Mechanisms of Murine RANTES Chemokine Gene Induction by Newcastle Disease Virus*

(Received for publication, January 18, 1996, and in revised form, March 8, 1996)

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We have previously defined the lipopolysaccharide (LPS)-responsive element (LRE) in the promoters of murine RANTES (regulated on activation normal T-cell expressed) (MuRantes) and murine IP-10/crg-2, chemokines which have potent chemotactic properties for inflammatory cells including monocytes and T lymphocytes. In the present work, we studied the transcriptional mechanism of MuRantes gene induction by virus and compared it with that of LPS in an effort to understand the host responses to virus and bacterial toxins at the molecular level. MuRantes mRNA expression is induced by Newcastle disease virus (NDV) and LPS in the RAW 264.7 macrophage cell line and peritoneal macrophages of LPS-responsive C3HeB/FeJ mice. In LPS-hyporesponsive C3H/HeJ mice, only NDV induces this chemokine gene, indicating that the pathways of transcriptional activation by NDV and LPS are not identical. Using a transient transfection assay, the minimal virus-responsive element (VRE) was localized between nt −175 and −116. The VRE contains previously defined LRE motif 1 (TCAYRCTT) and motif 3 ((T/A)GRTT-TCA(G/C)TTT), which were shown to also be important for initiation of transcription by virus. NDV-stimulated nuclear extracts were tested for trans-activating factors able to bind the VRE. The chromosomal protein HMG-I(C) was shown to bind the 3′-AT-rich domains of the VRE, and the presence of HMG-I(C) was demonstrated in the VRE-protein complex formed with nuclear extracts from NDV-stimulated, but not unstimulated cells. These findings demonstrate the role of HMG-I(C) in activation of MuRantes promoter by NDV.

In order to understand the early host responses to infection, much effort has been focused on the transcriptional activation of inducible genes by viruses. DNA viruses such as adenovirus and herpesviruses encode regulatory proteins that affect the activities of cellular transcription factors. These factors play a role in regulating cell growth and neoplastic transformation through activation of inducible genes (1–5). Retroviruses are known to affect activation of cellular genes in part through regulating enhancer activities (6). The Paramyxoviridae, a family of negative sense RNA viruses, are potent activators of inducible genes, in particular cytokines (7–10). This family includes measles virus, canine distemper virus, Sendai virus, and Newcastle disease virus (NDV), all of which are neurotropic (11, 12).

Regarding transcriptional activation of cellular genes by Paramyxoviruses, a large body of work has centered on elucidating the mechanisms of IFN-β gene induction. In addition to NF-κB, interferon regulatory factor 1, c-Jun, and ATF-2 (activating transcription factor 2), a DNA-binding protein HMG-I(Y) is required for IFN-β gene induction by Sendai virus (10, 13). HMG-I(Y) is a member of the high mobility group (HMG) family of chromosomal, non-histone proteins (for review, see Refs. 14 and 15). HMG-I(Y) binds to AT-rich regions of double-stranded DNA and increases the binding affinity of NF-κB and ATF-2 for their respective sites. HMG-I(Y) also induces DNA bending, presumably allowing interactions among multiple transcriptional activators bound at distant sites on the promoter (10).

It has been noted that Paramyxoviruses and bacterial LPS stimulate overlapping, but distinct, sets of cytokine genes (8, 11, 16–21). In order to determine the similarities and differences between antiviral and antibacterial host response mechanisms at a molecular level, we have examined the inducibility of the murine homolog of RANTES (MuRantes), a member of β or C-C chemokine superfamily, in murine macrophages upon stimulation by NDV as compared with LPS. Involvement of RANTES in inflammation through its chemotactic activity for monocytes and eosinophils has been well documented (22–24). In addition, RANTES is chemotactic for memory T lymphocytes (22). RANTES gene is expressed in a number of cell types including fibroblasts (25), T-cell lines (26), endothelial cells (27), macrophages and macrophage-like cell lines (28), mesangial cells (29), and brain astrocytes and microglia (30).

We have found that the NDV virus-responsive element (VRE) is defined by sequences spanning from nt −175 to −116, which includes the entire region responding to LPS (LRE).

*This work was supported by Grants RO1 CA1411320, RO1 AI19622, RO1 NS 15662, and NS 20022 from the National Institutes of Health.

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1 The abbreviations used are: NDV, Newcastle disease virus; LPS, lipopolysaccharide; LRE, LPS-responsive element; VRE, virus-responsive element; nt, nucleotide(s); IFN, interferon; HMG, high mobility group; NF, nuclear factor; IP-10, inflammatory protein, 10 kDa; crg, cytokine-responsive gene; AP-1, activator protein 1; CAT, chloramphenicol acetyltransferase; EMSA, electrophoretic mobility shift assay; m.o.i., multiplicity of infection; FBS, fetal bovine serum; CHX, cycloheximide; PB, polymyxin B; UV-NDV, ultraviolet-irradiated NDV; DTT, dithiothreitol; wt, wild type, ISRE, interferon stimulus response element.
MuRantes Gene Induction by Virus and LPS

Electrophoretic Mobility Shift Assay (EMSA)—Cell monolayer was stimulated with NDV in the presence of 10 μg/ml CHX in serum-free RPMI for 2 h. After washing with phosphate-buffered saline, pelleted cells were suspended in an equal volume of buffer A: 10 mM HEPES, pH 7.9, 1.5 mM MgCl₂, 10 mM KCl, 0.5 mM phenylmethylsulfonyl fluoride,
1 mM dithiothreitol (DTT), then lysed by repeated aspiration through a 25-gauge needle until over 90% were lysed. Nuclei were stirred for 30 min at 4°C in extraction buffer (20 mM HEPES, pH 7.9, 25% glycerol, 0.42 mM NaCl, 1.5 mM MgCl2, 0.2 mM EDTA, 0.5 mM phenylmethylsulfonyl fluoride, 1 mM DTT), then centrifuged at 14,000 rpm at 4°C in an Eppendorf Microfuge. The supernatants were dialyzed for 2 h in 20 mM HEPES, pH 7.9, 20% glycerol, 100 mM KCl, 0.2 mM EDTA, 0.5 mM phenylmethylsulfonyl fluoride, 1 mM DTT. Protein concentrations were determined by the BCA method (Pierce).

For EMSA, 2–3 μl of nuclear extracts containing 5 μg of protein were mixed with 1 μg of bovine serum albumin and 2 μg of poly(dI:dC)(dI:dC) or poly(dG:dC)(dG:dC) (Pharmacia Biotech Inc.) in a final 20-μl volume by adding 10 mM HEPES, pH 7.9, 16% glycerol, 20 mM NaCl, 4 mM MgCl2, 0.5 mM KCl, 0.1 mM EDTA, 2 mM DTT, and 2 μM spermidine (28). After incubation at room temperature for 10 min, 0.5 to 5 ng of 32P-probe was added, and the mixtures were incubated for 15 min at 37°C. After addition of 1 μl of 10 × TBE (0.9 M Tris borate, 20 mM EDTA), samples were separated on a 6% native polyacrylamide gel (28). DNA probes—MuRantes probes (−185/−116 and −215/−116) were generated by polymerase chain reaction using 5′ flanking Sal I site and 3′ flanking HindIII site. Oligonucleotides were appropriately digested for 1 h at 37°C and labeled by filling in with [32P]dCTP and [32P]dGTP as described previously (28). The NF-κB probe was HIV-long terminal repeat, TCA(A/G)GACTTTCGGT-GGGGACTTTCCCTCCTT.

Antibodies—The antibodies to JunD, CREB, c-Fos, p50, and p65 were from Santa Cruz Biotechnology (Santa Cruz, CA). The c-jun and J unB antibodies were obtained from Oncogene Science (Uniondale, NY). Anti-HMG-I(C) IgG was a gift from J. Maher.

RESULTS

NDV Induced MuRantes mRNA Accumulation in RAW 264.7 Cells—The kinetics of NDV-induced MuRantes gene expression and the dose of NDV required were examined in RAW 264.7 cells by Northern analysis (Fig. 1). MuRantes transcripts were detected at 4 h, reached the maximum between 8 and 24 h (Fig. 1A), then markedly reduced at 48 h (data not shown). At 6 h of stimulation, MuRantes mRNA expression was increased with increasing m.o.i. of NDV (Fig. 1B). MuRantes mRNA was induced by live virus, but not by mock NDV or NDV-depleted supernatants (Fig. 2). Induction also occurred when cells were stimulated by NDV in the presence of cycloheximide (CHX) or polymyxin B (PB), indicating that MuRantes gene induction by NDV occurred in an immediate early manner, as has been shown for LPS stimulation (28), and was not due to contaminating LPS. UV-irradiated virus (UV-NDV) also induced MuRantes. Induction of MuRantes gene by NDV does not require viral replication, since UV and CHX treatments render the NDV unable to replicate, a finding also seen in induction of complement C3 and IP-10/crg-2 genes by UV-NDV (37, 38).

Induction of MuRantes mRNA Expression in Peritoneal Macrophages—To examine possible differences between NDV and LPS as stimuli, macrophages were obtained from LPS-responsive strain C3HeB/FeJ mice and C3H/HeJ mice which carry a mutation of the lps gene rendering them hyporesponsive to LPS (39). NDV-induced MuRantes mRNA accumulation in both strains of mice, C3HeB/FeJ and C3H/HeJ, while LPS failed to elicit any induction in C3H/HeJ, as expected (Fig. 3). In the presence of CHX, NDV superinduced MuRantes in macrophages of both strains, as in primary rat astrocytes (30), but not in RAW 264.7 cell line (28). Since NDV induced MuRantes mRNA in LPS-hyporesponsive macrophages, the pathways of transcriptional activation by LPS and NDV cannot be identical. Studies to evaluate this issue by examining signal pathways using inhibitors are shown in Fig. 4. Tyrosine kinase inhibitor herbimycin A had a potent inhibitory effect on the NDV-mediated mRNA expression, whereas the LPS-induced expression was much less sensitive (Fig. 4A). The potent pro-

![Fig. 3.](https://example.com/fig3.png)
considered as 100%, deletion to nt 2100 and 2100 to 185 completely abolished the activity. The 3' boundary was closely aligned to the ISRE core since this promoter is not inducible by IFNs (28). Cells were stimulated with LPS and NDV side by side, whereby the previously described 5' and 3' boundaries of LRE (−175/−125) (28) have been verified in this study (data not shown). The pattern of relative CAT activity induced in these constructs by LPS and NDV show marked similarities. Therefore, the 5' boundary of the VRE (−175) was closely aligned to that of the LRE and the 3' boundary of VRE (−116) was found to extend further than the LRE.

Mutational Analysis of the MuRantes VRE—Both the VRE and LRE contain 2 conserved sequences shared with mulP-10/ crg-2 LRE (28): motif 1, TCAYRCTT, and motif 3, (T/A)GRTTT-TCA(G/C)TJT (Fig. 7). Since the VRE also contains an AP-1 site (8/10), possible utilization of these sites for transcription was examined by mutational analysis. Results from 4 separate experiments revealed two regions critical for NDV inducibility (Fig. 8). A half AP-1 site (TCA) in motif 1 is flanked on the 3' side by 5 nt, and on the 5' side by the other half of the AP-1 site (Fig. 8A). The first required domain was identified by mutations 1 through 4 (M1-M4). Mutation 1 (M1) in the 5'-half AP-1 site resulted in a moderate
loss of activity (37.3% ± 7.3 in relation to nt -185 to -8 wild type construct). M3 which involves the 3'-half of the AP-1 site and the 5'-half of motif 1 caused dramatic loss of activity. M2, which altered both 5'- and 3'-halves of the AP-1 site as well as motif 1, had an even more profound loss of activity. M4, which changed 3 bases flanking the half AP-1 site in motif 1, reduced the activity to 48.4% ± 4.1. M5 and M6 carrying mutated bases of motif 2 between motif 1 and motif 3, did not influence the CAT activity. A second critical region was identified through the use of M8 through M12 constructs. M8 decreased the VRE activity close to 60%. M9 and M10, which affect A-T-rich domains within motif 3, totally abolished the VRE activity. It was significant that M10 which lies within motif 3, but outside of the NF-κB-like site, as well as M11 abolished the promoter activity (0.3% ± 0.3). M12 showed significant VRE activity upon NDV stimulation (57%). In addition, M7, which alters the highly conserved nucleotides of the potential NF-κB site, had no effect on virus inducibility. These functional data indicate that in addition to motif-1, three A-T-rich domains, two of them located within motif 3, are required for the VRE activity. The data also imply that the NF-κB-like site within the VRE is unlikely to participate in NDV induction of MuRantes, as was previously found for LPS (28), even though both LPS and NDV can induce NF-κB DNA binding activity (data not shown), as reported by others (6, 41, 42). The CAT activity induced by LPS determined along with the virus using M1–M10 constructs, which was closely similar to the previously published values (28), also showed a similarity to the activity induced by NDV, except that mutation M9 produced partial reduction in LPS-treated cells, but a near-complete loss in NDV-infected cells. NDV and LPS also produced similar results for M11 and M12.

Examination of the DNA-binding Factors Involved in MuRantes Induction—The properties of the DNA-binding factors were examined by EMSA using poly(dG:dC)(dG:dC) and poly(dI:dC)(dI:dC) as nonspecific competitors (Fig. 9A). With poly(dI:dC)(dI:dC), formation of VRE-protein complexes in unstimulated or stimulated nuclear extracts was markedly reduced when compared to those formed with poly(dG:dC)(dG:dC). Using poly(dG:dC)(dG:dC), a single slower mobility band in unstimulated extracts and two closely spaced faster mobility bands in NDV-stimulated extracts were observed, all of which were competed away with 20-fold excess of cold wt VRE (nt -185 to -116) (Fig. 9, A and B). As shown in Fig. 9, A and B, unstimulated nuclear extracts formed a single band of slower mobility that can be competed away with wt VRE. The nature of this band is currently unknown. As shown in Fig. 9B, VRE complexes formed with NDV-stimulated extracts that can be competed away with wt VRE (lanes 3 and 4), were not competed with a wt- or mutation 6-containing 30-mer (-167/-137) (lanes 5 and 6). However, full-length VRE (-185/-116) with M7, M10, and M12 were effective as competitive inhibitors (lanes 7, 8, and 10). M11 VRE partially inhibited the complex formation (lane 9). A significant finding is that M7 (mutation of the NF-κB-like site) inhibited the complex formation with similar efficiency as wt VRE. The inability of truncated wt 30-mer sequences to inhibit the VRE-complex formation was correlated with the failure of a wt 30-mer (-167/-137), used as a probe, to form DNA-protein complexes (Fig. 9C). These results collectively indicate that both motif 1 and motif 3 plus A-T-rich sequences may be required to form VRE-protein complexes in NDV-stimulated nuclear extracts. The finding that complex formation was inhibited by M10, M11, and M12 VRE, which containing mutations affecting a single A-T-rich domain, suggested a cooperative binding to the A-T-rich domains. We have not tested VRE in which all of A-T-rich domains are mutated.

Presence of HMG-I(C) in NDV-stimulated Nuclear Extract and Binding of HMG-I(C) to MuRantes VRE—Since formation of the VRE-protein complex was inhibited by poly(dI:dC)(dI:dC) which appears similar to A-T-rich DNA with respect to hydrogen bond formation in the minor groove, and since MuRantes VRE also contains A-T-rich regions in the 3’ border, a possible role for the HMG-I family of proteins was explored. Presence of HMG-I(C) in VRE-protein complexes was detected by anti-HMG-I(C) antibody, which supershifted the complexes formed with NDV-stimulated nuclear extracts (Fig. 10A, lanes 9–12), but not with unstimulated extracts (lanes 5–8). Purified HMG-I(C), 10 nM, formed two bands with wt VRE probe, and the complexes were also supershifted with antibody (lanes 1–4). In EMSA, purified HMG-I(C) formed a single mobility complex with a wt 30-mer (-167/-137) (Fig. 10B), and the HMG-I(C) binding to this 30-mer probe was markedly diminished when any one of the 2 A-T-rich domains was mutated (M10, M11). The binding of HMG-I(C) to a 30-mer (-161/-131)
which contained M12 was also significantly decreased. Although each of these A-T rich domains is the target for HMG-I(C) binding, the role of M12 site in transcriptional activity of the VRE may not be as important as the A\_T-rich sites effected by M9, M10, and M11, based on the results of the CAT assay. The supershift with anti-HMG-I(C) carried out with LPS-stimulated nuclear extracts was far below the level achieved with virus-stimulated nuclear extracts (data not shown).

Studies of AP-1-binding Factors and NF-\kappa\B in VRE-Protein Complexes—Proteins capable of binding to NF-\kappa\B and AP-1 sites were examined using antibodies (Fig. 11). Only anti-c-jun supershifted the VRE-protein complex (lane 11). Although the effect was detected only in overexposed autoradiograms, this finding was consistently reproduced in 4 separate experiments. Antibodies to c-Fos, J unB, J unD, CREB, p50, and p65 were unable to supershift the VRE-protein complexes. NF-\kappa\B binding to the HIV-long terminal repeat NF-\kappa\B probe was induced in NDV- or LPS-stimulated nuclear extracts, and the binding was not competed away with wt VRE or M7 VRE (data not shown).

**DISCUSSION**

In this study, we have shown that the murine RANTES (MuRantes) chemokine gene is induced by NDV in an immediate early manner in RAW 264.7 cells. MuRantes mRNA induction does not require the synthesis of viral proteins or double-stranded viral RNA since CHX and UV-NDV showed induction efficiency similar to live virus. These results were reproduced in primary peritoneal macrophages elicited with starch from C3HeB/FeJ mice. However, MuRantes gene was induced by NDV, but not by LPS in macrophages from C3H/HeJ mice, an LPS-hyporesponsive strain. In addition, MuRantes mRNA expression induced by NDV and LPS showed stimulus-specific susceptibility to signal pathway inhibitors. Herbimycin, a tyrosine kinase inhibitor, preferentially inhibited NDV-stimulated mRNA accumulation, whereas HA1004, a cyclic nucleotide-dependent kinase inhibitor, was more effective in inhibiting the LPS effect. These results indicate that induction of MuRantes gene by NDV and LPS is through distinctly different pathways. In this context, it is interesting that the VRE and LRE of the MuRantes promoter shared extensive...
sequence homology: the minimal VRE lies between nt -175 and -116 and the LRE between nt -175 and -125. The VRE also shared with LRE certain DNA motifs, designated motif 1 and motif 3, which were required for MuRantes transcription, as shown by mutational analysis. Motif 3 contains two A-T-rich domains, each of which when mutated as M9 or M10 abolished the VRE activity. In contrast, mutation of the first A-T-rich domain (M9) reduced the LRE activity only partially (28). The VRE carries additional A-T-rich sequences, thereby allowing it to compete with minor groove binding proteins like HMG-I(Y) participates in transcription of IFN-β gene induced by Sendai virus by enhancing the affinity of NF-κB and ATF-2 to their respective binding sites (10, 13). We have demonstrated that HMG-I(C), a member of the HMG-I family of proteins (46, 47), was present in the VRE-protein complex formed with NDV-stimulated nuclear extracts, but not the VRE complex of unstimulated extracts. These data indicated that NDV-induced post-transcriptional activation of HMG-I(C) allows the assembly of the VRE-protein complex needed for transcription rather than induction of HMG-I(C) synthesis, since MuRantes gene induction by NDV was not affected by CHX. The presence of multiple HMG-I(C) binding sites and the failure of VRE containing M9, M10, or M11 to induce transcription suggest possible cooperative activity among HMG-I(C) proteins and between HMG-I(C) and other DNA-binding factors. LPS-induced CAT activity was only partially affected by M9 and the potency of anti-HMG-I(C) to supershift the LRE-protein complexes was reduced significantly compared with that of virus. Thus, the possible effects of HMG-I(C) on MuRantes transcription in response to virus and LPS may be quantitative.

It was unexpected that the 8/10 NF-κB binding site failed to play a major role in virus-mediated activation of this protein. It is possible that the binding site sequences are not favorable for NF-κB binding. Activated NF-κB may still play a role through binding to transcription factors such as c-jun (48). As shown here, it is likely that c-jun in the VRE-protein complexes may interact with motif 1 and the 5'-flanking half AP-1 site. The interaction among DNA-binding proteins may be regulated by HMG-I(C) in the VRE and the binding specificities, and possible partners that may dimerize with c-jun in the VRE and LRE may not be identical. Various trans-activating proteins,
through homo- or heterodimer formation, are known to generate response diversity by affecting binding affinity and/or selecting different flanking sequences for binding (for review, see Ref. 49). The A-T-rich sequences in the VRE that can bind multiple HMG-I(C) may also play a critical regulatory role in generating additional diversity by enhancing the binding of specific transcription factors and by allowing protein-protein interaction through DNA bending.

It would be surprising if the molecular mechanisms used to induce common cytokines by bacterial and viral pathogens evolved as totally separate pathways. Therefore, the extensively overlapping sequence motifs between the LRE and VRE in MuRantes induction are not unexpected. These findings also indicate that host defense mechanisms to viral and bacterial infection may be achieved by utilizing similar or closely overlapping molecular events.

Acknowledgments—We express sincere appreciation to Dr. Daniel Nathans for critically reviewing the experimental data and the manuscript. We thank William Paznekas and Chun-Min Chi for their valuable technical assistance.

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