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Lysine-specific demethylase 1 (LSD1) and histone deacetylase 1 (HDAC1) synergistically repress proinflammatory cytokines and classical complement pathway components

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ABSTRACT

Histone modifying enzymes confer epigenetic marks, directing the changes in gene expression required for diverse cellular processes. Lysine-specific demethylase 1 (LSD1) functions as a transcriptional coregulator by demethylating histone H3 on lysine 4 and lysine 9. Analyzing transcriptomes on microarrays, we identified genes which represent inflammatory-related targets of LSD1. We demonstrate a repressive role of LSD1 in proinflammatory cytokine expression such as IL1α, IL1β, IL6 and IL8 and classical complement components. Consistently, LSD1 occupies and regulates the promoter of these genes. In addition, we demonstrate that HDAC1 and LSD1 synergistically regulate these inflammatory-related genes. Our data reveal a novel role for LSD1 in suppressing immune responses.

1. Introduction

Chromatin remodeling is a dynamic process in which inaccessible, compact and repressed chromatin is converted into an open accessible form for active transcription or vice versa. Posttranslational modifications of histones participate in the regulation of transcription by altering chromatin structure and recruiting regulatory complexes that recognize and bind to the modified histone tails [1]. Among these modifications, lysine acetylation confers transcriptional activation [2] and histone H3 lysine methylation (H3Kme) is associated with either gene activation or repression, depending on the specific chromatin site. Methylation of lysine 4 in histone H3 (H3K4) correlates with gene activation [3], whereas H3K9 methylation is associated with transcriptional repression [4]. Histone lysine methylation was considered to be a permanent mark, until recent discoveries showed that these processes are reversible by a diverse set of enzymes [1].

LSD1 confers transcriptional regulation by catalyzing demethylation of mono- and di-methylated H3K4 and H3K9 [5,6]. Initially discovered as a part of the CoREST-complex [7], LSD1 was also found as a component of the NuRD complex [8] or in cooperation with steroid hormone receptors [6,9]. The mechanisms that control this dual specificity of demethylation seem to be modulated by other proteins associated with LSD1 [6,10,11] and by other histone marks displayed on the histone tail [12–14].

HDAC1 and HDAC2 are often associated with LSD1 in corepressor complexes [11]. HDAC1/2 first deacetylate the histone tail and subsequently LSD1 is able to demethylate H3K4 [10]. LSD1 regulates different physiological processes including hematopoiesis, adipogenesis [15], developmental processes, maintenance of the DNA methylation [8,16,17] and tumorigenesis [18–22].

Inflammatory responses require the activation of a complex gene expression program that involves the inducible transcription of hundreds of genes whose products restrain microbial colonization, recruit and activate leukocytes, increase vascular permeability, amplify the immune response, and protect inflammatory and tissue cells from apoptosis [23]. Changes in lysine methylation were detected at inflammatory gene promoters upon stimulation [24–26] indicating a possible role for histone demethylases in gene regulation. The results of the present study provide evidence for epigenetic regulation of proinflammatory and complement genes and indicate that LSD1 and HDAC1 specify repressive chromatin marks in proinflammatory cytokines and classical complement pathway genes.

2. Materials and methods

2.1. Cell culture

MDA-MB231 cells were cultured in DMEM (Invitrogen) and HepG2 cells were cultured in RPMI (Invitrogen) containing 10% FCS, L-glutamine and antibiotics.

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2.2. siRNA transfection

MDA-MB231 and HepG2 cells were transfected as described [18]. Scrambled or LSD1 (siRNA-1: s618), (siRNA-2: s617), (siRNA-3: s619) and HDAC1 (s73) specific siRNA (Ambion) were used in a range of 8–20 nM.

2.3. RNA isolation and quantitative RT-PCR (qRT-PCR)

After siRNA transfection cells were harvested and RNA was isolated using TRIZOL reagent (Invitrogen) and qRT-PCR experiments were done as previously described [18]. Expression values were normalized to the mean of hypoxanthine–guanine phosphoribosyltransferase (HPRT). The results are presented as fold change to scrambled siRNA transfected samples which were set to one. Error bars indicate standard error of the mean (SEM). Results present the mean of five independent experiments.

2.4. Western blots

Protein lysates were extracted from cells and blotted as described [19]. Membranes were incubated for 1–2 h using the following antibodies and dilutions: β-actin (1:5000, A5441, Sigma–Aldrich), H3K9/14Ac (1:500, 17-615, Millipore), HDAC1 (1:500, sc-6238, Santa Cruz), LSD1 (1:1000, NB100-1762, Novus Biologicals).

2.5. Inhibition with Tranylcypromine and MS-275

500,000 Cells were seeded in 6 well plates in normal growth medium. Cells were treated with 100 μM Tranylcypromine (Biomol) or 1 μM MS275 (Enzo Life Science) for 24 h.

2.6. IL1β ELISA

IL1β ELISA Ready-Set-Go (eBioscience) was done according to the manufacturer's instructions.

2.7. C3 ELISA

Cells were seeded to serum reduced medium 24 h before treatment and stimulated with IL1α and IL1β and cell supernatants were collected. C3 ELISA was done using the Assay Max Human Complement C3 ELISA Kit (Assay Pro).

2.8. Chromatin immunoprecipitation (ChIP)

ChIP experiments were performed essentially as described in Lim et al. [18]. Immunoprecipitation was performed with specific antibodies to LSD1 (Novus Biologicals, NB 100-1762), H3K4me2 (Millipore, 05-1938), H3K9me2 (Millipore, 07-441), H3K9/14Ac (Millipore, 17-615) and as a negative control IgG (Diagenode, KCH 50429) on protein G coupled Dynabeads (Invitrogen). Scrambled siRNA treated sample (control) was set to one and results are presented as fold change to control.

2.9. Statistic analysis

For statistic analysis a regular *t*-test or one-sample *t*-test was performed. Results were considered significant with *p*-value <0.05 and marked with a*.

Primer sequences are available in Supplementary information.

3. Results

Recently, we have shown that LSD1 knockdown using small interfering RNA (siRNA) resulted in growth retardation of breast cancer cells *in vitro* [18]. We identified targets of LSD1 in ER-negative breast cancer cells by microarray analysis [18]. The data were released into the GEO-database (GSE 30775). Silencing of LSD1 leads to differential expression of 283 genes encoding for proteins involved in inflammation. Statistical analysis showed that 39 of these genes were differentially expressed >2-fold with ($p < 0.05$). To further analyze the relevance of LSD1 in regulation of mRNA of inflammatory genes, MDA-MB231 cells were transiently transfected with three different siRNA directed against LSD1 or with a scrambled control siRNA. A significant knockdown of LSD1 in all samples was detected on both mRNA and protein level (Fig. 1A). Upon treatment with LSD1 specific siRNA-1, significant induction of the steady state transcript levels of interleukins (IL) 1α, 1β, 6 and 8 genes was detected in qRT-PCR (Fig. 1B). In addition, siRNA-2 and -3 show similar effects on ILs transcript levels (data not shown). Fig. 1C showed that IL1β protein levels were significantly enhanced in the supernatant of the cells after LSD1 knockdown.

To asses whether LSD1 can bind directly to the promoter of ILs, we performed ChIP assays. MDA-MB231 cells treated with siRNA directed against LSD1 or with a scrambled control siRNA were subjected to ChIP using α-LSD1, α-H3K4me2 and α-H3K9me2 antibodies. Fig. 1D and E shows that LSD1 binds directly to the promoter of the IL1β and IL6 genes. Knockdown of LSD1 diminished LSD1 occupancy on the IL1β and the IL6 promoter, while promoter occupancy on those promoters could not be detected with an IgG control antibody (Fig. S1A). Inhibition of LSD1 by an siRNA approach was accompanied by an increase of the active histone mark H3K4me2 and a decrease in the repressive H3K9me2 mark, resulting in activation of IL1β and IL6 genes after LSD1 silencing (Figs. 1D and E, S1B and S1C).

Since exogenous siRNA usually evokes the potential induction of inflammatory cytokines and interferons [27], we used an enzymatic inhibitor of LSD1 to exclude the influence of siRNA on transcriptional induction of inflammatory cytokines [19,28]. Consistent with the transcriptome data upon siRNA transfections, Tranylcypromine (TCM) treatment of MDA-MB231 cells also resulted in a significant increase of expression of IL1α, IL1β, IL6 and IL8 (Fig. 1F), indicating that the catalytic activity of LSD1 is required for regulation of inflammatory cytokines. In addition, ChIP analysis shows that chemical inhibition of LSD1 does not influence occupancy of LSD1 on the promoter of the IL1β and IL6 genes, but influence the dimethylation level on H3K4 on these promoters (Fig. 1G and H).

In addition to genes of proinflammatory cytokines also genes of the complement system are regulated after LSD1 knockdown [18]. The classical complement pathway typically requires antigen–antibody complexes for activation, whereas the alternative and mannose-binding lectin pathways can be activated by C3 hydrolysis or antigens without the presence of antibodies. All three pathways generate homologous variants of the protease C3-convertase, which cleaves and activates component C3, causing a cascade of further cleavage.

The classical complement pathway is initiated by the formation of the C1 complex, which comprises of C1q, C1r and C1s. These initiate a cleavage cascade over C2, C4, C3 and C5 which leads in the end to the formation of the membrane attack complex [29]. Since the proteins that constitute the complement system are synthesized mainly by hepatocytes, we analyzed the effect of LSD1 knockdown (Fig. 2A) on the expression of components of the complement system in the HepG2 cell line (Fig. 2B–D). qRT-PCR analysis showed that the reduction of LSD1 levels strongly enhanced the expression of C1r and C1s and the C3a receptor (C3aR), while other

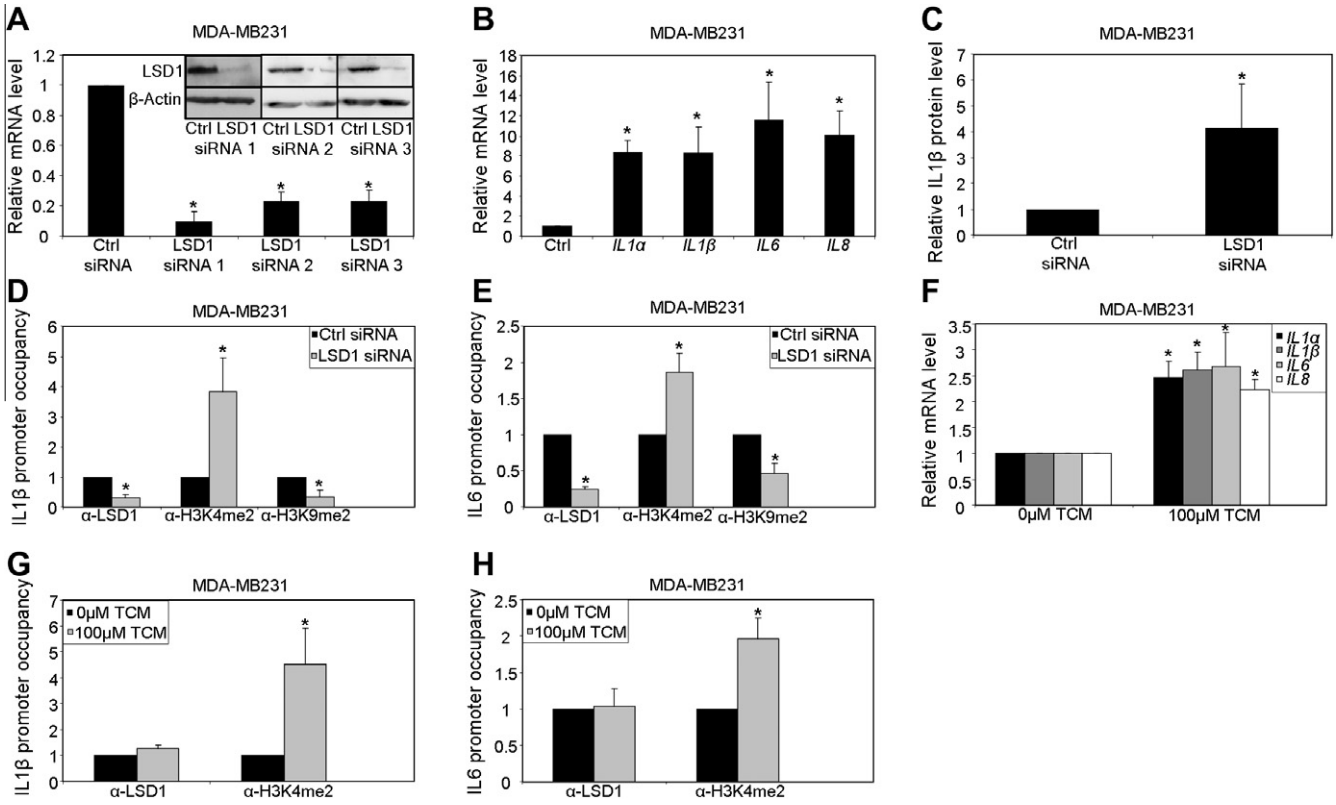

Fig. 1. Downregulation of LSD1 in MDA-MB231 cells leads to induction of proinflammatory cytokines. (A) Knockdown of LSD1 in MDA-MB231 by different siRNAs against LSD1 confirmed by qRT-PCR and Western Blotting. (B) Changes in mRNA level of proinflammatory cytokines analyzed after LSD1 knockdown. (C) IL1β ELISA was performed using supernatant from MDA-MB231 after LSD1 knockdown (p-value < 0.01). (D + E) LSD1, H3K4me2 and H3K9me2 occupancy was observed on human IL1β (D) and IL6 promoters (E) by ChIP analysis. (F) mRNA expression changes of proinflammatory cytokines after treatment with 0 or 100 μM of Tranylcypromine (TCM). (G + H) Enrichment of H3K4 dimethylation in the promoter of *IL1β* (G) and *IL6* gene (H) was observed upon inhibition of LSD1 by TCM.

components of the classical complement pathway e.g. C2, C3, C4, C5, C7 and C8 remained unaffected (Fig. 2B).

The lectin pathway uses MBL-associated serine proteases (MASP)-1 and -2 and MBL. We investigated the regulation of the lectin pathway by LSD1 and could detect significant expression reduction of MASP-1, but none of MASP-2 or MBL after LSD1 knockdown (Fig. 2C).

The alternative pathway is initiated by the spontaneous hydrolysis of C3, which leads to a cleavage of Factor B (CFB) by Factor D (CFD) and thereby results in formation of a functional C5 convertase.

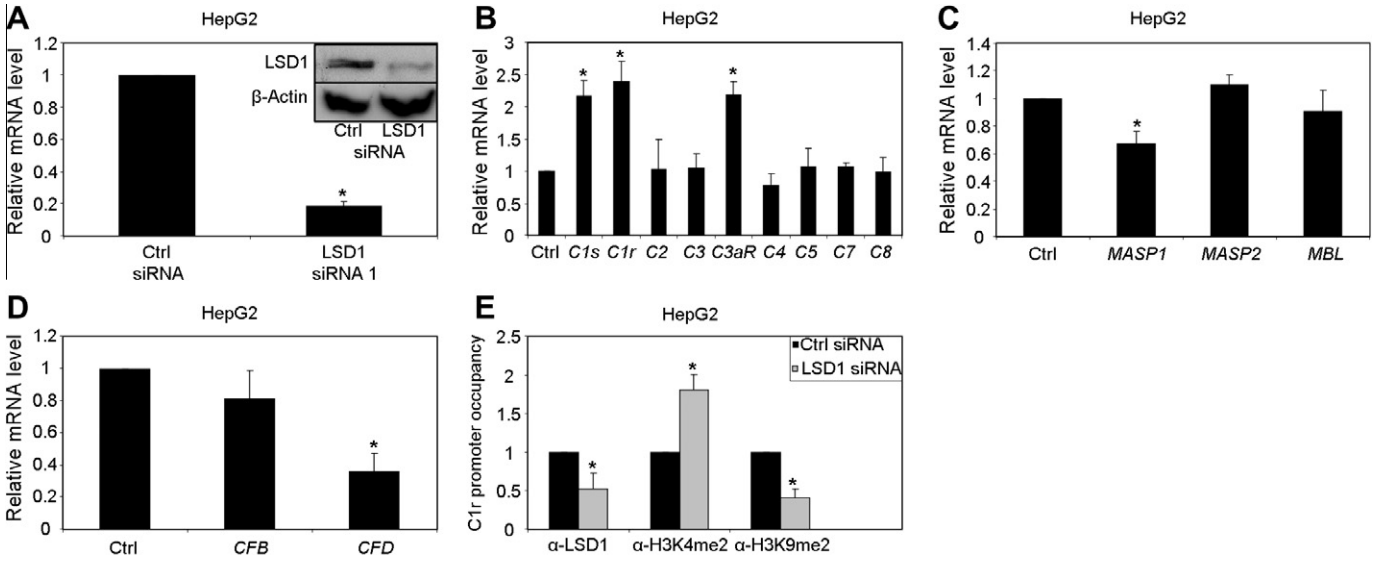

Fig. 2. LSD1 regulates several genes of the complement system in HepG2 cells. (A) LSD1 knockdown in HepG2 confirmed by qRT-PCR and Western Blotting. Changes in expression level of (B) classical complement components, (C) MBL-pathway and (D) alternative pathway genes analyzed by qRT-PCR after LSD1 silencing. (E) ChIP analysis showed reduced LSD1 and H3K9me2 but increased H3K4me2 level at C1r promoter after LSD1 knockdown.

Upon silencing of LSD1 CFD was significantly repressed, while expression of CFB was not significantly changed (Fig. 2D). To determine whether LSD1 knockdown influences gene specific methylation status, HepG2 cells were subjected to ChIP experiments after siRNA treatment. LSD1 directly binds to the distal promoter of C1r and knockdown of LSD1 diminished LSD1 occupancy on the C1r promoter. We found significantly induced levels of H3K4me2 and reduced levels of H3K9me2, consistent with activation of C1r after silencing of LSD1 (Fig. 2E). Taken together, LSD1 represses the classical complement pathway and promotes the alternative and MBL-pathway in hepatocytes.

Previously, Andrews et al. [30] depicted enhanced C3 production after IL1 induction pointing to a connection between the IL1-pathway and the complement system. Therefore, we first analyzed the IL1 receptor complex, consisting of IL1 receptor (IL1R) and IL1 receptor accessory protein (IL1RAP). In HepG2 cells, expression of IL1R and IL1RAP were low, but IL1R expression was enhanced apparently whereas the IL1RAP expression was increased significantly upon LSD1 knockdown (Fig. 3A), indicating a regulatory function of LSD1 in immune gene regulation. Next, we stimulated HepG2 cells with IL1α and IL1β twice within 48 h and determined C3 by an ELISA. Fig. 3B shows that stimulation of cells with IL1α and IL1β leads to a significant increase in C3 protein production within 48 h. As previously shown LSD1 does not affect the expression of C3 in HepG2 cells, however these results offer the possibility that LSD1 can indirectly influence C3 production by direct regulation of ILs and the IL1R-complex.

LSD1 was previously found to be part of multi-enzyme complexes including transcription factors, as well as HDAC1 to regulate the respective genes [11]. Knockdown of LSD1 decrease the occupancy of HDAC1 on the promoter of the IL1β and IL6 genes (Figs. 4A and B and S1D), indicating that HDAC1 and LSD1 are present at the proximal promoters of the IL1β and IL6 genes. Next, we inhibited HDAC1 by a siRNA approach in either MDA-MB231 or HepG2 cells and confirmed the down-regulation of LSD1 on mRNA and protein level (Fig. 4C and D). Consistently, IL1α, IL1β, IL6 and IL8 were up-regulated in MDA-MB231 cells after treatment with HDAC1-specific siRNA (Fig. 4E). Silencing of HDAC1 resulted also in an increased expression of C1s in HepG2 cells (Fig. 4F).

ChIP analysis confirmed that LSD1 and HDAC1 are present on the promoter of the IL6 gene. Treatment of MDA-MB231 cells with siRNA against HDAC1 decreased the occupancy of both factors, indicating that LSD1 and HDAC1 together bind to the promoter of the IL6 gene (Fig. 4G).

In addition, we treated the MDA-MB231 cells with the specific HDAC1 inhibitor MS-275 [31]. Inhibition of HDAC1 led to a significant increase of global acetylation of K9 and K14 on histone H3 (H3K9/14Ac), which is a feature of active transcription, and a significant induction of proinflammatory cytokine expression (Fig. 4H). ChIP analysis showed that genomic DNA corresponding to the IL1β and IL6 promoter was significantly enriched by an α-H3K9/14Ac antibody upon HDAC inhibition (Figs. 4I and J, S1E). These results suggest that LSD1 regulates synergistically with HDAC1 the expression of proinflammatory cytokines and genes of the classical complement pathway.

To investigate further a connection between LSD1 expression and inflammation, we retrospectively analyzed LSD1 expression in inflamed breast and prostate tissue (Fig. S2A and S2D). We analyzed 40 biopsies using immunohistochemical staining of LSD1 and leukocyte common antigen (LCA). All lymphocytes showed a positive LCA staining reaction (Fig. S2B and S2E). Immunohistochemical staining using an antibody against LSD1 revealed moderate nuclear expression in both breast and prostate epithelial cells. In contrast, only single lymphoblasts were positive for LSD1, whereas the majority of differentiated small lymphocytes showed no expression of LSD1 (Fig. S2C and S2F).

4. Discussion

Our results demonstrate a repressive role of LSD1 in proinflammatory cytokine expression such as IL1α, IL1β, IL6 and IL8. The decrease of LSD1 occupancy on IL1β and IL6 promoters after LSD1 knockdown substantiates a direct action of LSD1 at the promoter sites of these genes. Our results are supported by ChIP-DSL-analyses of Wang et al. showing LSD1 at the promoter of IL6 in MCF7 cells [8]. In addition, Reddy et al. demonstrated decreased LSD1 levels at the activated IL6 promoter in vascular smooth muscle cells [32]. We also could show reduction of repressive mark H3K9me2 and induction of the active mark H3K4me2 on these promoters supporting the regulatory role of LSD1 on these genes.

Aberrant proinflammatory cytokine expression is associated with different diseases [33,34]. Our results show that in inflamed tissue of breast and prostate only single lymphoblast were positive for LSD1, the majority of lymphocytes showed no expression of LSD1. In this regard, we demonstrated a dependency of LSD1 regulation and inflammation *in vivo*.

While most of the genes of the complement system remain unaffected by siRNA approach treatment, we identified central genes in the three pathways of the complement system influenced by LSD1 knockdown. Interestingly, the either repressive or activating effect of LSD1 is specific for the different involved pathways. While the classical complement pathway seems to be repressed by LSD1 through decreased C1 complex expression, the alternative and the MBL pathway seem to be activated by LSD1 through increased CFD expression or increased MASP-1 expression. We further identified C1r as a direct target of LSD1 and demonstrated that the C1r promoter also displays significant altered levels of H3K4me2 and H3K9me2. Moreover, both signals follow inverse patterns of enrichment, H3K9 dimethylation prevents gene activation, whereas H3K4 dimethylation maintains the chromatin in a receptive state, allowing induction of this gene.

The fact that LSD1 might activate the alternative and MBL pathway while repressing the classical and vice versa offers the interesting possibility that LSD1 is a balancer between the different complement pathways.

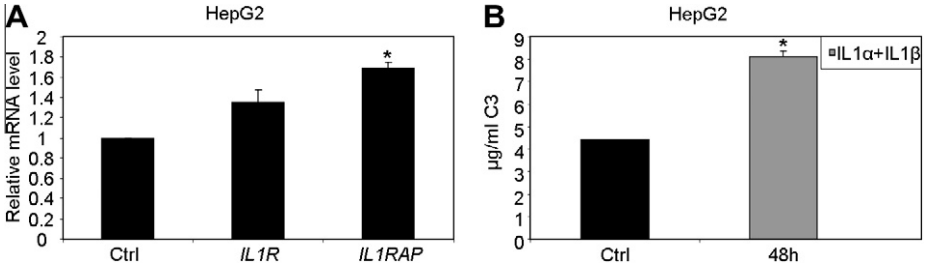

Fig. 3. Crosstalk between proinflammatory cytokine signalling and the complement system. (A) mRNA expression changes of *IL1R*-complex genes after LSD1 knockdown in HepG2. (B) C3 ELISA of HepG2 supernatant after stimulation with IL1α and IL1β for 48 h.

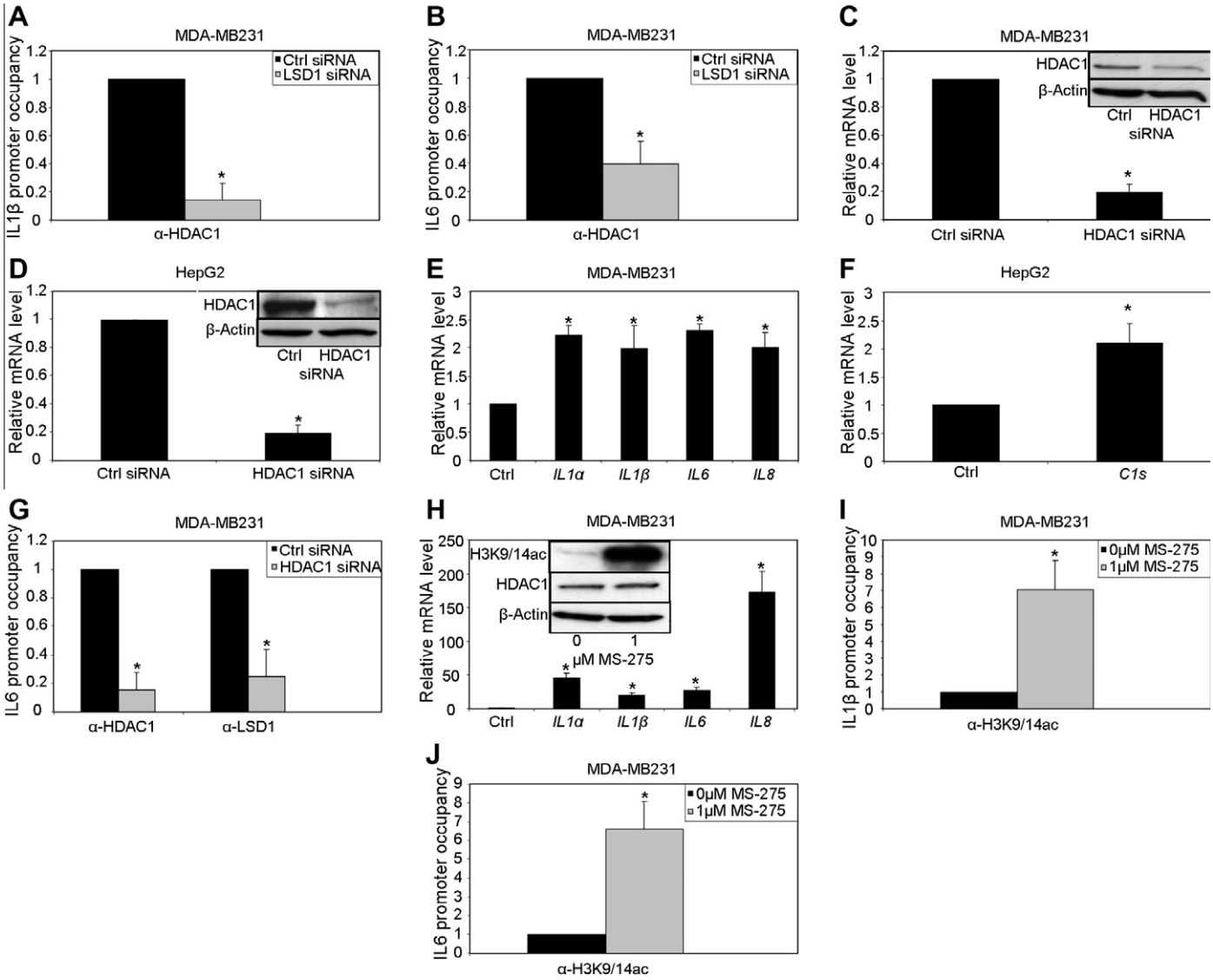

Fig. 4. HDAC1 represses proinflammatory cytokine expression and classical complement pathway genes. (A + B) Inhibition of LSD1 by siRNA approach in MDA-MB231 leads to a decreased promoter occupancy of HDAC1 on the *IL1α* (A) and *IL6* (B) genes. (C + D) Knockdown of HDAC1 in MDA-MB231 (C) and HepG2 (D) confirmed on RNA and protein levels. (E) Expression of proinflammatory cytokines *IL1α, IL1β, IL6* and *IL8* and (F) classical complement component *C1s* were increased upon HDAC1 knockdown. (H) Treatment of MDA-MB231 cells with 0 or 1 μM MS-275 and conformation of inhibition by Western Blotting. Expression levels of *IL1α, IL1β, IL6* and *IL8* after MS-275 incubation. (I + J) Acetylation level of H3 at the promoters of *IL1β* (I) and *IL6* (J) were analyzed.

In addition, we showed that IL1α and IL1β are able to stimulate the expression of C3. Similar effects for IL6 were also described previously [35]. There is also evidence that proinflammatory cytokines are able to increase C1r/C1s [36]. Taking into consideration that LSD1 is not able to directly regulate expression of C3, the direct regulation of ILs levels and the IL1R-complex by LSD1, enables a possibility of an indirect regulation of C3.

Here, we demonstrated that HDAC1 works synergistically with LSD1 at the expression regulation of proinflammatory cytokines and classical complement pathway components in breast cells and hepatocytes. Recently, it has been shown that HDAC1 represses IL1α expression in human melanoma cells [37]. In addition, HDAC1 together with a Foxp1/2/4-NuRD complex can repress transcription of IL6 in lung epithelial cells [38].

These data are supported by chemical inhibition of HDAC1 through MS-275. Upregulation of proinflammatory ILs after MS-275 treatment was dramatically higher increased compared to siRNA-experiments. Our findings portends that a complex of LSD1 and HDAC1 regulate proinflammatory cytokines and classical complement pathway components. In line with our results, HDAC1 was previously linked to inhibition of NFkB signalling by binding directly to NFkB subunits like p50 [39]. In addition, it seems likely that there might be different complexes in different cell types involved. While Chokas et al. described the NuRD complex being involved in IL6 regulation in lung cells [38], Saijo et al. described a Nurr1–CoREST complex to be involved in repression of IL1β in microglia and astrocytes [40].

Understanding the regulation of immune genes on epigenetic levels will help us to understand the immune response and the diseases associated with deregulated immune gene expression. Targeting LSD1 might even provide new options for therapeutic approaches since specific inhibitors of LSD1 might offer pharmacological manipulation of these pathways.

Acknowledgments

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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.2012.04.057.

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