20] S. Han, H. Choi, M.-g. Ko, Y.I. Choi, D.H. Sohn, J.K. Kim, D. Shin, H. Chung, H.W. Lee, J.-B. Kim, S.D. Park, R.H. Seong, Peripheral T cells become sensitive to glucocorticoid- and stress-induced apoptosis in transgenic mice overexpressing SRG3, J. Immunol. 167 (2001) 805–810.
[21] H. Ding, K. Descheemaeker, P. Marynen, L. Nelles, T. Carvalho, M. Carmo-Fonseca, D. Collen, A. Belayew, Characterization of a helicase-like transcription factor involved in the expression of the human plasminogen activator inhibitor-1 gene, DNA Cell Biol. 15 (1996) 429–442.
[22] J. Ahn, M. Ko, C. Lee, J. Kim, H. Yoon, R.H. Seong, Srg3, a mouse homolog of BAF155, is a novel p53 target and acts as a tumor suppressor by modulating p21WAF1/CIP1 expression, Oncogene 30 (2011) 445–456.
[23] A. Morozov, E. Yung, G.V. Kalpana, Structure–function analysis of integrase interactor 1 hSNF5L1 reveals differential properties of two repeat motifs present in the highly conserved region, Proc. Natl. Acad. Sci. USA 95 (1998) 1120–1125.
[24] E. Craig, Z.-K. Zhang, K.P. Davies, G.V. Kalpana, A masked NES in INI1/hSNF5 mediates hCRM1-dependent nuclear export: implications for tumorigenesis, EMBO J. 21 (2002) 31–42.
[25] J. Wu, Y. Chen, L.Y. Lu, Y. Wu, M.T. Paulsen, M. Ljungman, D.O. Ferguson, X. Yu, Chfr and RNF8 synergistically regulate ATM activation, Nat. Struct. Mol. Biol. 18 (2011) 761–768.
[26] J.L. Dunaief, B.E. Strober, S. Guha, P.A. Khavari, K. Alin, J. Luban, M. Begemann, G.R. Crabtree, S.P. Goff, The retinoblastoma protein and BRG1 form a complex and cooperate to induce cell cycle arrest, Cell 79 (1994) 119–130.
[27] Z.K. Zhang, K.P. Davies, J. Allen, L. Zhu, R.G. Pestell, D. Zagzag, G.V. Kalpana, Cell cycle arrest and repression of cyclin D1 transcription by INI1/hSNF5, Mol. Cell. Biol. 22 (2002) 5975–5988.
[28] M. Tsikitis, Z. Zhang, W. Edelman, D. Zagzag, G.V. Kalpana, Genetic ablation of cyclin D1 abrogates genesis of rhabdoid tumors resulting from Ini1 loss, Proc. Natl. Acad. Sci. USA 102 (2005) 12129–12134.
[29] C.W. Roberts, S.H. Orkin, The SWI/SNF complex – chromatin and cancer, Nat. Rev. Cancer 4 (2004) 133–142.
[30] D.A. Bochar, L. Wang, H. Beniya, A. Kinev, Y. Xue, W.S. Lane, W. Wang, F. Kashanchi, R. Shiekhattar, BRCA1 is associated with a human SWI/SNF-related complex: linking chromatin remodeling to breast cancer, Cell 102 (2000) 257–265.
[31] A.J. Levine, p53, The cellular gatekeeper for growth and division, Cell 88 (1997) 323–331.
[32] M.S. Isakoff, C.G. Sansam, P. Tamayo, A. Subramanian, J.A. Evans, C.M. Fillmore, X. Wang, J.A. Biegel, S.L. Pomeroy, J.P. Mesirov, C.W. Roberts, Inactivation of the Snf5 tumor suppressor stimulates cell cycle progression and cooperates with p53 loss in oncogenic transformation, Proc. Natl. Acad. Sci. USA 102 (2005) 17745–17750.
[33] J. DelBove, Y. Kuwahara, E.L. Mora-Blanco, V. Godfrey, W.K. Funkhouser, C.D. Fletcher, T. Van Dyke, C.W. Roberts, B.E. Weissman, Inactivation of SNF5 cooperates with p53 loss to accelerate tumor formation in Snf5(+/−); p53(+/−) mice, Mol. Carcinog. 48 (2009) 1139–1148.
[34] K. Sentani, N. Oue, H. Kondo, K. Kuraoka, J. Motoshita, R. Ito, H. Yokozaki, W. Yasui, Increased expression but not genetic alteration of BRG1, a component of the SWI/SNF complex, is associated with the advanced stage of human gastric carcinomas, Pathobiology 69 (2001) 315–320.
[35] A. Sun, O. Tawfik, B. Gayed, J.B. Thrasher, S. Hoestje, C. Li, B. Li, Aberrant expression of SWI/SNF catalytic subunits BRG1/BRM is associated with tumor development and increased invasiveness in prostate cancers, Prostate 67 (2007) 203–213.
[36] K.A. Link, S. Balasubramaniam, A. Sharma, C.E.S. Comstock, S. Godoy-Tundidor, N. Powers, K.H. Cao, A. Haelens, F. Claessens, M.P. Revelo, K.E. Knudsen, Targeting the BAF57 SWI/SNF subunit in prostate cancer: a novel platform to control androgen receptor activity, Cancer Res. 68 (2008) 4551–4558.
[37] K.A. Link, C.J. Burd, E. Williams, T. Marshall, G. Rosson, E. Henry, B. Weissman, K.E. Knudsen, BAF57 governs androgen receptor action and androgen-dependent proliferation through SWI/SNF, Mol. Cell. Biol. 25 (2005) 2200–2215.