Switching of chromatin-remodelling complexes for oestrogen receptor- α

Maiko Okada¹, Shin-ichiro Takezawa^{1,2}, Yoshihiro Mezaki¹, Ikuko Yamaoka^{1,2}, Ichiro Takada¹, Hirochika Kitagawa¹ & Shigeaki Kato^{1,2*}

¹The Institute of Molecular and Cellular Biosciences, University of Tokyo, Bunkyo-ku, Tokyo, Japan, and ²ERATO, Japan Science and Technology Agency, Kawaguchi, Saitama, Japan

The female sex steroid hormone oestrogen stimulates both cell proliferation and cell differentiation in target tissues. These biological actions are mediated primarily through nuclear oestrogen receptors (ERs). The ligand-dependent transactivation of ERs requires several nuclear co-regulator complexes; however, the cell-cycle-dependent associations of these complexes are poorly understood. By using a synchronization system, we found that the transactivation function of ER α at G2/M was lowered. Biochemical approaches showed that ER α associated with two discrete classes of ATP-dependent chromatin-remodelling complex in a cell-cycle-dependent manner. The components of the NuRD-type complex were identified as G2/M-phase-specific ER α co-repressors. Thus, our results indicate that the transactivation function of ER α is cell-cycle dependent and is coupled with a cell-cycle-dependent association of chromatin-remodelling complexes.

Keywords: oestrogen receptor; cell cycle; chromatin-remodelling complex

EMBO reports (2008) 9, 563–568. doi:10.1038/embor.2008.55

INTRODUCTION

Sex steroid hormones exert their biological actions by directly binding to and activating their cognate nuclear receptors (Mangelsdorf *et al*, 1995). Steroid receptors are members of the nuclear receptor superfamily that function as sequence-specific and hormone-inducible transcriptional regulators in target gene promoters. Distinct classes of co-regulators and multiprotein co-regulator complexes are indispensable for the chromatin reorganization that occurs during the hormone-dependent transcriptional control by nuclear receptors (Mellor, 2005; Rosenfeld *et al*, 2006). These complexes seem to modify chromatin configuration in a highly regulated manner by controlling

nucleosomal rearrangement and enzyme-catalysed modifications of histone tails (Workman, 2006; Li *et al*, 2007).

Two main classes of chromatin-modifying complexes that co-regulate nuclear receptors have been well characterized (Rosenfeld *et al*, 2006). One class is a histone-modifying complex (Bannister & Kouzarides, 2005; Klose & Zhang, 2007; Lee & Workman, 2007) and the other class is an ATP-dependent chromatin-remodelling complex (Berger, 2007; Kouzarides, 2007). The latter complex uses ATP hydrolysis to rearrange nucleosomal arrays in a non-covalent manner to facilitate or to prevent the access of nuclear receptors to nucleosomal DNA. These ATP-dependent chromatin-remodelling complexes have been classified into three subfamilies depending on which core catalytic components have DNA-dependent ATPase activity. Brg-1/Brm is a core component of the SWI/SNF-type complex, SNF2h is a component of the ISWI-type complex and Mi2 is a component of the NuRD-type complex (Kitagawa *et al*, 2003; Fujiki *et al*, 2005; de la Serna *et al*, 2006; Denslow & Wade, 2007). The combination of the catalytic ATPase subunits with the components of the complex defines the role of each complex in transcriptional control. The SWI/SNF- and ISWI-type complexes potentially co-activate the function of nuclear receptors (Belandia & Parker, 2003), whereas the NuRD-type complex is assumed to co-repress the function of nuclear receptors, owing to the presence of histone deacetylase (HDAC) in the complex (Denslow & Wade, 2007; Manavathi *et al*, 2007).

Dynamic structural changes of the chromosome are evident during the cell cycle and control global gene regulation (Martinez & Danielsen, 2002; Swedlow & Hirano, 2003; Narayanan *et al*, 2005; Groth *et al*, 2007; Takezawa *et al*, 2007). The role of chromatin-remodelling complexes in the alteration of chromatin structure over much of the cell cycle has been studied (Baumann *et al*, 2007; Groth *et al*, 2007). However, the role of chromatin-remodelling complexes in the cell-cycle-dependent transcriptional function of nuclear receptors during the S–M cell-cycle stages is unknown.

Oestrogen stimulates both cell proliferation and cell differentiation of target cells (Deroo & Korach, 2006), presumably by means of cell-cycle-dependent co-regulator function. Therefore, the transactivation functions of oestrogen receptors (ERs) and also their co-regulators at

¹The Institute of Molecular and Cellular Biosciences, University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan

²ERATO, Japan Science and Technology Agency, Kawaguchi, Saitama 332-0012, Japan

*Corresponding author. Tel: +81 3 5841 8478; Fax: +81 3 5841 8477;

E-mail: uskato@mail.ecc.u-tokyo.ac.jp

Fig 1 | Behaviour of oestrogen receptor- α over the cell cycle. (A) Schematic for cell-cycle synchronization. (B) The E2-induced transactivation functions of ER α in asynchronous (Asy) cells or synchronized cells at G1/S or G2/M phase. Luciferase assays were performed in MCF7 or MDA-MB132 cells transfected with an ERE-TATA luc reporter plasmid (ERE-TATA LucP). (C) Establishment of a HeLa S3 stable transformant expressing Flag-HA-ER α (HeLa-ER α). A pcDNA3 expression vector of ER α , tagged with Flag and HA, was introduced into HeLaS3 cells. Expression levels of ER α in HeLa-ER α cells were compared with those in the MCF7 cell line. A 10 μ g portion of whole extracts was subjected to SDS–polyacrylamide gel electrophoresis for western blotting (WB). (D) Purification schematic of the cell-cycle-dependent interactants of liganded ER α . (E) The interactants of Flag-ER α were separated by SDS–polyacrylamide gel electrophoresis and visualized by silver staining (left panel) and western blotting (WB; right panel). The arrowheads indicate G1/S- or G2/M-phase-specific ER α interactants. E2, 17 β -oestradiol; ER, oestrogen receptor; HA, haemagglutinin; HDAC1, histone deacetylase 1; IP, immunoprecipitation; wt, wild type.

specific cell-cycle stages are an area of considerable interest for further research. Here, the cell-cycle-dependent switching of chromatin-remodelling complexes is described.

RESULTS

Transactivation function of ER α was lowered at G2/M

To investigate whether the transactivation function of activated ER α varies across the cell cycle, we tested the transactivation function of endogenous ER α activated by 17 β -oestradiol (E2) in synchronized MCF7 (ER α -positive) or MDA-MB231 cells (ER α -negative breast carcinoma cell line; Fig 1A; supplementary Fig S1 online). The synchronization of each phase was confirmed by DNA content analysis using flow cytometry, as reported previously (Takezawa *et al*, 2007). In a luciferase assay with an ERE-TATA reporter (a PEST sequence was tagged to luciferase for rapid protein degradation (Hill *et al*, 2001)), the transcriptional activity of ER α seemed to be unaltered at G1/S (Fig 1B, compare lane 4 with lane 2 in asynchronous cells), whereas at G2/M, its activity was significantly lower in MCF7 cells (Fig 1B, compare lane 2 with lane 6). As expected, the ER α activity was undetectable in MDA-MB231 cells.

To explore the molecular basis of cell-cycle-dependent alteration of ER α activity, we generated a HeLa S3 stable transformant cell line (HeLa-ER α) expressing human ER α tagged

with Flag and haemagglutinin epitopes at the amino termini (Fig 1C). The cell-cycle-dependent transcriptional activity of ER α was also confirmed in these cells (supplementary Fig S2A online).

Given that cell-cycle-related proteins such as cyclins are regulated by both their cellular localization and their relative abundance over the cell cycle (Moore *et al*, 2003), we examined the expression levels and localization of ER α in synchronized HeLa cells. The expression levels of ER α were slightly reduced at G1/S and were higher at G2/M (supplementary Fig S2B online, left panel). Immunofluorescence using an ER α antibody showed that ER α was localized mainly in the nucleus and seemed to associate with chromosomes at G2/M, as well as G1/S, regardless of stimulation with E2 (supplementary Fig S2B online, right panel). Certain classes of sequence-specific regulators, however, dissociated from mitotic chromosomes (Martinez-Balbas *et al*, 1995; Nuthall *et al*, 2002; Prasanth *et al*, 2003).

As ER α is localized in chromosomal areas even at G2/M, we suggested that ER α -interacting proteins define the transactivation function of ER α in each cell-cycle phase. To test this, we biochemically purified ER α interactants from synchronized cells in the presence of E2 (Fig 1D). Nuclear extracts of asynchronous or synchronized HeLa stable transformants were subjected to sequential affinity column purification by using an anti-Flag M2 affinity resin column. The interactants were separated by

Fig 2 | Cell-cycle-dependent exchange of chromatin-remodelling complexes. (A) G2/M-phase-specific exchange of chromatin-remodelling complexes associating with ER α . The nuclear extracts were prepared from synchronized MCF7 cells treated with E2 for 1.5 h. ER α interactants were co-immunoprecipitated (IP) with an ER α antibody from the nuclear extracts of MCF7 and then subjected to western blotting (WB). (B) Cell-cycle-dependent recruitment of components of the chromatin-remodelling complex on the *ebag9* and *c-fos* promoters. By using asynchronous (Asy) or synchronized MCF7 cells or MDA-MB231 cells treated with E2 for the indicated time (left panel), the chromatin immunoprecipitation assay was performed with specific antibodies for the tested factors. For PCR, primers were designed to the *ebag9* and *c-fos* promoter regions including the ER α response element site. The right panel shows the results of the chromatin immunoprecipitation assay with the target promoter regions ({ERE}) and ({Distal}) 60 min after E2 treatment. The antibodies against the indicated proteins were used in MCF7 and MDA-MB231 cells (used as a negative control). E2, 17 β -oestradiol; ER, oestrogen receptor; HDAC, histone deacetylase.

SDS-polyacrylamide gel electrophoresis and silver stained. By comparing the interactants of the cells at G1/S versus G2/M, we found that the association of ER α with several interactants was cell-cycle stage dependent (Fig 1E, left panel, arrowheads). As ER α activity was lowered at G2/M, we focused on cell-cycle-stage-specific interactants and identified them by using mass fingerprinting. One of them, Mi2, was a G2/M-phase-specific interactant; Mi2 is a core ATPase component of the NuRD-type chromatin-remodelling complex (Sif, 2004; Denslow & Wade, 2007). Western blotting verified known components of the NuRD complex in the interactants only at G2/M, and detected components of the SWI/SNF complex in asynchronous and G1/S-phase cells (Fig 1E, right panel).

Switch of ER α -bound chromatin-remodelling complexes

From those purification results, we hypothesized that, at G2/M, association of ATP-dependent chromatin-remodelling complexes with ER α leads to suppression of the transactivation function of ER α in the ER α target gene promoters. To test this hypothesis, the association of ER α with the components of the NuRD-type complex was examined by immunoprecipitation of ER α from the nuclear extracts of asynchronous or synchronized MCF7 cells (Fig 2A) and HeLa-ER α cells (Fig 1E, right panel), treated with or without E2. The core components of the NuRD-type complex were detected in the immunoprecipitants of endogenous ER α from the E2-treated MCF7 cells only at G2/M (Fig 2A, lane 6). The core component of the SWI/SNF-type chromatin-remodelling complex, Brg-1, was co-immunoprecipitated with activated ER α in asynchronous cells as reported previously (Belandia et al, 2002) and in synchronized MCF7 cells at G1/S in a ligand-independent manner (Fig 2A). However, the association of Brg-1 with ER α disappeared at G2/M (Fig 2A). Thus, there is a cell-cycle-

dependent switching of the ATP-dependent chromatin-remodelling complexes associated with ER α . Next we examined the recruitment of components of the complex and ER α to oestrogen response elements in the endogenous oestrogen receptor binding site *ebag9* (Tsuchiya et al, 2001) and *c-fos* gene (Ohtake et al, 2003) promoters by chromatin immunoprecipitation analysis of synchronized MCF7, MDA-MB231 and HeLa-ER α cells (Fig 2B; supplementary Fig S2C online). Consistent with co-immunoprecipitation data with ER α from synchronized MCF7 cells at G2/M, the components of the NuRD-type complex were recruited to both gene promoters in an E2-dependent manner (Fig 2B, right panel, lanes 3,6). E2-dependent recruitment of Brg-1 was seen in both an asynchronous and G1/S-phase-specific manner (Fig 2B, left panel). Unexpectedly, at G2/M, ER α anchored to the promoter regions in an E2-independent manner (Fig 2B, left panel).

NuRD complex inhibits ER α transcriptional activity at G2/M

To investigate whether a NuRD-type chromatin-remodelling complex co-represses the function of ER α in cells at G2/M, we examined the cellular colocalizations of Mi2 with E2-bound/unbound ER α by using immunofluorescence with antibodies against Brg-1, Mi2 and ER α (Fig 3A). At G1/S, Brg-1 and Mi2 were distributed primarily in the nucleus and ER α was partly colocalized with Brg-1 but not Mi2 (Fig 3A, left panel). At G2/M, however, Mi2 was detected on the mitotic chromosomes and partly colocalized with ER α only in the presence of E2 (Fig 3A, right panel). Brg-1 was localized in the cytosol apart from the mitotic chromosomes, as reported previously (Muchardt et al, 1996). Thus, ER α seemed to associate with a NuRD-type chromatin-remodelling complex on mitotic chromosomes at G2/M in the presence of E2.

Fig 3 | Co-repressive functions of components of the NuRD-type complex for oestrogen receptor- α at G2/M. (A) Colocalization of liganded ER α with chromatin-remodelling factors at G1/S or G2/M. MCF7 cells were synchronized at G1/S or G2/M and then treated with or without E2 (for 30 min). Brg-1 or Mi2 (green) colocalized with ER α (red) at G1/S or G2/M, respectively. DNA was stained with To-PRO (blue). (B) Abrogation of the G2/M-phase-specific suppression of transactivation function by TSA or siMTA1/2/3. Synchronization at G2/M and transfection were performed as shown in Fig 1A. Short interfering RNA (siRNA) for MTA1/2/3 was transfected into MCF7 or MDA-MB231 cells 36 h before synchronization. TSA treatment was carried out at the same time as E2 treatment. (C) Repression of *ebag9* or *c-fos* expression at G2/M by components of the NuRD-type complex. The expression levels of the indicated genes were measured by quantitative real-time PCR with total RNA extracted from synchronized MCF7 cells at G2/M. E2 and/or TSA treatments were for 6 h. (D) Lowered E2-dependent cell proliferation of MCF7 cells by MTA knockdown. MCF7 cells transfected with siRNAs were cultured with or without E2 for 4 days. A cell proliferation assay was performed by using the Cell-Counting Kit-8 (Dojindo, Kumamoto, Japan). The data are shown as the ratio of E2-dependent proliferation in siMTA cells to siControl cells (siCont). E2, 17 β -oestradiol; ER, oestrogen receptor; TSA, trichostatin A.

Finally, the putative co-repressive function of Mi2 for ER α was tested in MCF7 cells synchronized at G2/M (Fig 3B). The E2-dependent transcriptional activity of ER α was lower at G2/M. Either knockdown of the known components (MTA1/2/3) of the NuRD-type complex (supplementary Fig S2D online) or treatment with an HDAC inhibitor, trichostatin A (TSA), abrogated the G2/M-phase-specific suppression of the transactivation function of ER α (Fig 3B). The MTA family member proteins (MTA1/2/3) seemed to associate physically with ER α in a glutathione S-transferase pull-down assay (supplementary Fig S2E online). This was consistent with the function of a NuRD-type complex at least partly mediating G2/M-phase-specific suppression (Fig 3B). Furthermore, either RNA interference of MTAs or TSA treatment restored the endogenous expression of *ebag9* or *c-fos* at G2/M phase (Fig 3C). Knockdown of MTAs resulted in a decrease in E2-dependent proliferation of MCF7 cells (Yanagisawa et al, 2002; Fig 3D). These findings further support the hypothesis that a NuRD-type complex at G2/M lowers the E2-dependent transcriptional activity of ER α and mediates oestrogen-induced cell proliferation (Mazumdar et al, 2001; Manavathi et al, 2007).

DISCUSSION

Consistent with a previous report (Belandia et al, 2002), ER α associated with components of the SWI/SNF-type chromatin-remodelling

complex, and these complexes were recruited to ER α target gene promoters in asynchronous cells. Similarly, at G1/S, the components were also recruited (Fig 2B). Thus, the SWI/SNF-type complex seems to support the ligand-induced transactivation function of liganded ER α in a cell-cycle-stage-specific manner (Fig 4, left panel).

In this study, we biochemically identified Mi2 as an ER α interactor in the cells at G2/M; associations with the other components of the NuRD-type chromatin-remodelling complex were also detected. Furthermore, recruitment of the core components of the NuRD-type complex to the ER α target gene promoters was seen only at G2/M and not at the other stages (Fig 2). Given that the NuRD-type complex contains HDAC1 (Denslow & Wade, 2007), which, in this study, interacted with ER α at G2/M, the NuRD-type complex might suppress the transcriptional function of ER α at G2/M (Fig 4, right panel). As knockdown of MTAs lowered E2-dependent cell proliferation, this association seems to be significant for the actions of E2. Although we cannot exclude the possibility that activated ER α induces expression of co-repressor genes responsible for cell-cycle regulation during G2/M, it is more likely that the expression of ER α target genes is suppressed through association with the NuRD-type complex. ER α might be transcriptionally silent at G2/M, but it might still contribute to cell-cycle progression by reorganizing

Fig 4 | Schematic representation of the cell-cycle-dependent exchange of chromatin-remodelling complexes. ER α exerts cell-cycle-dependent transcriptional activity by switching of components of the associated ATP-dependent chromatin-remodelling complex. The transcriptional activity of liganded ER α is co-activated by components of the SWI/SNF-type complex at G1/S, whereas it is co-repressed by components of the NuRD-type complex at G2/M. ER, oestrogen receptor; ERE, oestrogen response element; HDAC1, histone deacetylase 1.

chromatin structure through its association with the NuRD-type complex. At present, the molecular basis of cell-cycle-dependent switching of the two ATP-dependent chromatin-remodelling complexes remains to be uncovered. A switching factor seems to associate, at least transiently, with these complexes and is presumably functional at specific cell-cycle stages. The appearance of such a factor might be under cell-cycle regulation, similar to a recently characterized cell-cycle-dependent co-repressor (Ret-CoR) that represses the constitutively transrepressive-type nuclear receptor (Takezawa *et al*, 2007).

METHODS

Cell-cycle analysis. Cells were synchronized 24 h after spreading (for suspension culture, at a cell density of 2×10^6 /ml) by treatment with 2.5 mM thymidine (Wako, Osaka, Japan) at G1/S phase or 10 ng/ml demecolcine (Wako) at G2/M phase under phenol red-free DMEM containing 5% serum. Each treatment was for 24 h except the luciferase assay. Cell synchronization was determined by using flow cytometry, as reported previously (Takezawa *et al*, 2007).

Transfection. Transfection with Lipofectamine Plus (Invitrogen, Carlsbad, CA, USA) was performed according to the manufacturer's protocol, before treatment with synchronization reagents. E2 and/or TSA treatment was 5 h before cell collection.

Purification of the ER α interactants. Nuclear extracts were prepared as described previously (Yanagisawa *et al*, 2002; Kitagawa *et al*, 2003; Ohtake *et al*, 2007; Takezawa *et al*, 2007) from synchronized HeLa-ER α cells treated with E2 for 1.5 h. Extracts (~400 mg) were loaded onto an anti-Flag M2 affinity resin column (approximately 200 μ l bed volume) and were washed extensively with washing buffer containing 300 mM KCl. Bound proteins were eluted from the column by incubation with $5 \times$ volume of Flag peptide (100 μ g/ml; Sigma, St Louis, MO, USA) three times for 5 min. Each sample was applied onto a 2–15% gradient polyacrylamide gel for mass fingerprinting (Ohtake *et al*, 2007; Takezawa *et al*, 2007).

Supplementary information is available at *EMBO reports* online (<http://www.emboreports.org>).

ACKNOWLEDGEMENTS

We thank F. Ohtake, S. Sawatsubashi, R. Fujiki, M.-s. Kim and A. Yokoyama for helpful discussion and plasmids; S. Fujiyama for technical assistance; H. Higuchi, K. Motoi and H. Yamazaki for manuscript preparation; and H. Ito and A. Miyajima for flow cytometric analysis. This work was supported in part by a grant-in-aid for priority areas from the Ministry of Education, Culture, Sports, Science and Technology (to H.K. and S.K.).

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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