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SIRT1 deacetylates RFX5 and antagonizes repression of collagen type I (*COL1A2*) transcription in smooth muscle cells

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ABSTRACT

Decreased expression of collagen by vascular smooth muscle cells (SMCs) within the atherosclerotic plaque contributes to the thinning of the fibrous cap and poses a great threat to plaque rupture. Elucidation of the mechanism underlying repressed collagen type I (*COL1A2*) gene would potentially provide novel solutions that can prevent rupture-induced complications. We have previously shown that regulatory factor for X-box (RFX5) binds to the *COL1A2* transcription start site and represses its transcription. Here we report that SIRT1, an NAD-dependent, class III deacetylase, forms a complex with RFX5. Over-expression of SIRT1 or NAMPT, which synthesizes NAD+ to activate SIRT1, or treatment with the SIRT1 agonist resveratrol decreases RFX5 acetylation and disrupts repression of the *COL1A2* promoter activity by RFX5. On the contrary, knockdown of SIRT1 or treatment with SIRT1 inhibitors induces RFX5 acetylation and enhances the repression of collagen transcription. SIRT1 antagonizes RFX5 activity by promoting its nuclear expulsion and proteasomal degradation hence dampening its binding to the *COL1A2* promoter. The pro-inflammatory cytokine IFN-γ represses *COL1A2* transcription by down-regulating SIRT1 expression in SMCs. Therefore, our data have identified as novel pathway whereby SIRT1 maintains collagen synthesis in SMCs by modulating RFX5 activity.

1. Introduction

Atherosclerosis is a multi-factorial process that involves complicated interplay between different cells [1]. One such cell–cell dialogue is the communication between smooth muscle cells (SMCs) and pro-inflammatory immune cells. During the early stages of atherogenesis, chemokines secreted by immune cells stimulate the migration and encroachment of SMCs, leading to the formation of a neointima [2]. In a mature atheroma, pro-inflammatory cytokines (e.g., interferon gamma/IFN-γ) released by immune cells may affect the production of extracellular matrix proteins, primarily type I collagen, by SMCs, determining the vulnerability of the fibrous cap and the ultimate prognosis of patients with atherosclerosis [3]. Therefore, delineating the molecular mechanism underlying decreased collagen transcription in SMCs may yield potential therapeutic solutions for the treatment of atherosclerosis-related complications.

A host of transcription factors and co-factors bind to the proximal promoters of collagen type I (*COL1A2*) gene to coordinately regulate its transcription in response to various cellular and environmental stress cues [4]. We have previously identified on the transcription start site of *COL1A2* a binding element for the regulatory factor for X-box (RFX) family of transcription factors [5,6]. RFX1 and RFX5, two members of the RFX family, bind to this site and down-regulate *COL1A2* transcription under different circumstances with RFX1 preferentially associated with methylated collagen promoter and RFX5 mediating the repression by IFN-γ [7,8]. Interestingly, both RFX proteins interact with class I histone deacetylases (HDAC). Furthermore, trichostatin A (TSA), a universal inhibitor of class I HDACs, abrogates the repression of *COL1A2* transcription by RFX proteins, indicating that transcription activities of RFX proteins are modulated by their acetylation status.

Protein acetylation is dynamically regulated by histone acetyltransferases (HATs) and HDACs. HDACs, based on phylogeny, can be categorized into three classes [9]. Whereas class I and II HDACs share significant homology and are sensitive to TSA, class III HDACs depend on NAD+ for their catalytic activity and are not inhibited by TSA. Sirtuin 1 (SIRT1), the best characterized member of class III HDACs, is a mammalian ortholog to silencing information regula-

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tor 2 (Sir2) in yeast that has been implicated in calorie restriction and longevity [10]. SIRT1 regulates a wide series of life activities, ranging from metabolism to cell cycle progression to immune homeostasis, mainly by deacetylating and fine-tuning the activities of protein factors including LXR, p53, and NF-κB [11]. A direct role for SIRT1 in the transcriptional control of collagen type I genes, however, has yet to be clearly defined.

Here we report that SIRT1 interacts with and deacetylates RFX5, antagonizing the repression of *COL1A2* transcription by IFN-γ. Our findings define a previously unknown function for SIRT1 and suggest that SIRT1 activation may maintain collagen transcription under pro-inflammatory conditions in SMCs. Therefore, targeting SIRT1 in SMCs may stabilize the atherosclerotic plaque and prevent rupture-induced complications.

2. Methods and materials

2.1. Cell culture and treatment

Rat vascular smooth muscle cell (A10) and human embryonic kidney cell (293FT) were maintained in Dulbecco's modified Eagle's medium (DMEM) (Invitrogen) supplemented with 10% fetal bovine serum (FBS, Hyclone). Human aortic smooth muscle cell (HASMC) was purchased from Lonza and maintained in SMBM with supplements supplied by the vendor. Nicotinamide, resveratrol, and sirtinol were purchased from Sigma. Human and rat recombinant IFN-γ were from R&D. Cycloheximide (40 μg/ml, Calbiochem) was incubated with cells for various time before harvesting.

2.2. Plasmids, transient transfection, viral infection, and luciferase assay

FLAG-tagged RFX5, *COL1A2* promoter luciferase construct (pH20), col1a1 promoter luciferase construct (α1-LUC), and SIRT1 promoter luciferase construct (Sir1-LUC) have been described previously [6,12,13]. Mammalian expression constructs for SIRT1 (WT and HY) were provided by Dr. Kouzarides [14]. NAMPT expression constructs (WT and WA) and short-hairpin RNA (shRNA) plasmid targeting human SIRT1 were a gift from Dr. Kraus [15]. Transient transfections were performed with Lipofectamine 2000 (Invitrogen). Luciferase activities were assayed 24–48 h after transfection using a luciferase reporter assay system (Promega). Experiments were routinely performed in triplicate wells and repeated three times.

2.3. Protein extraction, immunoprecipitation and Western

Whole cell lysates were obtained by re-suspending cell pellets in RIPA buffer (50 mM Tris pH7.4, 150 mM NaCl, 1% Triton X-100) with freshly added protease inhibitor (Roche). Specific antibodies or pre-immune IgGs (P.I.I.) were added to and incubated with cell lysate overnight before being absorbed by Protein A/G-plus Agarose beads. Precipitated immune complex was released by boiling with 1× SDS electrophoresis sample buffer. Alternatively, FLAG-conjugated beads (M2, Sigma) were added to and incubated with lysates overnight. Precipitated immune complex was eluted with 3× FLAG peptide (Sigma). Nuclear protein extracts were obtained essentially as previously described [7]. Western blot analyses were performed with anti-FLAG, anti-β-actin, anti-α-tubulin (Sigma), anti-RFX5 (Rockland), anti-acetyl lysine (Cell Signaling), anti-lamin B, anti-Myc, and anti-SIRT1 (Santa Cruz) antibodies.

2.4. Chromatin immunoprecipitation (ChIP)

Chromatin in control and treated cells were cross-linked with 1% formaldehyde. Cells were incubated in lysis buffer (150 mM NaCl, 25 mM Tris pH 7.5, 1% Triton X-100, 0.1% SDS, 0.5% deoxycholate) supplemented with protease inhibitor tablet and PMSF. DNA was fragmented into ~500 bp pieces using a Branson 250 sonicator. Aliquots of lysates containing 200 μg of protein were used for each immunoprecipitation reaction with anti-SIRT1 antibody, anti-RFX5 antibody, or pre-immune IgG. Re-ChIP was performed as described before [16]. Precipitated genomic DNA was amplified by real-time PCR with primers as previously described [6].

2.5. RNA extraction and real-time PCR

RNA was extracted using an RNeasy RNA isolation kit (Qiagen). Reverse transcriptase reactions were performed using a SuperScript First-strand synthesis system (Invitrogen). Real-time PCR reactions were performed on an ABI STEPONE Plus (Life Tech) with previously described primers [8,13].

2.6. Statistical analysis

One-way ANOVA with post hoc Scheffe analyses were performed using an SPSS package. *P* values smaller than .05 were considered statistically significant.

3. Results

3.1. SIRT1 interacts with and deacetylates RFX5

Since RFX5 has been demonstrated to interact with HDAC2 [7], a class I deacetylase, we asked whether it could also form a complex with SIRT1, a class III deacetylase. To this end, FLAG-tagged RFX5 plasmid and Myc-tagged SIRT1 plasmid were co-transfected into HEK293 cells and immunoprecipitation assays were performed to probe their interactions. Anti-FLAG antibody precipitated RFX5 along with SIRT1 whereas anti-Myc antibody co-precipitated both SIRT1 and RFX5 (Fig. 1A). Furthermore, reciprocal immunoprecipitation assays showed that endogenous RFX5 and SIRT1 formed a complex in human aortic smooth muscle cells (Fig. 1B), indicating that these two proteins are indeed associated with each other.

Next, we examined the functional relevance of the RFX5–SIRT1 interaction. When RFX5 was co-expressed with wild type (WT) SIRT1, its acetylation level was significantly decreased (Fig. 1C, compare lanes 1 and 2). An enzyme deficient SIRT1 (H363Y), however, slightly increased RFX5 acetylation (Fig. 1C, compare lanes 1 and 3). Moreover, nicotinamide, a SIRT1 inhibitor, augmented RFX5 acetylation whereas resveratrol, a SIRT1 activator, down-regulated RFX5 acetylation (Fig. 1D). Similar observations were made for endogenous RFX5 proteins in HASMCs (Fig. 1E). Together, these data suggest that SIRT1 interacts with and deacetylates RFX5.

3.2. SIRT1 antagonizes the repression of COL1A2 transcription by RFX5

Previously, we have reported that HDAC2 interacts with RFX5 and enhanced transcriptional repression of collagen type I gene (*COL1A2*) in lung fibroblast cells [7]. We sought to determine whether SIRT1 could modulate the repression of *COL1A2* transcription by RFX5 in SMCs. A *COL1A2* promoter luciferase construct (pH20) was transfected into cells to assess its transcriptional regulation. As expected, RFX5 repressed the *COL1A2* promoter activity. WT SIRT1, but not the HY mutant, alleviated the repression

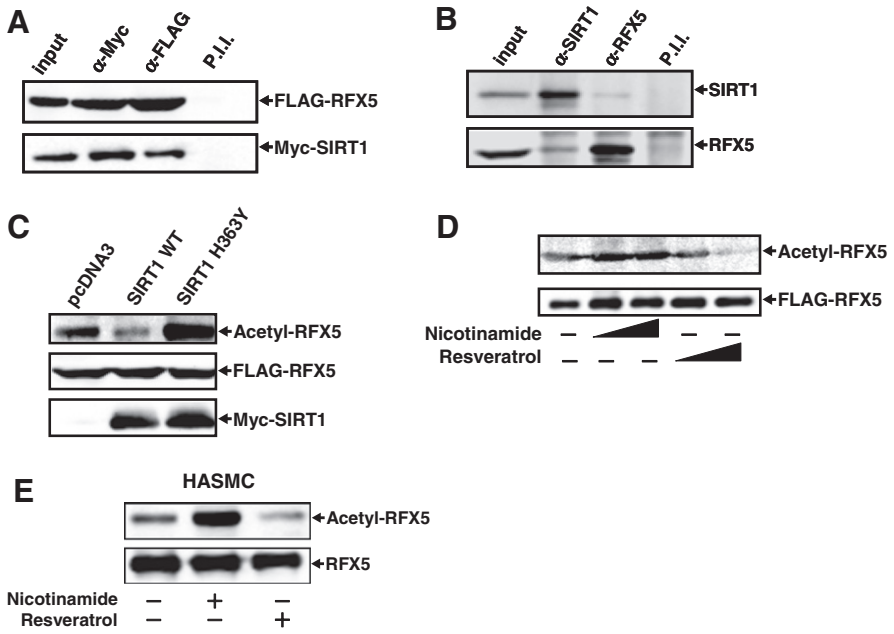

Fig. 1. SIRT1 interacts with and deacetylates RFX5. (A) FLAG-RFX5 and Myc-SIRT1 were transfected into HEK293 cells. Immunoprecipitation (IP) assays were performed with anti-Myc, anti-FLAG, or pre-immune IgG (P.I.I.) as indicated. 10% of the starting material was loaded as input. (B) IP assays were performed with human aortic smooth muscle cell (HASMC) lysate. 10% of the starting material was included as input. (C) FLAG-RFX5 was transfected into HEK293 cells with wild type (WT) or enzyme deficient (H363Y) SIRT1. IP assays were performed with anti-FLAG and acetylation of RFX5 was probed with anti-acetylated lysine. (D) FLAG-RFX5 was transfected into HEK293 cells followed by treatment with resveratrol or nicotinamide. IP assays were performed with anti-FLAG and acetylation of RFX5 was probed by Western with anti-acetylated lysine. (E) HASMCs were treated with resveratrol or nicotinamide as indicated. Immunoprecipitation was performed by anti-RFX5 and the acetylation of RFX5 was probed by Western with anti-acetyl lysine.

(Fig. 2A). In contrast, co-transfection with a plasmid encoding short-hairpin RNA for SIRT1 (shSIRT1) resulted in enhanced repression of *COL1A2* promoter by RFX5 (Fig. 2B). Similarly, the SIRT1 activator resveratrol ablated repression of the *COL1A2* promoter whereas two different SIRT1 inhibitors, nicotinamide and sirtinol, both enhanced the RFX5 repression (Fig. 2C–E). In addition, we also examined the effect of nicotinamide phosphoribosyltransferase (NAMPT), the enzyme that catalyzes the conversion of NAM to NAD+ required for SIRT1 activation, on RFX5-mediated collagen repression. As shown in Fig. 2F, wild type NAMPT instead of enzyme deficient (WA mutant) NAMPT antagonized *COL1A2* promoter repression by RFX5.

Transcription of *COL1A1* and *COL1A2* is coordinately regulated [6,12]. Indeed, SIRT1 exerted similar effects on the *COL1A1* promoter (Figs. 2B, C and G). Collectively, these data indicate that SIRT1 attenuates repression of collagen type I gene by RFX5.

3.3. SIRT1 promotes nuclear expulsion and proteasomal degradation of RFX5

SIRT1 regulates the activity of different transcription factors by modulating their stability and/or sub-cellular localization [17]. Therefore, we probed the effect of SIRT1 activation on RFX5 protein half-life and compartmentation. As shown in Fig. 3A, steady-state RFX5 is evenly distributed between cytoplasm and nucleus. Treatment with resveratrol promoted translocation of RFX5 from the nucleus to the cytoplasm. Sirtinol, on the contrary, increased nuclear enrichment of RFX5. Concomitantly, resveratrol treatment accelerated the degradation of RFX5 (Fig. 3B) while sirtinol extended the half-life of RFX5 protein (Fig. 3C). In agreement with these observations, binding of RFX5 to the *COL1A2* promoter, which is a function of both nuclear accumulation and stability of the RFX5 protein, was down-regulated by resveratrol and up-regulated by sirtinol (Fig. 3D). Together, these data suggest that SIRT1 influences RFX5-mediated repression of *COL1A2* transcription by excluding RFX5 from the nucleus and promoting RFX5 degradation.

3.4. IFN-γ represses COL1A2 transcription by down-regulating SIRT1 in smooth muscle cells

Since SIRT1 was able to maintain type I collagen expression in smooth muscle cells, we asked whether IFN-γ repressed collagen transcription by targeting SIRT1 thereby affecting RFX5 activity. IFN-γ treatment led to a decrease in SIRT1 mRNA (Fig. 4A) and protein (Fig. 4B) expression in SMCs in a dose-dependent manner. Of intrigue, IFN-γ also repressed SIRT1 promoter activity indicating that down-regulation of SIRT1 expression was likely a result of diminished transcription of the *SIRT1* gene (Fig. 4C). In addition, the SIRT1–RFX5 complex on the *COL1A2* transcription start site was disrupted by IFN-γ, reflecting a relief of RFX5 suppression by SIRT1 (Fig. 4D). Finally, pre-treatment with resveratrol attenuated repression of collagen type I synthesis by IFN-γ in VSMCs (Fig. 4E). Therefore, IFN-γ represses *COL1A2* transcription at least in part by down-regulating SIRT1 levels in VSMCs.

4. Discussion

The production of extracellular matrix proteins changes dynamically during atherogenesis. In the early stages of atherosclerosis, smooth muscle cells, under the influence of pro-fibrogenic humoral factors such as TGF-β, up-regulate the transcription of collagen type I gene, leading to the formation of a fibrous cap that can protect the plaque from rupturing [18,19]. Later on, as more pro-inflammatory immune cells including CD4+ T lymphocyte and mast cells are recruited, they exert anti-fibrogenic effects on the SMCs by releasing IFN-γ into the plaque [20,21]. Consequently, collagen transcription is repressed and the plaque becomes unstable and more prone to rupture. Here, we report that the group III

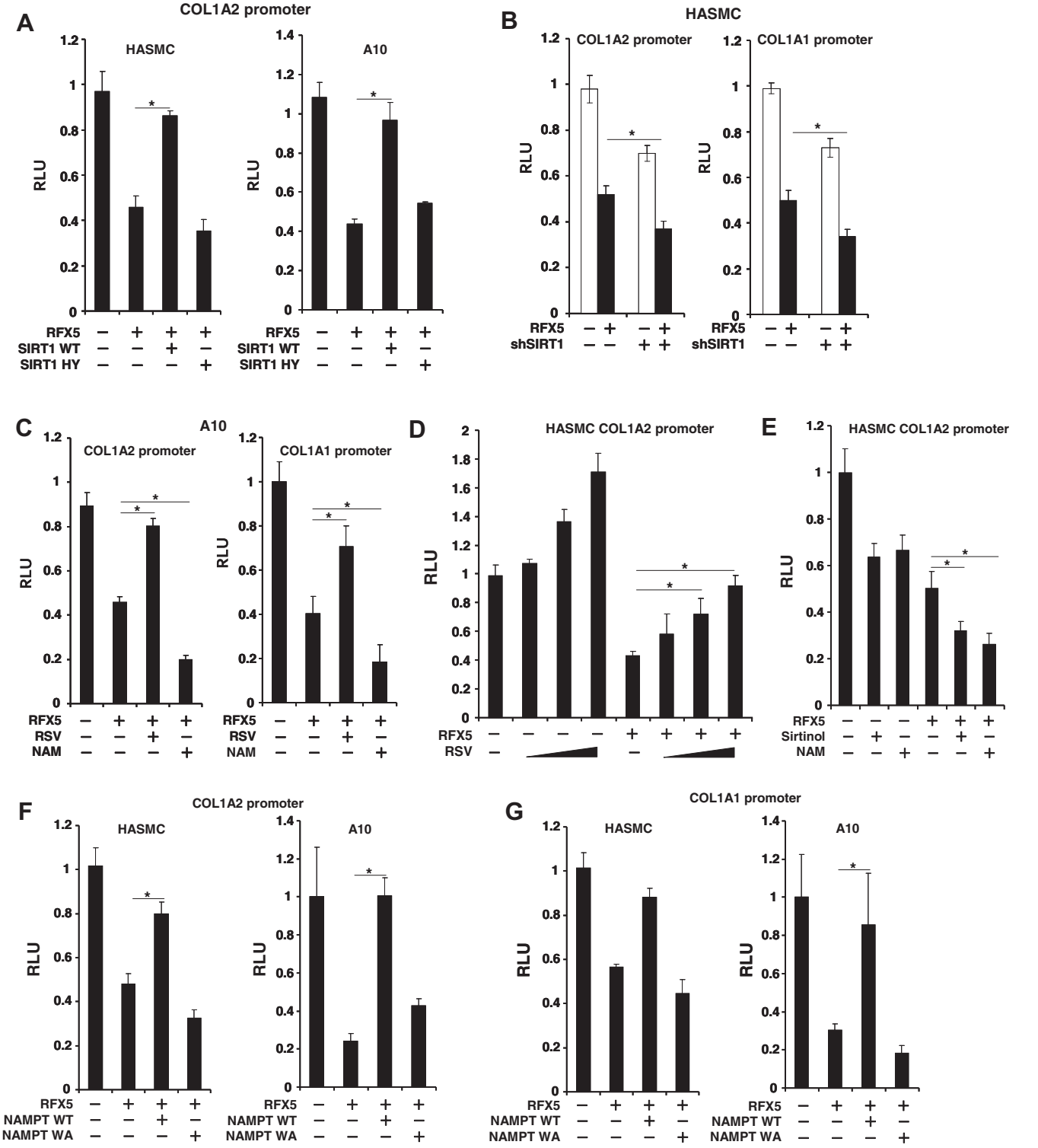

Fig. 2. SIRT1 antagonizes the repression of collagen type I transcription by RFX5. (A) pH20 and expression constructs for RFX5 and SIRT1 (WT and HY mutant) were transfected into A10 and HASMC. Luciferase activities are normalized by both protein concentration and GFP fluorescence. Data are expressed as relative luciferase unit (RLU) compared to the control group set arbitrarily as 1. (B) pH20 or α1-LUC were co-transfected with RFX5, and shSIRT1 into HASMCs. Luciferase activities are expressed as RLU. (C) pH20 or α1-LUC was transfected with RFX5 construct into A10 and HASMC followed by treatment with resveratrol (RSV, 25 μM), or nicotinamide (NAM, 10 mM) for 24 h. Luciferase activities are expressed as RLU. (D) pH20 and RFX5 constructs were transfected into HASMC followed by treatment with RSV (5, 10, or 25 μM). Luciferase activities are expressed as RLU. (E) pH20 and RFX5 constructs were transfected into HASMC followed by treatment with sirtinol (25 μM) NAM (10 mM). Luciferase activities are expressed as RLU. (F) pH20 and expression constructs for RFX5 and NAMPT (WT and WA mutant) were transfected into A10 and HASMC. Luciferase activities are expressed as RLU. (G) α1-LUC and expression constructs for RFX5 and NAMPT (WT and WA mutant) were transfected into A10 and HASMC. Luciferase activities are expressed as RLU.

deacetylase SIRT1 deacetylates RFX5 and antagonizes RFX5-mediated collagen type I gene repression by IFN-γ in SMCs, alluding to the potential of exploiting SIRT1 activation as means of preventing rupture-associated complications.

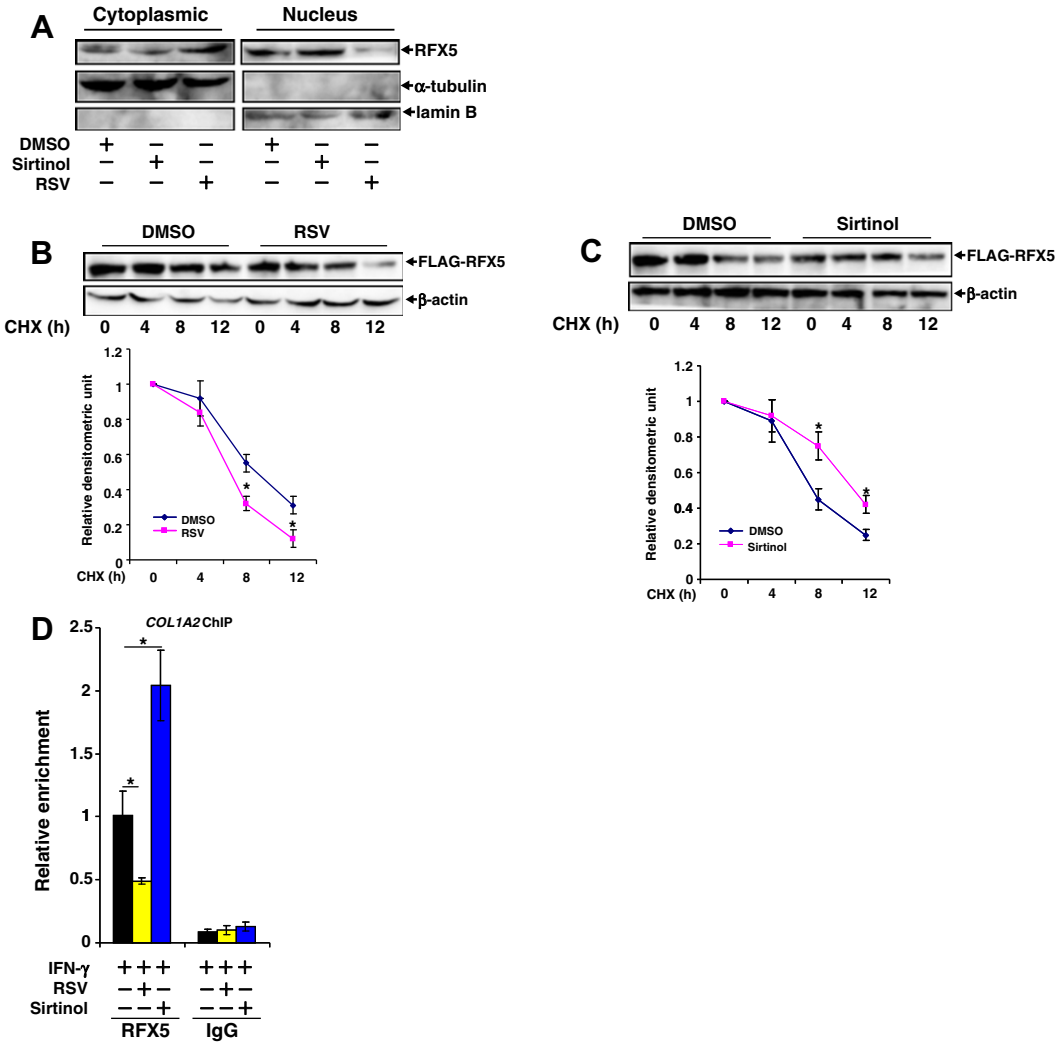

Fig. 3. SIRT1 promotes nuclear expulsion and proteasomal degradation of RFX5. (A) HASMCs were treated with resveratrol or sirtinol for 24 h. Compartmentation of RFX5 was probed by Western. (B, C) FLAG-RFX5 was transfected into HEK293 cells followed by treatment with resveratrol (B) or sirtinol (C). Cycloheximide (CHX) was added 24 h post-transfection and cells were harvested at different time points as indicated. RFX5 levels were measured by Western. (D) HASMCs were treated with IFN-γ, RSV, and/or sirtinol for 24 h. ChIP assay was performed with anti-RFX5. Precipitated DNA was amplified using primers surrounding *COL1A2* transcription start site.

In the present study, we have used a *COL1A2* promoter construct that harbors binding site for several other transcription factors in addition to RFX5, which include NF-κB [22] and Egr-1 [23]. SIRT1 is known to impact the expression and/or activity of these factors that are involved in *COL1A2* transcription. For instance, SIRT1 directly deacetylates NF-κB/p65 at lysine 310 and decreases the affinity of p65 for its target genes [24]. On other hand, SIRT1 has been shown to suppress the expression of endogenous Egr-1 in vascular endothelial cells and lymphoma cells [25,26]. Although we have provide solid evidence here that SIRT1 directly interacts with RFX5 (Fig. 1) and impairs its ability to bind to and repress collagen transcription (Figs. 2 and 3), it remains to be determined how the suppression of transcription factors other than RFX5 by SIRT1, either at pre-translational or post-translational level, may help maintain the steady-state collagen expression in SMCs.

Of note, SIRT1 activation may bring about additional benefit in terms of plaque stabilization other than antagonizing collagen repression in SMCs. SIRT1 is known to impair the production and release of pro-inflammatory cytokines including IFN-γ from immune cells [27]. Alternatively, SIRT1 has been documented to block the differentiation of CD4+ T lymphocyte, a major source of IFN-γ production [28]. Yet another layer of modulation is hinted by the discovery of Sestito et al. that SIRT1, by deacetylating STAT3, directly tempers the signaling cascade initiated by IFN-γ, effectively shutting down downstream events including collagen repression [29]. SIRT1 may also contribute to the maintenance of collagen content within the plaque by impeding with collagen degradation by metalloproteinase (MMP). Several independent reports indicate that activation of SIRT1 by resveratrol treatment down-regulates the expression of a host of MMPs including MMP2 [30], MMP9 [31], and MMP13 [32]. Finally, one factor that may limit the collagen synthesis capacity within the plaque is premature SMC senescence and/or apoptosis [33]. By virtue of deacetylating and deactivating p53, a key transcription factor regulating cellular senescence and apoptosis, SIRT1 may extend the replication cycle of SMCs, thereby sustaining collagen deposit [34].

In contrast to our previous finding that HDAC2 enhances collagen type I gene repression by RFX5, our new finding as summarized here indicates that SIRT1 opposes the down-regulation of collagen expression, pointing to an interesting model wherein collagen production and hence plaque stability are determined by the balance between HDAC2 and SIRT1. A couple of recent investigations, one contending that HDAC2 expression is up-regulated in the arteries during atherogenesis [35] and the other suggesting

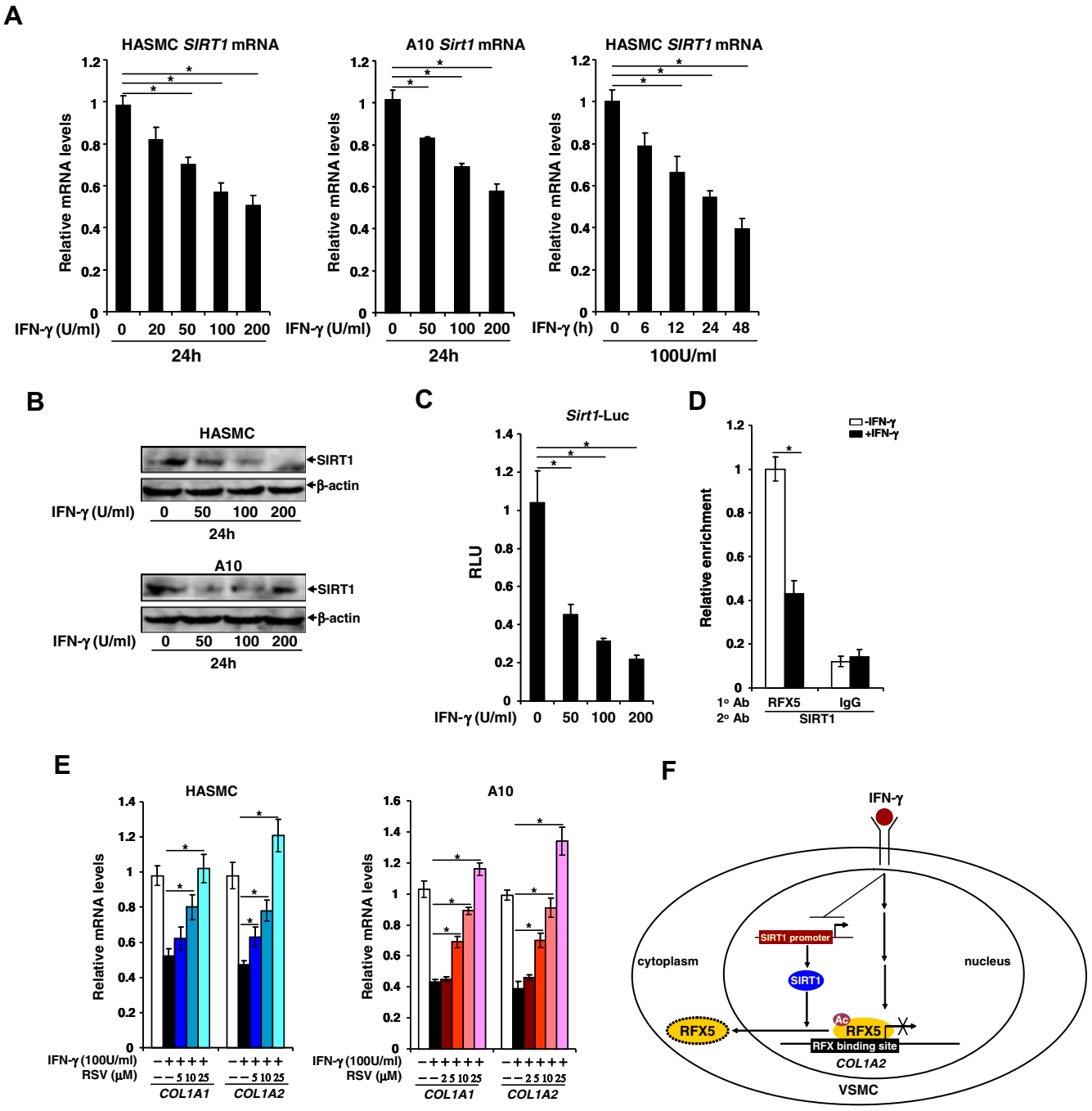

Fig. 4. IFN-γ suppresses SIRT1 transcription in smooth muscle cells. (A, B) HASMC and A10 cells were treated with IFN-γ of different concentrations. Cells were harvested at indicated time points and SIRT1 mRNA (A) and protein (B) levels were measured by qPCR and Western respectively. (C) Sirt1-LUC was transfected into A10 cells followed by treatment with IFN-γ. Luciferase activities are expressed as RLU. (D) HASMCs were treated with for IFN-γ for 24 h. Re-ChIP was performed as described under Section 2. (E) HASMC and A10 cells were treated with IFN-γ and RSV (5, 10, or 25 μM) for 24 h. Collagen type I gene expression was measured by qPCR. (F) A model illustrating the functional interaction between RFX5 and SIRT1 that contributes to the regulation of *COL1A2* gene transcription in vascular smooth muscle cells.

SIRT1 expression may be down-regulated during the same period [36], have provided support for this proposal to some extent. Further studies are warranted to justify the use of both an HDAC2 inhibitor and a SIRT1 activator in the treatment of late-stage atherosclerosis.

Acknowledgments

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