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De-repression of RaRF-mediated RAR repression by adenovirus E1A in the nucleolus

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ABSTRACT

Transcriptional activity of the retinoic acid receptor (RAR) is regulated by diverse binding partners, including classical corepressors and coactivators, in response to its ligand retinoic acid (RA). Recently, we identified a novel corepressor of RAR called the retinoic acid resistance factor (RaRF) (manuscript submitted). Here, we report how adenovirus E1A stimulates RAR activity by associating with RaRF. Based on immunoprecipitation (IP) assays, E1A interacts with RaRF through the conserved region 2 (CR2), which is also responsible for pRb binding. The first coiled-coil domain of RaRF was sufficient for this interaction. An in vitro glutathione-S-transferase (GST) pull-down assay was used to confirm the direct interaction between E1A and RaRF. Further fluorescence microscopy indicated that E1A and RaRF were located in the nucleoplasm and nucleolus, respectively. However, RaRF overexpression promoted nucleolar translocation of E1A from the nucleoplasm. Both the RA-dependent interaction of RAR with RaRF and RAR translocation to the nucleolus were disrupted by E1A. RaRF-mediated RAR repression was impaired by wild-type E1A, but not by the RaRF binding-defective E1A mutant. Taken together, our data suggest that E1A is sequestered to the nucleolus by RaRF through a specific interaction, thereby leaving RAR in the nucleoplasm for transcriptional activation.

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1. Introduction

Retinoic acid (RA) plays pleiotropic roles in development, cellular differentiation and proliferation through association with its receptors, retinoic acid receptor (RAR) and retinoid X receptor (RXR), which belong to the nuclear receptor (NR) superfamily [1–3]. As a transcription factor, RAR/RXR binds to the RA response element (RARE) of target genes and modulates their expression by recruiting corepressors or coactivators depending on the presence of the ligand RA [4–6]. In addition to these classic coregulators, another class of corepressors that interact with agonist-bound nuclear receptors including RAR, such as RIP140, LCoR, PRAME, REA, MTA1, NSD1, and COPR1, has been reported recently [7]. Among them, RIP140 and LCoR mediate RAR repression by recruiting HDAC to the RA target genes [8,9].

Additionally, the subnuclear localization of NR with cellular proteins plays a role in NR regulation. These subnuclear structures include PML nuclear bodies, as well as nuclear matrix and foci [10–13]. It has also been reported that some NRs (ER, GR, VDR, ERR, and LXR) are regulated by associating with the nucleolus through either nucleolar sequestration or release and direct interaction with nucleolar proteins [14–20]. At this time, no functional association between RAR and nucleolus has been documented. In addition to the primary site of ribosome biogenesis, the nucleolus serves as a target for various viruses and viral proteins [21,22]. The transcriptional activity of some NRs is directly or indirectly regulated by viral proteins [23]. It is known that adenovirus E1A functions as a coactivator of RAR, likely through a direct interaction with RAR [24,25]. Thus, functional associations among cellular RAR, viral E1A, and the nucleolus in response to RA should be explored.

Recently, we isolated a novel nucleolar protein that interacts with RAR in the presence of RA. After analyzing the functions of this protein in RAR regulation, we named it the retinoic acid resistance factor (RaRF) (manuscript submitted). Additionally, our previous study showed that RaRF interacts with ERRα and represses its transcriptional activity through nucleolar sequestration of ERRα

Abbreviations: RaRF, retinoic acid resistance factor; IP, immunoprecipitation; WB, Western blotting; GST, glutathione S-transferase; β-gal, β-galactosidase; Luc, luciferase; GFP, green fluorescent protein; HcRed, Heteractis crispa red fluorescent protein.

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[19]. In this study, we found that adenovirus E1A interacts with nucleolar RaRF and prevents RaRF-mediated sequestration of RAR to the nucleolus, thereby leaving RAR in the nucleoplasm for transcriptional activation. We also demonstrated a competition between E1A and RA-bound RAR for RaRF binding. Based on these results, the RaRF-E1A association in the nucleolus also plays a role in RAR regulation.

2. Materials and methods

2.1. Cell lines and cell culture

H1299 cells were maintained in RPMI 1640 medium supplemented with 5% heat-inactivated fetal bovine serum (FBS) with antibiotic–antimycotic drugs (all Invitrogen, Carlsbad, CA) in a 5% CO_2 atmosphere at 37 °C. Cells used in the transfection assays were grown in medium containing FBS pretreated with charcoal.

2.2. Cloning and plasmid construction

All cDNAs were constructed according to standard methods and verified by sequencing. Desired genes were created by PCR amplification and subcloned into the following vectors: Flag (2X)-tagged pcDNA3 for overexpression in mammalian cells, pEGFP-C3 and pHcRed-C1 (BD Biosciences, Palo Alto, CA) for GFP and red fluorescent protein fusion expression, respectively, and pGEX4T-1 (GE Healthcare, Piscataway, NJ) for the glutathione-S-transferase (GST)-fusion proteins. Adenovirus 2 E1A mutants (Δ39–64, Δ122–129, and Δ167–189), generated by recombinant PCR, were subcloned into modified pcDNA3 for Flag-tagged expression.

2.3. GST pull-down assays

For the GST pull-down assays, GST-fused RaRF and RARα were expressed in *Escherichia coli* and purified on glutathione–Sepharose beads (Millipore, Billerica, MA) according to the manufacturer's instructions. Either Flag-E1A or Flag-RaRF was translated in vitro in rabbit reticulocyte lysate (Promega, Madison, WI). An approximately equal amount of GST or GST-fusion was mixed with in vitro translated Flag-tagged protein. Bound proteins were visualized by Western blotting (WB) using an anti-Flag antibody (Sigma–Aldrich, St. Louis, MO) or an affinity-purified anti-RaRF antibody (rabbit polyclonal serum raised against recombinant human RaRF).

2.4. Immunoprecipitation (IP) and Western blotting (WB)

H1299 cells either transfected or non-transfected with the indicated plasmids were lysed in TEN-modified buffer [26] supplemented with protease inhibitors (Roche, Basel, Switzerland). Lysates were pre-cleared through incubation with Protein A/G PLUS-agarose beads (Santa Cruz Biotechnology, Santa Cruz, CA) for 30 min at 4 °C. Cleared supernatants were incubated with fresh Protein A/G Plus-agarose beads and the indicated antibodies. Beads were collected by centrifugation and washed three times with RIPA buffer. The immune complexes were released from the beads by boiling and analyzed by WB using the indicated antibodies. The following antibodies were used for IP and WB analyses: anti-RaRF (our study); anti-RARα (sc-551; Santa Cruz Biotechnology); anti-pRb (sc-50; Santa Cruz Biotechnology); anti-Flag M2 (F-3165;

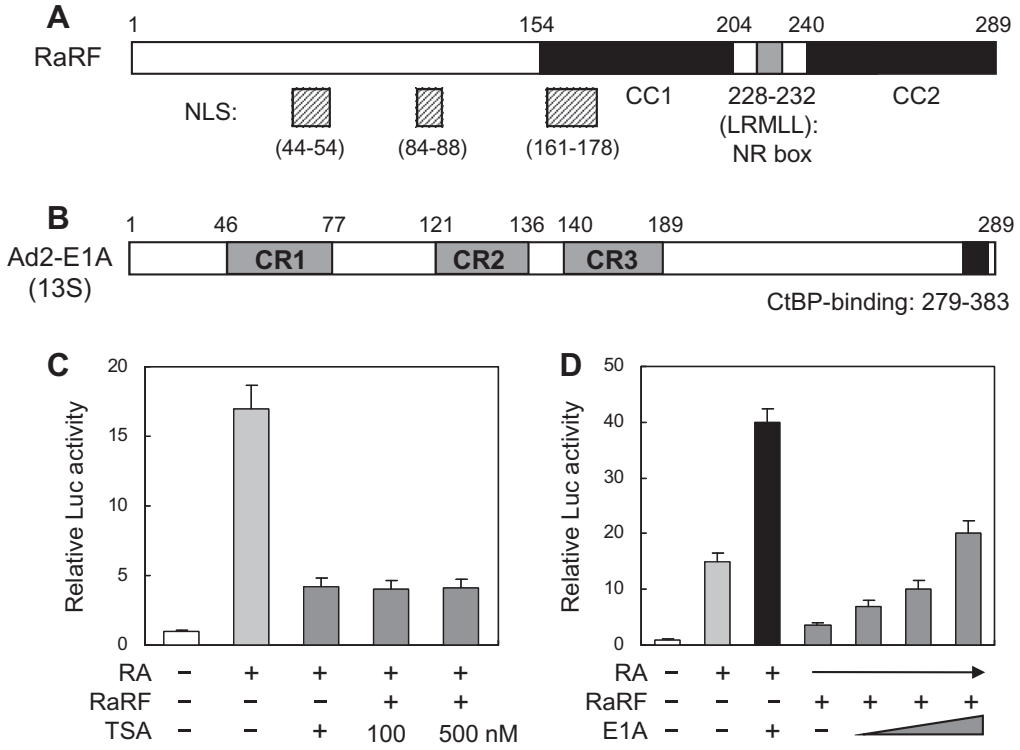

Fig. 1. Derepression of RaRF-mediated RAR repression by E1A. (A) Schematic representation of human hRaRF. Three nuclear localization sequences (NLS), two coiled-coil (CC) domains, and the NR box (LRMLL), responsible for NR binding, are indicated. (B) Schematic representation of 13S adenovirus 2 E1A. The conserved regions (CR1-3) and CtBP binding motif at the C-terminal region are shown. (C) Effect of TSA on the RaRF-mediated RAR repression. H1299 cells were transfected with 0.1 μg of a RARE-tk-luciferase reporter gene, RaRF expression vector (0.5 μg), and increasing concentrations (0, 100, 500 nM) of TSA, a specific inhibitor of HDAC, in the presence of all-trans retinoic acid (RA: 1 μM). (D) Effect of E1A on the RaRF-mediated RAR repression. H1299 cells were transfected with 0.1 μg of a RARE-tk-luciferase reporter gene, RaRF expression vector (0.5 μg), and increasing amounts (0, 0.1, 0.2, and 0.5 μg) of E1A in the presence of 1 μM RA. Extracts from the transfected cells were analyzed in luciferase (Luc) activity assays. Relative Luc activity is shown as the mean ± SD of three independent experiments.

Sigma–Aldrich); and anti-GFP antibody (sc-8334; Santa Cruz Biotechnology).

2.5. Luciferase reporter gene assays

H1299 cells were seeded on 12-well plates and transfected with RARE-tk-luciferase reporter, increasing amounts of RaRF or 13S E1A, and SV40-driven β-galactosidase expression vectors using Lipofectamine (Invitrogen). After transfection for 4 h, cells were fed DMEM containing 5% charcoal-stripped FBS and incubated overnight in the presence of 1 μM all-trans retinoic acid (RA) alone or together with Trichostatin A (TSA), as well as the HDAC inhibitor. Luciferase (Luc) activity was measured as described previously [19]. Relative Luc activity was defined as fold-change relative to the control.

2.6. Fluorescence microscopy

H1299 cells were seeded to coverslips and then transfected with GFP-E1A (and mutant Δ122–129) and HcRed-RaRF (individually or in combination) for 16 h. Cells were then washed with PBS and fixed through incubation with 3.7% formaldehyde in PBS for 10 min. For RARα staining, H1299 cells were treated with vehicle (DMSO) or 1 μM RA for 16 h, washed with PBS, fixed, and permeabilized for 1 h at room temperature in PBS containing 0.5% Triton X-100 and 3% BSA. Cells were then incubated with anti-RARα antibody (Ab41934; Abcam, MA) and AlexaFlur® 568 goat anti-mouse IgG (Invitrogen). After washing, cells were visualized under a fluorescence microscope (DM2500; Leica Microsystems, Wetzlar, Germany). Cell nuclei were stained with Hoechst reagent (Sigma–Aldrich).

2.7. Real-time reverse transcriptase PCR (RT-qPCR)

Total RNA was extracted using TRIzol Reagent (Invitrogen) from H1299 cells that had been transfected with the indicated expression vector, and 3 μg of RNA was reverse-transcribed using Superscript II reverse transcriptase (Invitrogen) and random oligo(dT) primers (New England Biolabs). The reverse transcripts were amplified using an Icycler CFX96 Real-Time PCR detection system (Bio-Rad) with the SYBR Green Realtime Master Mix (Toyobo Co. Ltd, Japan) and the following primer pairs (forward and reverse, respectively): RARβ2 (113-bp fragment), 5′-TTGTGTTCACCTTTGC CAAC-3′ and 5′-CGGTTCCTCAAGGTCCTGG-3′; and GAPDH (120 bp), 5′-CTGCACCACCAACTGCTTAGC-3′ and 5′-GGGCCATCCA CAGTCTTCTGG-3′. The gene expression level in each well was normalized using GAPDH as an internal standard. Fold expression was defined as the fold increase relative to control (minus RA).

3. Results and discussion

3.1. De-repression of RaRF-mediated RAR repression by E1A

By yeast two-hybrid screening using the ligand-binding domain of RARα as bait and a HeLa cell cDNA library as prey, we isolated a clone encoding a novel protein that interacts with RAR in the pres-

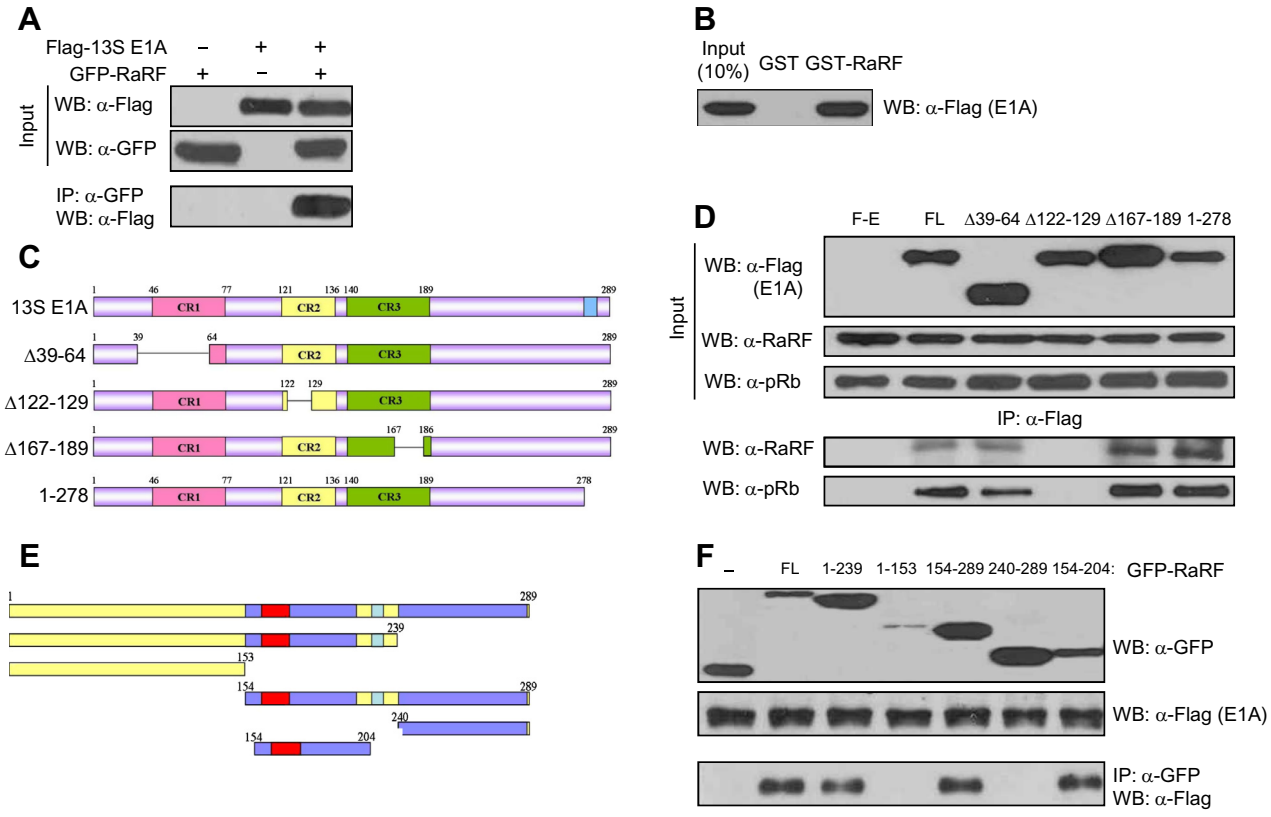

Fig. 2. Mapping of domains required for interaction between RaRF and E1A. (A) Interaction between RaRF and E1A in vivo. H1299 cells were transfected with Flag-13S E1A and/or GFP-RaRF. Cell lysates were prepared and immunoprecipitated with anti-GFP antibody. Precipitated proteins were identified by Western blotting (WB) using an anti-Flag antibody. (B) Direct interaction between RaRF and E1A in vitro. Flag-E1A was translated in vitro and incubated with purified GST or GST-fused RaRF. Bound proteins were visualized by SDS–PAGE and WB using an anti-Flag antibody. (C) Schematic representation of 13S E1A fragments. Various E1A deletions were generated by PCR and subcloned into Flag (2X)-tagged pcDNA3 vector. (D) Mapping the E1A region required for RaRF binding. H1299 cells were transfected with Flag-tagged E1A mutants. IP assays with anti-Flag antibody were examined by WB using anti-RaRF and anti-pRb antibodies. (E) Schematic representation of RaRF fragments. (F) Mapping of the RaRF region responsible for E1A binding. Various RaRF deletions, constructed in pEGFP-C3 vector, were introduced into H1299 cells together with Flag-E1A expression vector. The interactions were detected by IP using anti-GFP antibody and WB using anti-Flag antibody.

ence of the ligand retinoic acid (RA), which also has been deposited in NCBI database named as a coiled-coil domain containing 137 with no functional data (accession number: NM_199287). Based on the results of comprehensive studies including its role in RAR repression (manuscript submitted), we called it retinoic acid resistance factor (hereafter referred to as RaRF). Full-length human RaRF cDNA encodes a protein of 289 amino acids (aa) and possesses three structural features; nuclear localization sequences (NLS), two coiled coils (CC), and an LxxLL motif (or NR box) responsible for NR binding (Supplementary Fig. 1 and Fig. 1A). The key structural features of adenovirus 2 E1A protein are three conserved regions (CRs) and a C-terminal CtBP binding motif (Fig. 1B). To address the mechanism underlying RaRF-mediated RAR repression, we used the HDAC inhibitor TSA. Based on luciferase reporter assays, the RA-induced RAR activity was suppressed by RaRF overexpression, and this repression was not released by TSA treatment, suggesting that HDAC is not involved in this RaRF-mediated RAR repression (Fig. 1C). Second, we observed that the RaRF-repressed RAR activity was relieved upon E1A overexpression, suggestive of a functional correlation between RaRF and E1A (Fig. 1D). The coactivator function of E1A for RAR is consistent with previous reports [24,25].

3.2. Mapping of domains required for interactions

To substantiate a functional correlation between RaRF and E1A, we explored the physical interaction between RaRF and E1A in mammalian cells and in vitro using IP assays and GST pull-down assays, respectively. To probe the interaction in vivo, IP assays were performed using H1299 cells transfected with Flag-13S E1A and GFP-RaRF. IP with an anti-GFP antibody and subsequent WB using an anti-Flag antibody demonstrated an interaction between two proteins (Fig. 2A). We also observed the RaRF interaction with 12S E1A (data not shown). GST pull-down assays were performed using purified GST-fused RaRF and in vitro translated Flag-E1A. Based on WB using an anti-Flag antibody, Flag-E1A bound to glutathione beads containing GST-RaRF, suggesting that RaRF directly binds to adenovirus E1A (Fig. 2B).

To map the regions required for the interaction between E1A and RaRF, we first generated various deletion mutants for E1A, deleting parts of CR1, CR2, CR3, and the CtBP-binding region (Fig. 2C). Subsequent co-IP assays indicated that the CR2 region of E1A, responsible for pRb binding, is also required for the interaction with RaRF (Fig. 2D). To map the RaRF region, we generated five deletion mutants fused to GFP (Fig. 2E) and performed IP with anti-GFP antibody followed by WB analyses using an anti-Flag antibody. As shown in Fig. 2F, the first coiled coil region (amino acids 154–204) of RaRF is necessary and sufficient for the interaction with E1A. Among these RaRF deletions, a fragment containing amino acids 1–153 was marginally expressed. When we separately expressed this fragment, no interaction was observed (data not shown). Taken together, we concluded that the CR2 region of E1A is responsible for the interaction with the first coiled coil region of RaRF. Intriguingly, the NR box of RaRF is not involved in E1A binding, suggesting that RaRF utilizes two different regions for binding both E1A and RA-bound RAR, and may compete with E1A for RAR binding.

3.3. Effect of RaRF on the subnuclear localization of E1A

We previously reported that RaRF is located in the nucleolus and regulates ERRα repression by sequestering it to the nucleolus [19]. Based on these results, we investigated the role of RaRF in the subnuclear localization of E1A using fluorescence microscopy. When analyzing individual expression in H1299 cells, GFP-E1A and HcRed-RaRF were localized to the nucleoplasm and nucleolus, respectively (Fig. 3A). The E1A signal accumulated in the nucleolus upon overexpressing both GFP-E1A and HcRed-RaRF (Fig. 3B).

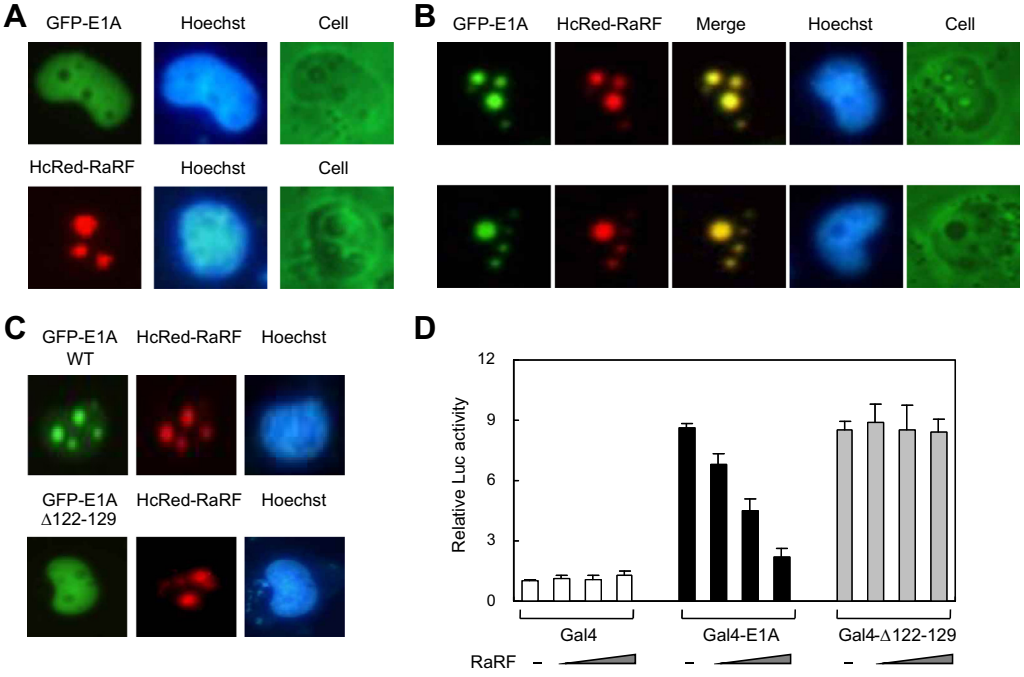

Fig. 3. Effect of RaRF on the subnuclear localization of E1A. (A) Subcellular localization of E1A and RaRF. Fluorescence microscopy was performed using H1299 cells transfected with the GFP-E1A or HcRed-RaRF expression vector. (B) Sequestration of E1A to the nucleolus by RaRF. H1299 cells were co-transfected with GFP-E1A and HcRed-RaRF. (C) Requirement of RaRF binding for nucleolar translocation of E1A. H1299 cells were co-transfected with GFP-E1A wild-type (WT) or GFP-RaRF binding-defective E1A mutant (E1A Δ122–129) and HcRed-RaRF. Hoechst was used to stain chromosomal DNA in the nucleus. (D) Effect of RaRF on the autonomous transcriptional activity of E1A. H1299 cells were transfected with 0.1 μg of Gal4-responsive 17mer-tk-luciferase reporter gene, expression vectors for Gal4-E1A WT and Gal4-E1A Δ122–129 (0.1 μg), and increasing amounts (0, 0.1, 0.2, and 0.5 μg) of RaRF. Relative Luc activity is shown as the mean ± SD of three independent experiments.

Using fluorescence microscopy followed by RaRF coexpression, we observed the nucleoplasmic retention of RaRF binding-defective E1A mutant (E1A Δ122–129), which differed from wild-type E1A (Fig. 3C). Therefore, the interaction between E1A and RaRF is required for the nucleolar translocation of E1A. To support this hypothesis, we determined the effect of RaRF on the transcriptional activity of E1A. When E1A is fused to heterologous Gal4 DBD, E1A showed strong transcriptional activity, which was significantly reduced upon overexpressing RaRF. However, RaRF had no effect on the transcriptional activity of E1A mutant Δ122–1299 (Fig. 3D). Overall, these data suggest that RaRF binding to E1A is critical for the nucleolar translocation and transcriptional inactivation of E1A.

3.4. Reciprocal regulation of RAR by E1A and RaRF

Since adenovirus E1A and RaRF function as a coactivator and corepressor of RAR, respectively, it is possible that they may compete for RAR binding. Prior to addressing this question, we monitored the RA-dependent interaction between RARα and RaRF. Based on co-IP assays, RARα interacts with RaRF in the presence of RA (Fig. 4A). Further GST pull-down assays demonstrated a direct association of RARα with RaRF in vitro (Fig. 4B). Subsequently, we found that the RA-dependent interaction between RARα and RaRF is impaired by E1A (Fig. 4C), suggestive of a competition between RaRF and E1A for RAR binding. To explore the physical competition at the cellular level, we investigated the effect of E1A on the RA- and RaRF-dependent nucleolar translocation of RAR. Upon overexpression of GFP-fused wild-type E1A, RAR accumulated more in the nucleoplasm than the nucleolus in the presence of RA, comparing to control cells without GFP-E1A transfection (Fig. 4D, left panel). However, RAR remained in the nucleolus upon overexpressing RaRF binding-defective E1A mutant, E1A Δ122–129 (Fig. 4D, right panel), suggesting that E1A may protect RAR from nucleolar sequestration by RaRF, leaving RAR in the nucleoplasm. To support this finding, we measured the effect of E1A on the RaRF-mediated RAR repression by RT-qPCR using a primer pair for RARβ2 gene as a RAR target gene. As shown in Fig. 4E, wild-type E1A, but not the E1A mutant Δ122–129, recovered RAR activity repressed by RaRF. Collectively, we propose that adenovirus E1A may increase RAR activity by associating with nucleolar RaRF, competing for RAR, and leaving RAR to the nucleoplasm in response to RA.

In summary, based on the release of RaRF-mediated RAR repression by adenovirus E1A, we investigated the interplay of RaRF, RAR, and E1A. We first demonstrated that RaRF interacts specifically with adenovirus E1A through the coiled-coil region and conserved CR2, respectively. Second, we found that RaRF promotes the nucleolar translocation of E1A from the nucleoplasm. Third, we observed that E1A disrupts the RA-dependent interaction of RAR with RaRF, and RAR translocation to the nucleolus. Finally, we demonstrated that E1A releases RaRF-mediated RAR repression through the association with nucleolar RaRF. Overall, our data suggest that E1A is

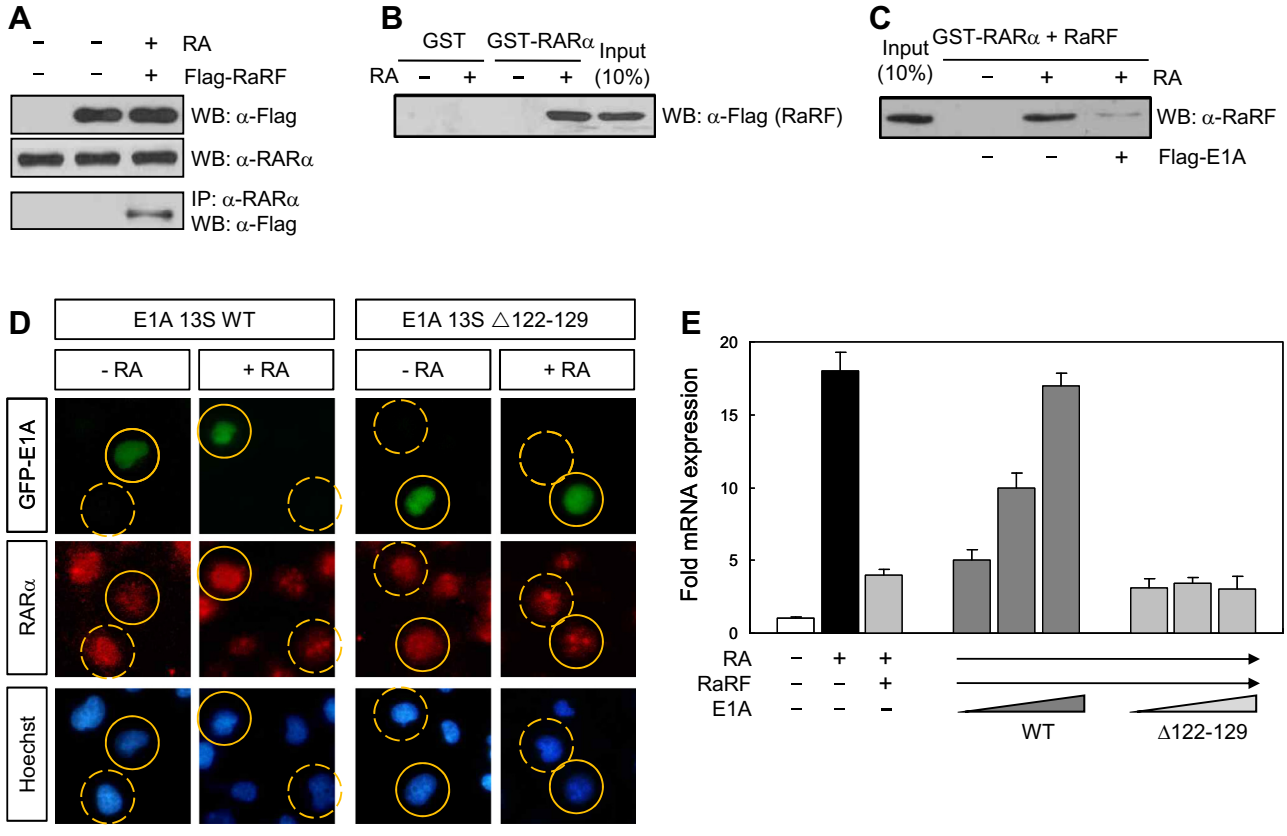

Fig. 4. Reciprocal regulation of RAR by E1A and RaRF. (A) RA-dependent interaction between RAR and RaRF in vivo. H1299 cells were transfected with Flag-RaRF in the presence of 1 μM RA. Interaction was monitored by IP using anti-RARα antibody and WB using anti-Flag antibody. (B) RA-dependent interaction between RAR and RaRF in vitro. Flag-RaRF was translated in vitro and incubated with purified GST or GST-RARα. Bound proteins were visualized by SDS–PAGE and WB using an anti-Flag antibody. (C) Effect of E1A on RAR-RaRF interaction. Flag-E1A synthesized in vitro was added to the reaction shown in B. Subsequently, GST pull-down assays were performed in the presence of RA. (D) Effect of E1A on the RA-dependent nucleolar translocation of RAR. H1299 cells were transfected with Flag-E1A WT (left panel) or Flag-E1A Δ122–129 (right panel) in the presence of 1 μM RA. Closed and dotted circles indicated cells transfected with GFP-E1A and cells without transfection, respectively. The subnuclear localization of RARα was monitored using fluorescence microscopy. (E) Effect of E1A-RaRF interaction on the RaRF-mediated RAR repression. H1299 cells were transfected as described in Fig. 1D, except using an additional E1A mutant Δ122–129. Subsequently, RT-qPCR was performed using a primer pair for RARβ2 gene as a RAR target gene. Fold mRNA expression is shown as the average of three independent experiments.

sequestered to the nucleolus by RaRF through a specific interaction, thereby leaving RAR in the nucleoplasm for transcription activation. We propose that adenovirus E1A plays an important role in RAR regulation by associating with RaRF in the nucleolus.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2014.01.105.

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