Agonists of retinoid X receptors (RXRs), which include the natural 9-cis-retinoic acid and synthetic analogs, are potent inducers of growth arrest and apoptosis in some cancer cells. As such, they are being used in clinical trials for the treatment and prevention of solid tumors and are used to treat cutaneous T cell lymphoma. However, the molecular mechanisms that underlie the anticancer effects of RXR agonists remain unclear. Here, we show that a novel pro-apoptotic pathway that is induced by RXR agonist is negatively regulated by casein kinase 1α (CK1α). CK1α associates with RXR in an agonist-dependent manner and phosphorylates RXR. The ability of an RXR agonist to recruit CK1α to a complex with RXR in cells correlates inversely with its ability to inhibit growth. Remarkably, depletion of CK1α in resistant cells renders them susceptible to RXR agonist-induced growth inhibition and apoptosis. Our study shows that CK1α can promote cell survival by interfering with RXR agonist-induced apoptosis. Inhibition of CK1α may enhance the anti-cancer effects of RXR agonists.

Retinoids (natural retinoic acids and their synthetic derivatives) exert biological effects by regulating gene transcription through two classes of nuclear receptors, the retinoic acid receptors (RARα, -β, and -γ) and the retinoid X receptors (RXRα, -β, and -γ) (1, 2). RXRs are unique among members of the nuclear receptor superfamily in their ability to heterodimerize with several other nuclear receptors. RXR agonists (the natural 9-cis-retinoic acid (3, 4) and its synthetic analogs) are potent inducers of growth arrest and apoptosis in a variety of malignant cells, such as lung and breast carcinomas, lymphomas, and leukemias (5–14). However, despite the ubiquitous expression of RXRs, many malignant cells are insensitive to RXR agonists, and it is, therefore, important to identify cellular mechanisms that mediate this resistance. RXRs associate with various proteins that play important roles in regulating cell survival. Nerve growth factor (NGF) induces the phosphorylation of the orphan nuclear receptor NGFI-B (Nur77 or TR3), which is heterodimerized with RXR, leading to translocation of the NGFI-B-RXR complex out of the nucleus (15). In the presence of apoptotic stimuli, NGFI-B is translocated from the nucleus to mitochondria, causing cytochrome c release and apoptosis (16, 17). RXRα binds insulin-like growth factor-binding protein-3 and is necessary for the induction of apoptosis by insulin-like growth factor-binding protein-3 or RXR agonists in cancer cells (18). We have shown that RXR agonists affect the proliferation of cells by promoting interaction of RXRα with β-catenin and the degradation of both of these molecules (19). The variety of roles that RXRs can play in regulating cell survival leads to the possibility that tumor cells may circumvent RXR-driven apoptosis.

Here we demonstrate the requirement of both RXR agonist and RXR protein for driving the pro-apoptotic and growth inhibitory effects in cells and identify a protective mechanism for the RXR action in which an RXR agonist-induced apoptotic pathway is negatively regulated by the protein kinase casein kinase 1α (CK1α).

**EXPERIMENTAL PROCEDURES**

Retinoids and Other Materials—The following synthetic retinoids were synthesized at Allergan Inc. (Irvine, CA) and were dissolved in Me2SO: RXR agonist (AGN194204), RXR antagonist (AGN195393), and RXR agonist (TTNPB). Monoclonal anti-FLAG (M2) antibody was from Sigma. Monoclonal anti-V5 antibody was from Invitrogen. Polyclonal anti-RXRs (D20), anti-CK1α, and CK1ε antibodies were from Stressgen or Santa Cruz Biotechnology.

Construction of Expression Vectors—Constructions of FLAG-RXR and its mutants (RXR-CDE, RXR-DE, RXR-E, RXR-CA, RXR-AFF2, RXR-CDEAF2, RXR-DEAF2, RXR-EAFF2) (19) and pRARαv5-V5 (20) have been described previously. Full-length human cDNA clones of CK1α were found in the expressed sequence tag data base and purchased from Invitrogen. The coding regions were amplified by PCR and inserted into the expression vector pCDNA3.1.

Cell Culture, Recombinant Protein Expression, and Transactivation Assay—Human embryonic kidney (HEK293), HeLa, CV-1, and Jurkat cells were from ATCC and grown according to ATCC instructions. DT40 cells were maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum. HircRCC cells, the rat fibroblasts that stably express the human insulin receptor and RXR, were kindly provided by Dr. Jyoti Kusari.

The effects of AGN194204 on the growth of cell lines were measured by counting viable cells after treatment with various doses for 3–6 days. Data are presented as a percentage of control (without treatment). Transfection of the cells with expression vectors was performed using LipofectAMINE. The cells were lysed with lysis buffer (30 mM Tris-HCl, pH 7.4, 1% Nonidet P-40, 10% glycerol, 150 mM NaCl, 1 mM EDTA) plus 40 μg/mL NaF, 1 mM sodium orthovanadate, and 0.5 mM phenylmethylsulfonyl fluoride, and 1× protease inhibitors (Roche Applied Science), and lysates were clarified by centrifugation at 12,000 × g.
Fig. 1. An RXR agonist induces growth arrest and apoptosis in DT40 and Jurkat cells that overexpress RXRα. a, increased expression of RXRα in stably transfected DT40 and Jurkat cells. b, RXR dependence of RXR agonist (AGN194204)-induced cell growth inhibition in transfected and parental DT40 and Jurkat cells. Cells (5 × 10⁵ cells/ml) were treated with various doses of AGN19424 for 3 days. Viable cells were counted and are presented as a percentage of cells in control (untreated) cultures. c, AGN194204-induced apoptosis in DT40RXR and JurkatRXR cells. Cells were treated with 10 nm AGN194204 for 3 days and then analyzed by fluorescence-activated cell sorter. DMSO, Me₂SO. d, dose and time dependence of AGN194204 activation of caspase-3 and -9 in DT40RXR cells. Caspase activities are presented as the fold increases relative to control (DT40 cells treated with Me₂SO). e, an RXR antagonist, AGN195393, blocks AGN194204 induced cell growth inhibition and caspase activation. DT40 RXR cells were preincubated with various doses of AGN195393 for 30 min and then treated with 10 nm of AGN194204 for 2 days. Viable cells were counted, and activities of caspase-3 and -9 were measured. Data are means of values obtained from three to four independent experiments.

To establish HEK293, DT40, Jurkat, and HeLa cells that stably express RXRα, the RXR insert was subcloned into pcDNA3.1 (neomycin) or pcDNA3.1 (hygromycin). Individual colonies were selected and expanded from transfected cells in medium that contained 0.6–2 mg/ml Geneticin or 0.3 mg/ml hygromycin B.

For the transactivation assay, CV-1 cells were seeded at a concentration of 1.5 × 10⁵ cells per well in 6-well plates. After overnight culture, cells were transfected as described in the legend to Fig. 4. All transfections contained a β-galactosidase expression vector (Promega) to correct transfection efficiency. The pRXRE-Luc is the report plasmid that contains five tandem repeats of a 35-base pair sequence (DR-1) upstream of thymidine kinase-luciferase. pRARE-Luc contains from the promoter of the mouse keratin promoter that contains five tandem repeats of a 35-base pair sequence (DR-1). pRXRE-Luc and pRARE-Luc were created according to the manufacturer’s protocols.

Small Interfering RNA (siRNA)—siRNA experiments were carried out as described previously (23). The previously described siRNA oligonucleotides for CK1α and CK1ε together with plasmid DNAs were transfected into cells with LipofectAMINE (24). To generate HEK293RXR and Jurkat cells with stable suppression of the expression of CK1ε, the same sequences of double-strand DNA oligonucleotides were inserted into pSiren-RetroQ (BD Biosciences), and lines were created according to the manufacturer’s protocols.

Immunoprecipitation, Immunoblot Analysis, and Flow Cytometric Analysis—Immunoprecipitations were performed at 4 °C by incubating clarified cell extracts with the antibodies (2–5 µg/ml) and protein A/G-agarose beads for 4 h or overnight. Cell extracts or immunoprecipitates were subjected to separation on SDS-PAGE, transferred to a polyvinylidene difluoride membrane, and immunoblotted with specific antibodies. The targeted proteins were detected using enhanced chemiluminescence immunodetection (Amersham Biosciences). DNA content analysis by fluorescence-activated cell sorter was performed on FACScan™ (BD Biosciences) as described (25).

Protein Kinase Assay and Phosphoamino Acid Analysis—Kinase reactions were initiated by adding 2 µl of 50 µl [γ-32P]ATP (10 µCi) to the immunoprecipitated complexes that were suspended in 15 µl of kinase assay buffer (30 mM Tris-HCl, pH 7.4, and 10 mM MgCl₂). Following incubation at 30 °C for 20 min, reactions were terminated by adding 6 µl of 4× SDS sample loading buffer, and mixtures were resolved onto SDS-PAGE. Incorporation of 32P into proteins was determined by autoradiography. Phosphoamino acid analysis was performed on thin layer cellulose plates using the Hunter thin layer electrophoresis system as described (26).

RESULTS AND DISCUSSION

RXR Agonist Induces Growth Inhibition and Apoptosis in Cells that Overexpress RXRα—To examine the mechanism of action of RXR on cell growth and apoptosis, chicken B lymphoma DT40 and human T lymphoma Jurkat cells that stably overexpress the RXRα protein (DT40RXR and Jurkat RXR)
Regulation of RXR Agonist-induced Apoptosis by CK1α

Fig. 2. RXRα associates with a protein kinase in the presence of RXR-specific ligands. a, AGN194204-dependent protein kinase activity in RXRα immunocomplexes from HEK293 cells transiently transfected with the FLAG-RXRα expression vector. Transfected cells were stimulated with vehicle (Me_2SO) (lane −) or 10^{-7} M AGN194204 (lane +) for 15 min. Total cell lysates were immunoprecipitated with anti-FLAG antibody (M2). Aliquots of the immunocomplexes were used for the in vitro kinase assay using [γ-32P]ATP followed by separation on SDS-PAGE. Phosphorylated proteins were detected by autoradiography (right panel). To show the presence of equal amounts of RXR in the immunoprecipitates, additional aliquots of the immunocomplexes were subjected to immunoblotting with polyclonal antibodies (D20) against RXR (left panel). b, dose dependence of the effect of AGN194204 on the recruitment of the protein kinase to a complex with FLAG-RXRα in HEK293 cells transfected with FLAG-RXRα. These cells were stimulated with different doses of AGN194204 for 15 min. Cell lysates were immunoprecipitated with anti-FLAG antibody (M2) in the absence (−) or presence (+) of the same concentration of AGN194204 (as indicated) in the immunoprecipitation buffer, and in vitro kinase assays were performed. c, co-expression of RARα-V5 does not affect recruitment of the protein kinase to the RXR complex. HEK293 cells that stably express FLAG-RXRα were transfected with vector alone or RARα-V5 expression cDNA and then stimulated with the vehicle (Me_2SO), AGN194204, TTPNB, or AGN194204 plus TTPNB as indicated. Anti-FLAG immunoprecipitates prepared from cell lysates were subjected to the in vitro kinase assays (bottom panel). Aliquots of the cell lysates were also immunoblotted to determine the expression levels of FLAG-RXRα (top panel) and RARα-V5 (middle panel).

were generated (Fig. 1a). These cells were dramatically more sensitive than parental cells to growth inhibition by the RXR agonist AGN194204 (Fig. 1b), and AGN194204 induced a significant level of apoptosis in these cells (Fig. 1c) but not in the parental cells (data not shown). Similarly, caspase-3 and -9 were activated by AGN194204 in a dose- and time-dependent manner in DT40RXR cells (Fig. 1d) and not in DT40 cells (data not shown). By contrast, H_2O_2 activated caspase-3 and -9 in both DT40RXR and DT40 cells (data not shown). Agonist-induced growth inhibition and caspase activation in DT40RXR cells both were blocked by the RXR antagonist AGN195393, and this agent had no effect by itself (Fig. 1e). These data show that both the RXR protein and its agonist are required for growth arrest and apoptosis in DT40 and Jurkat cells.

RXRα Associates with a Protein Kinase in the Presence of RXR-specific Ligands—Studies using HEK293 cells revealed a protein kinase activity that co-immunoprecipitated with over-expressed FLAG-RXRα in an agonist-dependent manner and that phosphorylated RXRα and a 160-kDa protein in the same complex (Fig. 2a). Phosphorylation of RXRs in response to the activation of various pathways by extracellular stimuli has been described before (27–29). However, the phosphorylation of RXR and the interaction between a protein kinase and RXR that is induced by RXR agonist have never been reported. Agonist treatment of cells recruited an activated kinase to the RXR complex rather than activating an already associated kinase, because RXR immunocomplexes from untreated HEK293 cells did not show kinase activity when treated subsequently with AGN194204 (data not shown). AGN194204 recruited the kinase in a dose-dependent manner (Fig. 2b). Furthermore, several other RXR agonists (but neither an RXR antagonist nor an RAR agonist (TTPNB)) recruited the kinase activity (data not shown). Also, cotransfection of HEK293 cells with RARα did not alter the specificity or efficacy of the AGN194204 response (Fig. 2c). Thus, the agonist-mediated recruitment of kinase activity is an RXR-driven response that is not mediated by classical RXR-RAR heterodimers.

The RXR-associated Kinase Is Identified as CK1α—Phosphoamino acid analysis demonstrated that the co-immunoprecipitated kinase phosphorylates RXRα primarily on Ser residues (Fig. 3a). The kinase of interest appears to be constitutively active as inhibition or stimulation of several protein kinase cascades had no effect on the RXR-associated kinase activity (data not shown). The A/B domain of human RXRα contains 26 Ser residues, and analysis using a program from Protein Kinase Resources (University of California, San Diego) (30) yielded many potential RXR α kinases. CK1α was of particular interest because of its known constitutive activity (31). Indeed, immunoblot analysis demonstrated the presence of CK1α in the RXR immunoprecipitates from lysates of cells treated with AGN194204 but not in immunoprecipitates from untreated cells (Fig. 3b). By contrast, CK1ε, CK1δ, and CK2 were not detected in any of the immunoprecipitates, although they were clearly present in the cell lysates (data not shown). Several RXR deletion mutants were transfected into HEK293 cells, and the corresponding immunoprecipitates were examined for in vitro kinase activity and for the presence of CK1α (Fig. 3c). All of the immunoprecipitates that had kinase activity contained CK1α. Moreover, an intact ligand-binding region (E domain) is both essential and sufficient for interaction of RXR with CK1α, and only those RXR mutants with intact A/B domains were phosphorylated by the associated CK1α.

To confirm that the RXR-associated kinase is CK1α, siRNA was used to significantly reduce the level of expression of CK1α in HEK293 cells without affecting levels of CK1ε and other proteins (RXRα and β-actin) (Fig. 3d). Reducing the level of CK1α dramatically reduced the RXR-associated kinase activity, whereas a reduction of the expression of CK1ε had no effect (Fig. 3d). Also, recombinant CK1 effectively phosphorylated
RXRα in vitro even in the absence of AGN194204 (data not shown). These data indicate that the RXR agonist functions in vivo to recruit CK1α to the RXR complex.

CK1α Is Not Required for Transcriptional Activities of RXR Homodimers or RXR-RAR Heterodimers—The transcriptional activity of certain hormone nuclear receptors and other transcription factors can be modulated by phosphorylation (32–35). We investigated whether changing the expression levels of CK1α affects the transcriptional activity of RXR. Increased or decreased expression of CK1α had no effect on either RXR agonist-induced transactivation of RXR homodimers or RAR agonist-induced transactivation of RXR-RAR heterodimers (Fig. 4). These data indicate that the direct transcriptional roles of RXR are independent of CK1α. Phosphorylation of RXR by activated c-Jun NH₂-terminal kinases has also been reported to not affect the transcriptional functions of RXR (28).

Correlation of RXR Agonist-induced Growth Arrest and the Presence of CK1α Kinase Activity in RXR Immunoprecipitates—To provide insight into the biological consequence of RXR/CK1α interaction, we examined cell lines that had in-
Fig. 4. CK1α is not required for modulating transactivation activities by RXRα homodimers or RXRα-RXRα heterodimers. a, CV1 cells were cotransfected with pFlag-RXRα (100 ng), reporter plasmid pRXRE-Luc (100 ng), β-galactosidase expression vector (100 ng), and increasing amounts of CK1α expression vector (first and second lanes, 0 ng; third lane, 50 ng; fourth lane, 100 ng; fifth lane, 200 ng), sense strand CK1α, siRNA CK1α, sense strand CK1e, or siRNA CK1ε (2 μg of oligonucleotides for each transfection). The transfected cells were treated with Me2SO (lane −) or AGN194204 (10−7 M) (lane +) for 16 h and then harvested and analyzed for luciferase and β-galactosidase activities. b, CV1 cells were cotransfected with pFlag-RXRα (100 ng), pRAR-V5 (100 ng), reporter plasmid pARE-Luc (100 ng), β-galactosidase expression vector (100 ng), plus sense strand CK1α or siRNA CK1α (12 μg for each transfection). The transfected cells were treated with Me2SO (lane −) or TTNPB (10−7 M) (lane +) for 16 h and then harvested and analyzed for luciferase and β-galactosidase activities. Data are presented as the fold increases of luciferase activities normalized to β-galactosidase activity that served as an internal control for transfection efficiency and are the mean of three independent experiments with triplicates for each. c, CK1α was effectively depleted in CV-1 cells by siRNA CK1α as judged by immunoblotting the total cell lysates with anti-CK1α.

creased RXR expression. In some instances, these had enhanced sensitivity to RXR agonist-induced growth inhibition and apoptosis, whereas other RXR overexpressing cells were resistant (Fig. 5a). We investigated whether the association of RXR with CK1α governs RXR agonist-induced growth inhibition in these cell lines. RXR/CK1α interaction was measured using the in vitro kinase assay and by immunoblot analysis. As shown in Fig. 5c, RXR immunoprecipitates from the cells that are insensitive to inhibition of growth by RXR agonist (HEK293RXR and HeLaRXR) had kinase activity. Kinase activity was not immunoprecipitated with RXR in the AGN194204-sensitive cells (DT40RXR, JurkatRXR, and HircRXR) even though these cells expressed CK1α (Fig. 5b). These results imply that the RXR complex that mediates the growth inhibitory effects of RXR agonists is inactive in the presence of CK1α.

Reducing the Level of CK1α in Cells Increases Efficacy of RXR Agonist-induced Cell Growth Inhibition and Apoptosis—We tested the possibility that RXR agonist-resistant cells may be rendered sensitive to growth inhibition by down-regulating the expression of CK1α. siRNA was used to reduce the expression of CK1α in HEK293RXR cells (Fig. 6a, left panel), and this led to a concomitant reduction in RXR-associated kinase activity (Fig. 6a, middle panel). Importantly, the cells with decreased levels of CK1α were then sensitive to growth inhibition by AGN194204 (Fig. 6a, right panel). Similarly, native Jurkat cells that do not overexpress RXR are insensitive to growth inhibition by AGN194204 and became sensitive when CK1α levels were decreased (Fig. 6b, first two panels). In addition, AGN194204 treatment of these CK1α-suppressed Jurkat cells resulted in the activation of caspases and the induction of apoptosis (Fig. 6b, last two panels).

RXRs play key roles in regulation of gene transcription by forming heterodimers with many other ligand-activated nuclear receptors. There have also been suggestions that RXRs have novel physiological functions besides the regulation of gene transcription (15–19). Casein kinase 1 was one of the first protein kinases discovered, yet its function and regulation remain poorly understood. CK1 represents a family of second messenger-independent Ser/Thr protein kinases. In mammals, CK1α, β, γ, δ, and ε have been identified and cloned, and each isoform appears to have different roles. CK1α is ubiquitously expressed, appears to be constitutively active (31), and has recently been identified as an essential component of the complex that controls β-catenin phosphorylation and degradation. Depletion of CK1α causes β-catenin protein accumulation in a manner similar to that caused by the lack of the functional tumor suppressor protein adenomatous polyposis coli (24).

We have clearly shown that RXR interacts in vivo with CK1α and that this interaction interferes with RXR agonist-driven...
inhibition of cell growth and induction of apoptosis. Interaction of CK1α with RXR does not affect the activity of RXR in regulation of gene transcription. Recently, Tanaka et al. (36) reported that in RXR agonist-unresponsive MDA-MB-231 cells, RXRα is located in interchromatin granule clusters and that forced nucleoplasmic expression of RXR renders these cells sensitive to induction of apoptosis by RXR agonist. These findings suggest that altered localization of RXRα coincides with loss of RXR agonist responsiveness. Interestingly, CK1α is also found in a multiprotein complex in interchromatin granule clusters (31, 37). Therefore, it is possible that RXR agonist-mediated apoptosis is regulated by a process of sequestration of phosphorylated RXR:CK1α into interchromatin granule clusters. It would be very interesting to investigate whether the phosphorylated RXR:CK1α complex is sequestered in interchromatin granule clusters. The exact molecular mechanisms by which RXR:CK1α interaction regulates cell growth and apoptosis are interesting subjects for future study.

Importantly, our findings add new insights into the novel mechanisms of RXR action and are of significant therapeutic importance in that inhibiting CK1α function can enhance the anti-cancer activities of RXR agonists.

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Casein Kinase 1α Interacts with Retinoid X Receptor and Interferes with Agonist-induced Apoptosis

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