Interferon regulatory factors are a growing family of transcription factors that have been implicated in cellular events such as cell-growth regulation, antiviral defense, and development of the immune system. Interferon regulatory factor 7 (IRF-7) is expressed predominantly in lymphoid tissues and has been studied extensively in the context of viral infection and the induction of interferon and cytokine gene expression. In this paper, the involvement of IRF-7 in monocyte differentiation was examined in U937, HL60, and human primary macrophages. We report the induction of IRF-7 expression by 12-O-tetradecanoylphorbol-13-acetate in U937 and HL60 cells and demonstrate that this induction is essential for the monocyte differentiation to macrophages. We show that the monocyte differentiation is inhibited in cells expressing a dominant negative IRF-7 mutant, as evidenced by decreased expression of two macrophage-differentiation markers, CD11b and CD11c, and impaired phagocytic activity. In addition, we demonstrate that overexpression of IRF-7 is sufficient to trigger monocyte differentiation and to induce cell cycle arrest. The identification of IRF-7 as a key regulator in monocyte differentiation suggests a novel function of IRF-7 in innate immunity.

Interferon regulatory factors (IRFs) are a growing family of transcription factors so far consisting of nine members and several viral IRF homologs (1). The biological activities of IRFs are manifested through the binding, via their highly homologous N-terminal DNA binding domains, to a specific DNA sequence termed interferon response element (IRF-E; consensus sequence AANNGAAA) located in the promoter region of their target genes. IRFs have been implicated in a variety of cellular events, including cell-growth regulation and host defense against viral infection (2, 3). Studies with knockout mice point out an important role of IRFs in development and function of the immune system. The numbers of CD8+ T cells and NK cells are dramatically decreased in IRF-1−/− mice, indicating an essential role of IRF-1 in their development (2). Both IRF-4 and IRF-8 are predominantly expressed in lymphoid or myeloid cells. The IRF-4−/− mice showed a profound reduction in serum immunoglobulin level and a lack of responses to both T cell-dependent and T cell-independent antigen stimulation (4). In contrast, IRF-8−/− mice showed a marked deficiency in myeloid cell development, featuring a dramatic expansion of granulocytes and a lack of mature macrophages (5).

IRF-7 was originally cloned from Epstein-Barr virus immortalized B cells as a repressor of the Qp promoter of Epstein-Barr virus nuclear antigen 1 gene (6). It has since been demonstrated that IRF-7 plays an important role in innate immunity where, together with IRF-3, it controls the expression of interferon α/β (IFN-α/β), as well as chemokines such as RANTES (regulated on activation normal T cell expressed and secreted) in virus-infected cells (7–15). Viral infection triggers the phosphorylation and subsequent nuclear translocation of IRF-3 and IRF-7. Both of these factors are components of a transcriptional enhancerome on the promoter region of IFN-β gene (7). Even though early studies suggested that IRF-7 needs to be modified by a virus-mediated phosphorylation to translocate into nucleus, several recent observations indicate that IRF-7 is also constitutively active in the uninfected cells. First, IRF-7 was found in the nucleus of uninfected cells (8, 16). Second, overexpression of IRF-7 in uninfected cells stimulated expression of IFN-A genes (17), and third, several potential target genes of IRF-7 such as transporter associated with antigen presentation 2 and histone H4 were identified in the absence of active virus infection (18, 19).

Like IRF-4 and IRF-8, IRF-7 is predominantly expressed in cells of lymphoid origin; however, its level of expression could be up-regulated by virus infection, interferon treatment, and LPS (6, 8). Although IRF-7 has been studied extensively in the context of induction of interferon genes its possible roles in the development of the immune system have not been addressed. U937 and HL60 cells are promonocytic cell lines that, upon TPA treatment, can differentiate into macrophages; hence they have been used extensively as a model system to examine the factors involved in monocyte differentiation. In this paper, we report the induction of IRF-7 expression by TPA in U937 and HL60 cells and provide evidence indicating that the IRF-7 induction is essential for the monocyte differentiation to macrophages. Finally, we show that overexpression of IRF-7 alone is sufficient to trigger monocyte differentiation. Thus, we have identified a novel function of IRF-7 in innate immunity.

EXPERIMENTAL PROCEDURES

Cells and Cell Culture—Human peripheral blood mononuclear cells were isolated from healthy donors by a density gradient centrifugation using Ficoll-Paqce Plus (Amersham Pharmacia Biotech). Monocytes were further purified by attachment assay. The purity of isolated monocytes was determined by FACS (at least 90% positive for CD14). Macrophages were obtained by culturing adherent monocytes in tissue culture flask containing 1 ng/ml M-CSF (PEPROTECH) for 5 days in RPMI 1640 (Life Technologies, Inc.) supplemented with 2 mM l-glutamine and 10% human serum (Gemini). U937 and 293T cells were purchased from Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% FBS.
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ATCC. HL60 cells were generously provided by Dr. Saul Sharkis at The Johns Hopkins University.

Retroviral Transduction—The retroviral construct, pBabe-ER, was a gift from Dr. Alan Friedman. It contains a modified murine estrogen receptor ligand binding domain (amino acids 281–599) that responds to 4-hydroxytamoxifen (4-HT) but not estradiol (20). Human IRF-7 DNA amplified by PCR was inserted into the polylinker region of the pBabe-ER vector to create a fusion protein of IRF-7 and estrogen receptor (pBabeIRF-7). As a control, an IRF-7 deletion mutant (IRF-7M) lacking the DNA binding domain was inserted into pBabe-ER (pBabeIRF-7M). The $\phi$-amphophoric helper DNA was a gift from Dr. O. Witte at UCLA.

To create IRF-7–N, 10 $\mu$g of pBabeIRF-7 and $\phi$-amphophoric helper DNA were transiently transfected into 293T cells. Supernatant collected 48 h post-transfection was used to infect U937 cells. Transduced cells were selected in the presence of puromycin (1.5 $\mu$g/ml) added 48 h after transfection. 4 days after transfection, cells were stimulated with 4-HT (1 $\mu$M) for 3 days and then collected for analysis. The transfection efficiency of U937 cells was between 25 and 35%. Virus titers were at least 1 $\times$ 10^5 in NIH3T3 cells.

Northern Blot Analysis and Reverse Transcription-PCR (RT-PCR)—Total cell RNA isolation by the Trizol method (Life Technologies, Inc.) and Northern blot analysis were described before (21). The RT-PCR primers were identified by Western blot using a polyclonal antibody (Santa Cruz Biotechnology).

Stable Transfection—IRF-7DN expression plasmid, containing the N-terminal region of IRF-7 (amino acids 1–237), was generated as described before (22) and transfected into U937 cells via electroporation. The transfected cells were selected in the presence of 800 $\mu$g/ml G418. A total of 20 clones were screened, and the positive clones (five in total) were pooled together for further analysis.

FACS and Cell Cycle Analyses—Cells were resuspended in PBS containing 1% bovine serum albumin, phosphatidylserine-labeled CD11b and CD11c antibodies were added into cell suspension according to the manufacturer’s recommendations. After 30 min of incubation, the cells were analyzed by FACSscan (Becton Dickinson) using Cell Quest software. CD11b, CD11c, and 7-AAD (for dead cell exclusion) were purchased from Pharmingen.

For the cell cycle analysis, the cells were washed twice with PBS and resuspended in 500 $\mu$l of PBS containing 0.6% Nonidet P-40, 3.7% formaldehyde, and 11 $\mu$l of Hoechst 33258 (Sigma). The cell cycle profiles were obtained by FACSscan (Becton Dickinson).

Phagocytosis Assay—The phagocytosis assay was performed as described before (23). Briefly, killed heat-stable Staphylococcus aureus (ATCC S. aureus 502A) was labeled with 0.01% fluorescein isothiocyanate isomer I (Sigma) and sonicated and opsonized with an equal volume of human serum at 37°C for 30 min. Bacteria at a final concentration of $\sim 10^8$ cells/ml were incubated with 10 ml of medium at 37°C for 2 h. Bacterial phagocytosis by cells was analyzed by FACSscan.

RESULTS AND DISCUSSION

Induction of IRF-7 Expression during Monocyte Differentiation—U937 and HL60 are the promonocytic cell lines that can differentiate into macrophages in the presence of TPA. The involvement of IRF family transcription factors in the macrophage differentiation is well documented. Using an antisense approach, IRF-1 has been reported to play an important role in the TPA-induced U937 cell differentiation (24). IRF-8 (25, 26) and IRF-4 (27) mice exhibit a profound defect in macrophage differentiation that was corrected by re-introduction of IRF-8 (4, 27). Ets family transcription factor PU.1, which dimerizes with IRF-4, has also been implicated in the macrophage differentiation (26). We examined the expression profile of the IRFs during the differentiation of U937 cells to gain further insights into their roles in U937 cell differentiation. The RT-PCR analysis (Fig. 1A) shows that there were no significant changes of IRF-1 and IRF-2 mRNA expression after TPA treatment. Although IRF-4 mRNA could be detected neither before nor after TPA treatment, the levels of IRF-8 expression decreased after TPA treatment. In contrast, the relative levels of IRF-7 mRNA increased significantly after TPA treatment, suggesting a unique role of IRF-7 in the differentiation of U937 cells. Next, the induction of IRF-7 expression by TPA was analyzed in detail in U937 cells. TPA treatment increased IRF-7 mRNA levels in a time-dependent fashion (Fig. 1B). The induction of IRF-7 mRNA became detectable 12 h after TPA treatment, peaked after 1 day and went down slightly at day 2 and 3, and increased again at day 5 and day 6. TPA also induced the levels of IRF-7 protein in the nucleus in a time-dependent fashion (Fig. 1B). The relative levels of IRF-7 mRNA and protein were also induced by TPA treatment in HL60 cells (Fig. 1C). Finally, IRF-7 mRNA and protein could also be detected in human primary macrophages (Fig. 1D).

The constitutive expression of IRF-7 was shown to rapidly increased upon stimulation by viral infection, LPS, latent membrane protein-1, and IFN-α/β (6, 8, 27). Here we report for the first time that TPA treatment induces IRF-7 expression. There is a slight increase in expression of IFN-α/β genes in U937 cells at day 6 (Fig. 1A); however, because the increase in relative levels of IRF-7 mRNA preceded the induction of IFN genes, these data indicate that the induction of IRF-7 by TPA is not mediated by interferon. In summary, our results clearly show that the expression of IRF-7 is stimulated during TPA-induced monocyte differentiation.

Requirement of IRF-7 for the Differentiation of U937 Cells—To determine whether IRF-7 plays a role in the monocytic differentiation, we stably transfected into U937 cells the N-terminal portion of IRF-7 (amino acids 1–237) containing the DNA binding domain but lacking the C-terminal protein association domain. This truncated IRF-7 has been shown to behave like a dominant negative mutant capable of inhibiting virus-mediated induction of the endogenous IFN-α/β genes (22). The clones expressing IRF-7DN were pooled, and the pooled transfectants were analyzed. The expression of IRF-7DN in the pool of transfectant was about 3-fold higher than that of IRF-7 in TPA-treated U937 cells (Fig. 2A). To determine whether the expression of IRF-7DN affects TPA-induced differentiation of U937 cells, IRF-7DN-expressing cells were treated with TPA for 3 days, and the expression of monocyte differentiation makers, CD11b and CD11c, was analyzed by FACScan analysis. Expression of these two markers was also analyzed in U937 cells and cells transfected with empty vector. Morphologically, 1 day after TPA treatment 80% of control U937 cells became adherent, and at day 3 all the cells adhered. In contrast, about 40–50% of IRF-7DN-expressing cells still remained in suspension at day 3, indicating an impact of IRF-7 expression on U937 cell differentiation. Consistent with the morphological changes, the FACScan analysis showed further a dramatic decrease in CD11b and CD11c expression in the IRF-7DN-expressing cells. Compared with the TPA-treated control U937 cells, the percentage of cells stained positive for CD11b decreased from 83.1% in U937 cells to 52.5% in U937 expressing IRF-7DN, and the percentage of cells stained positive for CD11c decreased from 90.3% in controls to 45.8% in IRF-7DN-expressing cells (Fig. 2A). These data indicate an impaired monocyte differentiation in the presence of IRF-7DN and the requirement for IRF-7 for the differentiation of U937 cells.

Next, we have examined whether the expression of IRF-7DN...
affected the full macrophage differentiation program or only on a selective set of differentiation marker genes. One hallmark of macrophage differentiation and function is the ability to phagocytose foreign antigens. Therefore, we compared the phagocytic abilities of control U937- and IRF-7DN-expressing cells after TPA treatment. The expression of IRF-7DN significantly impaired the phagocytic ability of the TPA-treated U937 cells (Fig. 2C). Taken together, these data clearly demonstrate the critical role of IRF-7 in the U937 cell differentiation into functional macrophages. However the IRF-7DN mutant shares a DNA binding site with other IRFs, such as IRF-1 and IRF-8, that have been also implicated in monocyte differentiation. We cannot exclude the possibility that the observed impairment of monocytes differentiation by IRF-7DN is not entirely specific for IRF-7 and could also be a result of the interference with the functions of other IRFs.

Overexpression of IRF-7 in U937 Cells Triggers Differentiation

**Induces Cell Cycle Arrest**—To determine whether IRF-7 overexpression is sufficient to drive the differentiation of U937 cells, we transduced retrovirus harboring IRF-7 into U937 cells. The retrovirus used was based on vector in which IRF-7 was inserted, upstream of and in frame with, an estrogen receptor ligand binding domain, which, when expressed, generates an IRF-7ER fusion protein that requires 4-HT for activation. After infection the transduced U937 cells were selected in the presence of puromycin and were cultivated in the presence of 4-HT for 3 days. The differentiation to macrophages was monitored by the expression of monocyte differentiation markers CD11b and CD11c by FACS analysis. Whereas in U937 cells 4HT treatment did not modulate expression of these antigens, 4-HT treatment of IRF-7-transduced U937 cells significantly increased the percentage of cells stained positive for CD11b (from 24.6 to 75.4%) and CD11c (from 15.6 to 70.8%) (Fig. 3A) indicating that overexpression of IRF-7 triggers the differentiation of U937 cells. To further confirm that the effect is specific for IRF-7, U937 cells were transduced with pBalbeIRF-7M, a mutant construct in which the DNA binding domain of IRF-7 was deleted. As shown in Fig. 3A, there were no significant changes in the expression of CD11b and CD11c in U937 cells transduced with IRF-7DN after 4-HT treatment. These results suggest that IRF-7 overexpression triggered the monocyte differentiation and that the DNA binding domain of IRF-7 is required for this activity. This experiments also rules out the possible involvement of ER protein in the differentiation process. The relative levels of IRF-7ER in transduced cells were comparable with the levels of IRF-7 in TPA-treated cells (Fig. 3B).

To address the molecular mechanism of the IRF-7-mediated differentiation, we have examined the level of expression of IRFs and IFN-α/β genes in the IRF-7-overexpressing and IRF-7DN-expressing U937 cells (after 3 days of 4-HT or TPA treatment, respectively). The results of RT-PCR analysis shown in Fig. 3C indicate that the expression profiles of IRF-1, IRF-2, and IRF-8 are similar to those detected in TPA-stimulated U937 cells (see Fig. 1A), suggesting that overexpression of IRF-7 or IRF-7DN mutant did not affect levels of expression of IRF-1, -2, and -8. However, the levels of IFN-α/β transcripts were decreased in the TPA-treated IRF-7DN-expressing cells, and the expressions of IFN-α/β genes were significantly increased after 4-HT treatment in the IRF-7-overexpressing cells (compare with the Fig. 1A). However, exogenous IFN-α (500 units/ml) did not stimulate differentiation of U937 cells (data...
not shown). Further studies will be required to determine whether induction of type I IFN by IRF-7 plays a significant role in the differentiation of U937 cells.

Differentiation-inducing agents are known to have a negative effect on cell growth. Here we sought to determine whether the differentiation-promoting effect of IRF-7 is associated with the inhibition of cell proliferation. For this purpose, we examined the cell cycle distribution of TPA-treated control cells and cells expressing IRF-7DN. In addition, the cell cycle profiles of IRF-7-expressing U937 cells were also analyzed in the presence or absence of 4-HT. As seen in Fig. 3D, in U937 cells treatment with TPA for 3 days decreased the percentage of cells in S phase from 43.3 (control cells) to 6.4%, whereas the cells in G1 phase increased from 38.7 (control cells) to 78.3%, indicating that TPA treatment induced a cell cycle arrest. However, in U937 cells expressing IRF-7DN TPA treatment did not result in significant changes. As many as 34.2% of IRF-7DN cells were still in S phase, and only 56.8% of IRF-7DN cells stayed in G1 phase after TPA treatment, indicating that unlike the U937 cells, the IRF-7DN-expressing U937 cells were still able to proliferate in the presence of TPA. Consistent with the findings is cell cycle analysis of IRF-7-overexpressing U937 cells. In these cells only 13.4% of 4-HT-treated cells (3 days treatment) were in S phase compared with 39.6% of untreated cells. Also 67.1% of 4-HT-treated cells and only 47.3% of untreated cells were in G1 phase. These results indicate that overexpression of IRF-7 is sufficient to induce a cell cycle arrest. It should be also pointed out that we did not detect prominent apoptosis in IRF-7-overexpressing cells in this analysis (data not shown).

However the IRF-7-overexpressing U937 cells showed some distinct morphological differences from the TPA-treated cells. For example, even though most of the IRF-7-expressing cells showed different degrees of membrane and cytoplasmic ruffling like TPA-treated cells, only a small amount of IRF-7-transduced cells (about 15%) became adherent after 4-HT treatment. This suggests TPA treatment induces additional factors, which, together with IRF-7, may constitute an optimal environment for monocytes to differentiate. Nevertheless, our data clearly demonstrate the essential role of IRF-7 in monocyte differentiation as evidenced by the requirement for IRF-7 in U937 cell differentiation and by the fact that overexpression of IRF-7 alone was sufficient to induce cell cycle arrest and macrophage differentiation.

It has been known that circulating monocytes can be recruited by inflammatory and immune stimuli to the site of infection and give rise to activated macrophages. Activated macrophages elicit many functions that are essential for the host defense against infection. The molecular mechanisms that result in the differentiation of newly recruited monocytes once they have left the circulation are still not clearly understood. It is generally believed that the local environment, especially the cytokines milieu, plays a key role in this differentiation (28). The importance of IRF-7 in the innate immunity has been illustrated by its involvement in the induction of interferon and cytokine gene expression. The finding that IRF-7 is also required for monocyte differentiation has been unexpected. Even more surprising has been the demonstration that overexpression of IRF-7 could alone stimulate monocyte differentiation. Previous studies have shown that transcription factors Blimp-1 (24), HOXA10 (29), and WT1 (Wilms tumor suppressor) (30), when overexpressed in U937 cells, can induce their differentiation. IRF-7 is generally expressed in cells at very low levels but can be rapidly induced by interferon and inflammatory stimuli such as virus infection, LPS, and proinflammatory cytokines such as TNF-α. This ability to respond to inflamma-

\[ \text{Unpublished data.} \]
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...inducers of differentiation in U937 monocytes to macrophages. We demonstrate that IRF-7 is not only necessary but also sufficient to identify IRF-7 target genes. In conclusion, our results clearly demonstrate that disregulation of IRF-7 expression such as by promoter hypermethylation could play a role in leukemogenesis. Future efforts will be devoted to examine this possibility and to identify IRF-7 target genes. In conclusion, our results clearly demonstrate that IRF-7 is not only necessary but also sufficient to induce differentiation in U937 monocytes to macrophages.

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