We have previously demonstrated that up-regulation of STAT1 protein by all-trans-retinoic acid (RA) in interferon (IFN)-unresponsive cells permits growth inhibition by IFNs. Here, we show that the promoter of STAT1 directly responds to retinoic acid treatment. Sequence and functional analysis of the murine STAT1 promoter have identified a direct repeat motif that serves as a retinoic acid response element. Mutagenesis of this element resulted in a loss of response to RA. This element is activated by RA receptors α, β, and γ. In vivo, RA receptor β and retinoid X receptor α preferentially interacted with this element. Thus, these data define a molecular basis for the synergy between IFNs and retinoids in tumor growth inhibition.

Interferons (IFNs)1 regulate cellular antiviral, antitumoral, and immunological responses via specific gene induction (1). Ligand-bound IFN receptors induce the tyrosine phosphorylation of cytoplasmic STAT (signal transducers and activators of transcription) proteins employing Janus kinases (JAKs). Activated STATs then migrate to the nucleus and bind to specific response elements to induce the expression of IFN-stimulated genes (2). IFNs-α/β induce cellular genes via an IFN-stimulated response element, which binds several transacting factors of which ISGF-3 is the primary regulator (2). This factor consists of a 48-kDa DNA binding protein (ISGF3-γ) and three tyrosine phosphorylated proteins, STAT1α, STAT1β, and STAT2 (2). Two Janus kinases, tyk2 and JAK1, are essential for the activation of STATs in response to IFN-α/β. Ligand-stimulated IFN-γ receptor, employing Janus kinases JAK1 and JAK2, induces phosphorylation of STAT1 but not STAT2. STAT1 then migrates to nucleus, binds to γ-IFN-activated site, and induces gene expression (2). Cell mutants lacking STAT1 and JAK1 fail to respond to IFN-α/β and IFN-γ (3, 4). Thus, JAK1 and STAT1 are common signaling components for all IFNs.

All-trans-retinoic acid (RA), a potent biological response modifying metabolite of vitamin A, induces cellular gene expression utilizing nuclear receptors that also act as transcription factors (5). These receptors bind to retinoid acid response elements (RARE) to activate gene transcription. Retinoic acid receptors (RARs) and retinoid X receptors (RXRs) are the two major mediators of retinoid actions (5). Three major forms of RARs and RXRs, α, β, and γ, and the corresponding subtypes are known. Their expression is variable depending on cell type, organ, and status of cell differentiation. The preferred ligands for RAR and RXRs are RA and 9-cis-RA respectively, although RA at high concentrations activates RXR (5). RXRs form heteromeric complexes with RARs, bind to RAREs, and stimulate specific gene transcription (5). Heteromeric complexes of RXRs formed with other nuclear receptors such as those of thyroid hormone (TR), vitamin D3, and peroxisome proliferator activator also induce ligand-specific gene expression (6–10). Thus, RXRs are important cofactors for nuclear receptor-mediated gene regulation.

Several studies have indicated that IFN and RA in combination produce additive or synergistic antitumoral effects in vivo and in vitro (11). It is not known how these two disparate ligands and their corresponding signal transduction systems cross-talk in the mediation of antitumoral activity. We have shown previously that these effects are in part mediated by an increase in the level of IFN-stimulated gene factors upon RA treatment, thus allowing their functional activation by IFN (12). In particular, STAT-1 protein is induced in IFN-resistant tumor cells treated with RA (13). In the present investigation, we have identified the mechanism by which RA up-regulates the expression of STAT1.

MATERIALS AND METHODS

Cell Culture and Reagents—All cell lines were cultured in media supplemented with charcoal-treated, dialyzed fetal bovine serum.Murine embryonic tumor cell lines F9 and P19 and monkey kidney cell line COS-7 were cultured in Dulbecco’s modified Eagle’s medium. Human RARs β1 and γ and mouse RXR β expression vectors were provided by Pierre Chambon, IGBMC, France. Mouse RXRB expression vector was described previously (8). Human thyroid hormone receptor beta (TRβ) regulated by RSV-LTR was provided by Edwards Park, University of Tennessee. Rabbit anti-STAT1 antibodies were provided by Chris Schindler, Columbia University. Mouse anti-JAK-1 antibody was from Transduction Laboratories. Purified baculovirus-expressed RARβ and RXRβ, mouse monoclonal antibody against RXRβ (H2R1HB), and rabbit anti-RARβ antibody were gifts from Keiko Ozato, National Institutes of Health. Rabbit anti RARs, RARγ, and RXRs antibodies were purchased from Santa Cruz Biotechnology. All these antibodies cross-reacted with cognate proteins from mouse and human sources. Mouse IFN-γ was from Boehringer Mannheim. Purest preparations of all-trans-retinoic acid (99%), 9-cis-retinoic acid (high performance liquid chromatography pure) and 3,3’5 triido-t-thyronine (T3, or thyroid hormone) were purchased from Sigma and were reconstituted in ethanol. The oligonucleotides used in this study were shown in Table I. These were used for electrophoretic mobility shift assays (EMSA) and cloning

1 The abbreviations used are: IFN, interferon; DR-5, direct repeat element with 5 nucleotide spacing; EMSA, electrophoretic mobility shift assay; JAK, Janus tyrosine kinase; RA, all-trans-retinoic acid; RAR, retinoic acid response element; RXR, retinoid X receptor; STAT, signal transducing activator of transcription; pIRES, palindromic IFN response element; TR, thyroid hormone receptor; TK, thymidine kinase; kb, kilobase(s); bp, base pair(s); ISG, IFN-stimulated gene; LTR, long terminal repeat; MHC, major histocompatibility complex.

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into TK-luciferase. Probes for EMSA were prepared by filling in the ends with Klenow fragment in the presence of [α-32P]dCTP or by end labeling with [γ-32P]ATP. For site-directed mutagenesis, 5′-GATAATCAGGTTGATAA-3′ (RM1) and 5′-TAGAATCAGGTTGATAA-3′ (RM3) oligos were used.

**Gene Expression Analyses**—Northern blot, run off transcription, and Western blot analyses were performed as described elsewhere (12). Cells (2 × 10⁵) were electrophoresed with 5 µg of luciferase reporter construct, 0.5 µg of expression vectors of retinoid receptors, and 2 µg of β-actin-β-galactosidase plasmid, and luciferase assays were performed (14). β-Galactosidase assays were performed to normalize for variations in transfection efficiencies. Stable transfection of F9 cells with STAT1 cDNA, cloned in mammalian expression pCXN2, was performed as described previously (13). This plasmid also carried a G418 resistance marker for selection in mammalian cells. The resultant drug-resistant colonies (~150) were pooled and used in the experiments. COS-7 cell extracts, expressing individual retinoid receptors for EMSA, were prepared as described (15).

An adult BALB/c mouse liver genomic library (Clontech) in EMBL3 phage vector (5 × 10⁶ plaque-forming units) was screened with a 32P-labeled human STAT1 cDNA (16), and 6 clones were identified. All these clones contained the same 18-kb insert as analyzed by restriction digestion and Southern blotting. A 4.5-kb XhoI fragment was detected when probed with a 270-bp fragment representing the 5′ end of the cDNA. This fragment was cloned into pGL3-basic vector (Promega). pGL3-TK was constructed by excising the TK promoter (199 bp) from pTK-CAT vector and cloning into the pGL3-basic vector. Deletion and point mutations were constructed (17) using a polymerase chain reaction-based kit (Stratagene) and a reporter construct VKL-7 as template. Deletion and point mutations were constructed (17) using a polymerase chain reaction-based kit (Stratagene) and a reporter construct VKL-7 as template. All constructs were confirmed by sequencing.

**RESULTS**

**Retinoic Acid Modulates the IFN Stimulation of Transcription Factors in Embryonic Tumor Cells**—We have previously shown that treatment of F9 embryonal carcinoma cells with RA enhances the ISG transcription (12) due to an activation of ISGF-3 in dF9 (RA-differentiated) but not in undifferentiated F9 cells (Fig. 1, lanes 1 and 2). In F9 transfectants that carried the expression vector pcXN2 alone (lanes 1 and 2), IFN-γ failed to induce STAT1 binding to pIRE (lane 2). However, IFN-γ robustly activated STAT1 in cells transfected with the cDNA (Fig. 2A, lane 4). To further prove that the transfected STAT1 was functional, luciferase reporter assays were performed. As anticipated, no induction of luciferase activity was detected in the F9 cells that stably expressed the pcXN2 vector alone (lanes 1 and 2). Thus, F9 cells possessed the necessary receptors and protein kinases for the activation of IFN-γ-initiated JAK-STAT pathway, except STAT1. Over expression of STAT1 or treatment with RA restored IFN-γ responses in these cells. Consistent with this, JAK1 levels were not affected by RA-treatment in an immunoprecipitation assay (Fig. 2C). Western blot analyses (Fig. 2D) revealed no detectable STAT1 protein in undifferentiated F9 cells. However, it was strongly induced by RA-treatment (lanes 2 and 3). Thus, STAT1 appeared to be a target of retinoid-mediated regulation.

**RA Induces the Expression of STAT1 Gene**—Since STAT1 protein was induced by RA, we next determined whether such enhancement was due to an induction of STAT1 gene expression. Northern blot analysis (Fig. 3A) did not reveal detectable STAT1 mRNA (lanes 1 and 2) in untreated F9 cells or cells that received ethanol (the solvent in which RA was treated). Treatment of cells with 1 and 10 µM RA strongly induced the mRNAs of STAT1α and -β (lanes 3 and 4). The probe detected both the mRNAs because they were derived from the same gene (16). All the cells expressed similar levels of β-actin mRNA irrespective of treatments. To examine whether the induction of STAT1 by RA was due to de novo transcription, nuclear run off transcription assays (Fig. 3B) were performed. No detecta-
stable transfection of STAT1 cDNA restored IFN-sensitivity in F9 cells.

mRNA (30 μg) were indicated with (16) as a probe. A 1.85-kb mouse genomic clone was isolated using human STAT1 cDNA

6 g) were used in EMSA. Position of STAT1 complex is indicated. B, functional activity of the transfected STAT1 gene product. Cells used in

ble transcription of STAT1 was observed in untreated cells. However, RA induced the transcription by 24 h, which increased with prolonged treatment (48 h). All these cells expressed normal levels of glyceraldehyde-3-phosphate dehydrogenase transcripts, indicating that lack of STAT1 gene expression in F9 cells was not due to a global transcriptional blockade. Further, RA did not induce the expression of STAT2 mRNA (Fig. 3C). Induction of STAT1 mRNA by RA was observed in an IFN-unresponsive MCF-7 breast carcinoma cell line and an acute promyelocytic leukemia cell line (data not shown). Thus, STAT1 mRNA is up-regulated by RA in multiple cell types.

Identification of a RARE in STAT1 Promoter—To examine whether the STAT1 promoter was directly regulated by RA, a mouse genomic clone was isolated using human STAT1 cDNA (16) as a probe. A 1.85-kb HindIII fragment, containing 700 bp of upstream sequence, the first exon and intron (1.15 kb), was cloned into pGL-3 basic vector. The resultant reporter construct, VKL-2, responded to RA in COS-7 cells upon cotransfection with RARα (Fig. 4A). Since COS-7 cells lacked these nuclear receptors, the induction was due to the cotransfected receptor. Deletion of a 965-bp sequence consisting of first exon and a substantial portion of intron from VKL-2 (construct VKL-4) had no effect on RA inducibility (Fig. 4B). Following treatment with RA (1 μM), a strong up-regulation of luciferase activity was noted in cells that were cotransfected with RARα. Furthermore, two other nuclear receptors, RXRβ and TRβ, along with their ligands 9-cis-RA and T3 had no effect on gene expression (Fig. 4B). Two other constructs, VKL-6 and VKL-7, which contained up to −950- and −670-bp upstream elements of STAT1 promoter, respectively, were also strongly induced by RA in these cells (Fig. 4A). Thus, the cloned fragments contained necessary elements for a specific induction of STAT1 promoter by RA. Primer extension analyses identified the start site at 12 nucleotides upstream of ATG codon (data not presented). We then tested the effects of other members of the RAR family on STAT1 promoter. COS-7 cells were transfected with RARα, -β, and -γ expression vectors along with luciferase reporter VKL-4 (Fig. 4C). Although all the members of the RAR family induced the reporter gene expression, RARβ was a slightly better activator than the others. Luciferase gene did not express upon transfection of VKL-7 in F9 cells. RA treatment for 24 h caused a 12-fold increase in luciferase activity (Fig. 4D). It was further enhanced with longer treatment (48 h).

Sequence analysis of the promoter (Fig. 5) revealed a direct repeat element, at −467 bp, that could potentially serve as RARE. More significantly, this sequence had closer resemblance to H2RII of the MHC class I gene (8), than to the other RAREs. Unlike the previously described retinoid response elements (5), the STAT1-RARE had a near perfect repeat sequence of GGTCAGGTTGA with no spacer nucleotides (Fig. 5). Further, GGG residues were found in both the half-sites in place of AGG of most retinoid responsive half-sites. At −122 and −338 positions, TATA-like elements were present.

Mutational Analysis of the Retinoic Acid Response Element—Since RA stimulated STAT1 and sequence analysis identified a RARE in the promoter, we next examined whether this element alone was sufficient for RA inducibility. Using a PCR-based approach (17), we constructed a deletion mutant that lacked the direct repeat element in VKL-7 reporter. The wild-type construct (VKL-7) but not the mutant (ΔM) responded to RA in COS-7 cells when cotransfected with RARβ (Fig. 6A, bars 2–5).
Using the same PCR approach, we generated point mutants with RM1 and RM2 oligonucleotides in the native promoter (VKL-7). In RM1, GGG residues of the left half-site were replaced with AAA. RM3 bore mutations in the central G residue of the GGG bases of both the half-sites (see "Materials and Methods"). Transfection of these two point mutants into COS-7 cells along with RARβ did not significantly induce the promoter (Fig. 6B, bars 3–6). Thus, mutations in the GGG residues of either half-site abolished RA inducibility.

We next determined whether fusion of the synthetic STAT1-RARE conferred RA inducibility to a neutral promoter driving the expression of luciferase gene. COS-7 cells were transfected with the reporter constructs bearing either a wild-type or a mutant response element upstream of herpes simplex viral TK gene promoter, along with RARs, and were treated with RA. Insertion of two copies of a wild-type element (RW2X) produced a slightly higher activity than the one with a single copy (RW1X) in COS-7 cells (Fig. 6A, compare bar 4 with 6). Mutants that lacked the GGG residues in either half-site were unresponsive to RA (bars 8, 10, and 12). This observation was consistent with the data obtained with the same point mutants in the context of native promoter (Fig. 6B). Furthermore, mutation of a central G residue of both the half-sites (RM3) caused a similar loss of response. Therefore, the direct repeat element of STAT1 promoter was sufficient for induction by RA.

**Binding of Transcriptional Factors to the RA Response Element**—To identify the transcription factors that mediate these effects, we performed EMSA. In these experiments, untreated and RA-treated F9 nuclear extracts were incubated with a 32P-labeled synthetic RW (STAT1-RARE) to detect specific DNA binding (6). A slow mobility complex, A, appeared in RA-treated F9 cells (Fig. 7A, lanes 2–5) whose binding was enhanced with prolonged RA treatment. Binding of this complex to RW was eliminated upon preincubation of these nuclear extracts with the wild type (RW) oligonucleotide (lanes 6–8) but not by a mutant (RM4) oligonucleotide (lanes 9–11). Mutant oligos RM1, RM2, and RM3 also failed to compete out the binding (data not presented). Formation of complex-A was inhibited by pre-incubation of extracts with polyclonal antibodies specific for RARβ and RXRα (lanes 12 and 13) but not by those raised against RARα, RARγ, and RXRβ (lanes 14–16). Binding of this complex to RW was not eliminated by pre-incubation of cell extracts with DR-5 (19) and H2RII oligos at 5 or 25 × concentrations (Fig. 7B, lanes 2, 3, 6, and 7). However, at high concentrations (100 and 500 ×), DR-5 competed with the labeled RW (lanes 4 and 5), indicating a preferential formation of complex-A with the latter. H2RII failed to compete out the RW complex-A (lanes 6–9). RW also formed another complex, B, with untreated F9 cell extracts whose binding disappeared with RA treatment of cells (Fig. 7A, see lanes 1–3). RW binding factors in F9 cells exhibited interesting properties compared with those that bound to consensus RARE and DR-5. RW binding of complex-A was RA inducible (Fig. 7C, lanes 2–5), while DR-5 binding factors were constitutive (Fig. 7C, lanes 6–9). Formation of complex-A was not detected with untreated F9 cell extracts (Fig. 7A, lane 1). The DR-5 binding factors from untreated F9 cell extracts (lane 6) were recognized by antibodies against RARα and RARγ (data not presented). Under the same conditions, complexes were barely detectable with H2RII probe (lanes 10–13). Interestingly, complex-B was formed only with RW upon incubation with untreated F9 extracts but not with DR-5 or H2RII. Binding of this complex was eliminated upon preincubation of cell extracts with RW but not RM3, RM4, DR-5, or H2RII oligos (data not presented). Furthermore, complex-B was not recognized by antibodies specific for RARα, RARβ, RARγ, RXRα, or RXRβ (Fig. 7D). Thus, it...
and construct used in bars 3
response element. COS-7 cells were transfected and treated as described in Fig. 4. Bars 1 mutant bearing the element in RM3 oligo. C
Bars 1 mutants of RARE. STAT1 promoter. VKL-7 reporter vector was cotransfected with expression vectors for either RARβ or RXRα or the combination into COS-7 cells. RARβ, but not RXRα, alone induced gene expression (Fig. 8A, bars 2 and 3) upon RA (1 \( \mu M \)) treatment. However, the combination of these two receptors caused stronger expression (bar 4). To further test whether such induction was a result of binding of these receptors to RW, EMSA was performed with whole cell extracts of COS-7 cells transfected with the individual expression vectors. RARβ bound to RW, which was further enhanced when combined with extracts from RXRα expressing cells. (See Fig. 8B, lanes 3 and 5). RXRα alone bound very weakly to this element (lane 4). Pre-incubation of these extracts with cognate antibodies eliminated the binding of these complexes (data not presented). Interestingly, purified RARβ (expressed in a baculovirus vector) alone failed to form such a complex with RW, although it bound to DR-5 efficiently (data not shown). These data suggest that additional cellular factors may be necessary for the formation of RW binding complexes.

**DISCUSSION**

Dependence of IFN-γ responses in F9 cells on RA-treatment suggests two possibilities. RA may enrich the levels or activities of IFN-receptor components and the associated Janus kinases or of IFN-regulated transcription factors. Since transfection of STAT1 alone restores the IFN-γ-inducible gene expression, modulation of IFN responses by RA may not involve an enhancement of JAKs or other receptor components. Consistent with this, RA did not increase IFN receptors density or avidity in unresponsive cells (20). Furthermore, RA did not induce the tyrosine phosphorylation of JAK1 (data not shown). Thus, RA modulation of IFN responses occurs at the level of STAT1 gene expression in these cells.

Northern and nuclear run off transcription studies have shown that RA specifically induces transcription of STAT1 gene (Fig. 3, A-C). RA does not affect STAT2 expression. Further, STAT2 promoter does not possess a RARE (21). Analysis of the STAT1 promoter (Figs. 4–6) identified a RARE. This element has several unique properties: i) It is a direct repeat element with no spacing between the repeats. ii) It is not like elements and ATG codon are shown in italics. Transcriptional start site is indicated with +1 sign.

![Fig. 5. Nucleotide sequence of murine STAT1 gene promoter.](http://www.jbc.org/)

Retinoic acid response element is highlighted and underlined. TATA-like elements and ATG codon are shown in italics. Transcriptional start site is indicated with +1 sign.

![Fig. 6. Mutational analysis of the STAT1 promoter.](http://www.jbc.org/)

Conditions of transfection analysis were as described under Fig. 4. A, effect of deletion of a direct repeat element. WT represents VKL-7, and ΔM represents the same construct with a deletion of the RARE (Fig. 5). B, induction of point mutants of RARE. Bars 1 and 2, wild-type plasmid (VKL-7); bars 3 and 4, mutant bearing the element shown in RM1 oligo; and bars 3 and 6, mutant bearing the element in RM3 oligo. C, synthetic response elements from STAT1 (see Table I) confer RA inducibility to TK promoter-driven luciferase reporter. Bars 1 and 2, TK-luciferase plasmid; bars 3–6, wild-type element (RW) cloned upstream of TK promoter except that the construct used in bars 3 and 4 possessed two tandem copies (RW2X), and the one in bars 5 and 6 contained a single copy (RW1X), respectively; bars 7 and 8, RM1 element; bars 9 and 10, RM2 element; and bars 11 and 12, RM3 element. All these constructs contained a single copy of the mutant response element. COS-7 cells were transfected and treated as described in Fig. 4.
(19) or H2RII (8). The STAT1-RARE requires GGG residues in both the half sites, since mutagenesis of these in any half site of the direct repeat element abrogates the RA responses. Its specificity for RARβ and RXRα is quite intriguing because a similar oligonucleotide with 5-bp spacing between the direct repeat elements (RW-DR5) has not formed the same complex (data not presented). These data indicate the importance of close apposition of the repeat elements for specific binding. Although the direct repeat elements with two or five nucleotide spacing have been shown to respond to RA in several genes (5), the gene for human medium chain acyl coenzyme A dehydrogenase has a unique element with eight nucleotide spacing and another one with no spacing (22). The human oxytocin and mouse laminin B1 gene promoters also contain RA responsive elements with 13 and 47 nucleotide spacing (23–25). The STAT1-RARE appears to belong to this class of unique nuclear receptor response elements where spacing between the half-sites is not a primary determinant of retinoid responsiveness (26, 27).

Preferential binding of RARβ and RXRα heteromers to STAT1-RARE may permit a selective regulation of STAT1 gene by RA. This notion is supported by the observation that despite the abundance of DR-5 binding factors in F9 cells, they did not bind to RW (Fig. 7C). The DR-5 binding factors were recognized by specific antibodies against RARα and RARγ (data not presented). The observations that regulation of transcription by nuclear receptors is dependent on the promoter context, response element orientation, and DNA binding domain interface (19, 28–35) are also suggestive of such preferential interactions. The facts that RARβ gene is inducible by RA (36, 37) and that the binding of RARβ to RW is increased upon exposure of F9 cells to RA also support the notion of preferential binding of RARβRXRα to STAT1-RARE. Consistent with these observations, cotransfection and EMSA assays with individual receptors in COS-7 cells resulted in a stronger induction of gene expression (Fig. 8). Since whole cell extracts containing RARβ, but not the purified RARγ, form specific complexes with RW, it appears that additional cellular factors are necessary for the binding to occur. Given the unique organization of the repeat elements in STAT1-RARE, such factors may play a crucial role in the formation of high affinity complexes. Further investigation is necessary to address these issues. Lastly, the F9 cellular factor (complex-B in Fig. 7A) that binds to STAT1-RARE, may be a negative regulator since it disappears with RA-treatment.
Fig. 8. Induction of STAT1 promoter by RARβ/RXRα combination. A, reporter gene expression. Cell transfection, RA-treatment, and luciferase assays were performed as described in Fig. 4. COS-7 cells were electroporated with VKL-7 reporter (5 μg) and the indicated effector plasmids (0.5 μg). The total amount of DNA transfected was normalized with pSG5. B, binding of RAR and RXR proteins expressed in COS-7 cells to STAT1-RARE. Cells were electroporated with 25 μg of the indicated reporter plasmid, and whole cell extracts were prepared after 48 h (15). Extracts (15 μg) were assayed for DNA binding in EMSA with RW probe. Lane 5, 7.5 μg of extract from each preparation was incubated with the probe. Position of the specific complex is indicated with an arrow.

is and absent during STAT1 transcription. An important outcome of our study is that it demonstrates for the first time a molecular basis for the modulation of IFN action by RA. This observation indirectly connects the retinoids to cell cycle regulation. For example, recent studies indicate that IFNs inhibit cell growth using STAT1 (38) and induce the expression of p21/WAF1/Cip-1 gene, whose product inhibits the cyclindependent kinases (39). Elevation of STAT1 levels may thus permit a robust activation of STAT1 by IFNs, leading to growth arrest.

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Additions and Corrections

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Hsp90 is obligatory for the heme-regulated eIF-2α kinase to acquire and maintain an activable conformation.

Sheri Uma, Steven D. Hartson, Jane-Jane Chen, and Robert L. Matts

Page 11653, next to the last sentence before “Discussion”: The word “fast mobility” should be changed to “slow mobility.” The correct sentence should read:

Thus, in RLL, only HRI that had been autophosphorylated and transformed (slow mobility form) was resistant to denaturation and aggregation following inactivation of chaperone machinery by NEM.

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Modulation of interferon action by retinoids. Induction of murine STAT1 gene expression by retinoic acid.

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