The Acute Phase Response of Mouse Liver

GENETIC ANALYSIS OF THE MAJOR ACUTE PHASE REACTANTS*

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We have examined changes in translatable liver mRNA's during the acute phase response in several inbred mouse strains. Induction of mRNA's for the known acute phase reactants serum amyloid A, haptoglobin, haptoglobin, and α1-acid glycoprotein was observed. Two α1-acid glycoproteins, termed AGP-1 and AGP-2, differing in size and charge, were found in all mice and appear to derive from distinct yet closely related mRNA's. Polymorphism in the structure of AGP-1 among strains was used to map the structural gene, *Agp-1*, to chromosome 4 near the *b* locus. Structural variation for serum amyloid A enabled mapping its structural gene, *Saa*, to chromosome 7, near *Gpi-1*. A wild-derived population of mice, *Mus spretus*, contains several variations of interest, including structural variations in many acute phase proteins and a putative regulatory variation specific to AGP-1. Further analysis of these genetic variants should provide novel insights into the acute phase response and the factors that mediate it.

Mammals undergo a complex response to a variety of systemic injuries such as infection or inflammation. For example, injection of bacterial cell wall lipopolysaccharides or other irritants into mice causes immigration of neutrophils and monocytes to the site of injury, mitogenic stimulation and maturation of B-lymphocytes, release of a multitude of active components (interferon, interleukins, and leukotrienes) by mononuclear cells, and a dramatic increase in the levels of a variety of liver-derived serum proteins, termed the acute phase reactants (1). One well characterized acute phase reactant of the mouse, serum amyloid A, is a component of high density lipoproteins and is also the precursor to the major phase reactants in mice as well as in other mammals include haptoglobin, hemopexin, and α1-antitrypsin, apolipoprotein A-I, major urinary proteins, α1-antichymotrypsin, apolipoprotein A-I, major urinary proteins, α1-antichymotrypsin, apolipoprotein A-I, and serum amyloid A has been carried out by immunoprecipitation of cell-free translation system derived from animal cells (12) in the presence of [35S]methionine.

Extensive studies at the biochemical and cellular levels, while providing critical information on the nature of the acute phase response, have answered few questions relating to the regulation of the response and the effectors that are involved. A genetic approach offers the potential to identify and locate structural genes encoding the acute phase reactants and regulatory genes governing their expression both prior to and following the stress response; such information is crucial to understanding the regulation of this complex process.

In the present paper, we report biochemical and genetic studies on the mRNA's encoding the acute phase reactants in mice as well as in inbred mice. In addition to defining the spectrum of the acute phase response (i.e. the spectrum of responding gene products), we have identified structural and regulatory variation for the expression of several acute phase reactants, and have mapped the structural genes for AGP and SAA.

**MATERIALS AND METHODS**

**Animals**—Laboratory inbred strains and AKXD recombinant inbred strains derived from the strains AKR17 and DBA127 were purchased from the Jackson Laboratory, Bar Harbor, ME. *Mus spretus* is from a randomly breeding colony of mice maintained by Dr. Verne Chapman. These mice were originally trapped in Southern France. Animals were used at 2-3 months of age. An acute phase response was induced either by subcutaneous injection of 50 μl of turpentine into the lumbar region or by intraperitoneal injection of bacterial lipopolysaccharide in phosphate-buffered saline. A trichloroacetic acid-extracted lipopolysaccharide preparation from *Escherichia coli* serotype 0.27:BS was obtained from Sigma.

**Hepatocytes**—Hepatocytes were obtained by collagenase perfusion of adult livers according to Seglen (4). The conditions for culturing cells and labeling with [35S]methionine will be described elsewhere (3). To obtain non-N-glycosylated secretory proteins, the cells were incubated for 2 h in medium containing 2 μg/ml of tunicamycin and labeled with [35S]methionine for 6 h. Early precursor forms of glycoproteins were purified by concanavalin A-Sepharose chromatography of extracts from cells pulse-labeled with [35S]methionine for 10 min (5).

**Extraction and Blot Analysis of RNA**—Total liver RNA was extracted by the guanidine HCl procedure (6, 7). RNA was separated on agarose gels containing formaldehyde (8), transferred to nitrocellulose (9), and hybridized to [32P]-labeled p10-14 DNA, which contains a cDNA insert complementary to the mRNA for rat α1-acid glycoprotein (10). Hybridizing RNA species were observed by autoradiography. Mouse ribosomal RNA's were used as markers.

**mRNA Selection**—Plasmid DNA was immobilized on a nitrocellulose filter and used to isolate complementary RNA as described previously (11). Selected RNA was translated in a cell-free system.

**Cell-free mRNA Translation**—Total or plasmid-selected mRNA was added to a fractionated cell-free translation system derived from animal cells (12) in the presence of [35S]methionine.

**Acrylamide Gel Analysis**—Cellular and cell-free synthesized protein products were subjected to two-dimensional polyacrylamide gel electrophoresis (12, 13) and were visualized by fluorography (14). Identification of spots representing haptoglobin, hemopexin, α1-antitrypsin, α1-antichymotrypsin, apolipoprotein A-I, major urinary proteins, albumin, and serum amyloid A has been carried out by immunoprecipitation of cell-free synthesized proteins with monospecific antibodies to the plasma proteins, mRNA selection with cloned cDNA probes, and proteolytic comparison to the appropriate plasma protein as described elsewhere (3). Proteolytic mapping of protein spots cut out

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of the two-dimensional gels was accomplished with Staphylococcus aureus V8 protease (Miles Laboratories Inc.) according to the method of Cleveland et al. (15). Assessment of the number of N-glycans/molecule was achieved by partial endo-β-N-acetylglucosaminidase H digestion in a polyacrylamide gel (5).

RESULTS

Domain of the Hepatic Acute Phase Response—To establish the basic pattern of the acute phase response in mouse liver, we analyzed the qualitative and quantitative changes in composition of functional mRNAs in the livers of animals treated with bacterial lipopolsaccharides or with turpentine. Total liver RNA was extracted and translated in a cell-free system, and the products were separated by two-dimensional polyacrylamide gel electrophoresis. We have observed striking changes in the cell-free translation patterns following inflammation in several inbred strains. As a representative example, the patterns for strain C3H/HeJ are given in Fig. 1. The mRNA levels for several proteins (spots 1–8 in Fig. 1) are increased, while those for others (spots 9–11 and 13) are decreased. Determination of the relative incorporation of radioactivity

\[
\begin{align*}
\text{MW} & \times 10^{-3} \\
7.5 & \quad 7 \quad 6 \quad 5 \quad 4
\end{align*}
\]

![Fluorograph of protein separation by two-dimensional electrophoresis](http://www.jbc.org/)

**Fig. 1.** Modulation of translatable mRNAs in the liver of C3H/HeJ male mice by an acute inflammation. Males of strain C3H/HeJ received an intraperitoneal injection of 300 μl of phosphate-buffered saline (control), 300 μl of phosphate-buffered saline containing 10 μg of trichloroacetic acid-extracted lipopolysaccharides, or two subcutaneous injections of 25 μl of turpentine. Liver RNAs were extracted 24 h later and translated in a cell-free system. The products in 5-μl translation mixtures were separated by two-dimensional polyacrylamide gel electrophoresis. The fluorographs were exposed for 24 h. Numbers 1–8 indicate proteins which are increased, numbers 9–11 and 13 indicate those which are decreased, and numbers 14–16 indicate proteins which remain constant. Identified proteins are described in the text. BPB, bromphenol blue.
into each of the protein spots (data not shown) indicated that the magnitude of changes varied considerably, from a reduction of less than 2-fold (spot 11) to an increase of more than 100-fold (spots 1-3). Although both irritants are capable of inducing the same major changes, we found that liposaccharides, when used in doses below 50 μg/animal, were consistently less effective than turpentine (see spots 2, 4, 10, and 13).

We could identify some of the protein spots as precursor forms of previously identified major plasma proteins whose circulating concentrations are known to be altered during the acute phase reaction in mice (16). Among the proteins which are increased by inflammation are serum amyloid A (spot 3), haptoglobin (spot 4), and hemopexin (spot 5); among those which are reduced are albumin (spot 9), apolipoprotein A-I (spot 10), and the major urinary proteins (spot 11). No significant changes in mRNA levels for α1-antichymotrypsin (spot 15) and α1-antitrypsin (spot 16) were detected. The mRNA for actin (spot 14) appears to be unaffected, although it has been reported that the synthesis of this protein in liver is increased 5-fold during the acute phase response (17).

From analysis of proteins secreted from primary cultures of mouse hepatocytes, we know that α1-acid glycoprotein is a major acute phase reactant (3). Indeed, we can find a protein (Fig. 1, spot 1) which has an electrophoretic mobility indistinguishable from the AGP precursor of the rat (12). However, this assignment was uncertain because there was an additional inducible protein (spot 2) with slightly larger molecular weight and more acidic charge. To demonstrate which spot is AGP, we took advantage of a cloned cDNA probe to rat AGP (10). When tested with mouse RNA, this probe was found to hybridize to an inflammation-inducible mRNA of length 0.85 kilobases (Fig. 2). This mRNA was isolated by capturing onto nitrocellulose filters affixed with the cDNA plasmid and was translated in the cell-free system. mRNA from the liver of a male (AKR/J × DBA/2)F, hybrid was used because of the presence of two electrophoretic forms of spot 1 (see below). As shown in Fig. 3, both forms of spot 1 as well as spot 2 were present in translation products of the selected RNA, indicating that mRNAs encoding both polypeptides were specifically recognized by the cDNA plasmid. These results suggest the presence of mRNAs for two AGPs in the mouse.

To substantiate this finding, we compared the proteolytic digestion patterns of spot 1, spot 2, and the corresponding cellular proteins synthesized and secreted by tumicamycin-treated mouse hepatocytes. Spots 1 and 2 (Fig. 4, lanes 2 and 3), synthesized in a cell-free system, yield digestion products that are similar to each other and to authentic rat AGP (12). In addition, the patterns of the cellular forms (lanes 4 and 5) were indistinguishable from the cell-free forms. Thus, there are two closely related forms of AGP, henceforth termed AGP-1 and AGP-2, that are probably encoded by distinct yet closely related mRNAs.

Although it appears that AGP-1 and AGP-2 share sequence homologies, translation of their mRNAs in the presence of dog pancreatic membranes revealed a major processing difference between the two. Electrophoretic analysis of the glycosylated intermediates after their purification by concanavalina-A sepharose chromatography (12) suggested that AGP-1 acquires five glycan units, while AGP-2 acquires six (Fig. 5A). To confirm this, we have determined the number of glycan units in cellsecreted precursor forms. The fully glycosylated precursor forms of AGP-1 and AGP-2 were isolated from pulse-labeled mouse hepatocytes by lectin chromatography (5) and separated by two-dimensional gel electrophoresis (Fig. 5C); as controls, nonglycosylated AGPs secreted by tunicamycin-treated cells were also analyzed (Fig. 5B). Fully glycosylated AGP-1 appears as single spot; fully glycosylated AGP-2, however, appears as two equally intensive spots with identical isoelectric points and a molecular weight difference of 2000. Partial endoglycosidase H digestion indi-
dimensional acrylamide gels. Samples were digested with 150 ng of endo-B-N-acetylglucosaminidase H in an 11% polyacrylamide gel, as described (35). Exposure times of the fluorograph varied between 24 h and 3 weeks, as necessary. Lane 1, undigested AGP-1 synthesized by cell-free translation; lanes 2 and 4, digested AGP-1 synthesized by cell-free translation and by cultured hepatocytes, respectively; lanes 3 and 5, digested AGP-2 synthesized by cell-free translation and by cultured hepatocytes, respectively.

Fig. 4. Proteolytic mapping of AGPs. Nonglycosylated forms of AGP-1 and AGP-2, either synthesized by cell-free translation of C57BL/6J RNA or secreted into the medium of tunicamycin-treatment primary hepatocytes, were recovered from preparative two-dimensional acrylamide gels. Samples were digested with 150 ng of S. aureus V8 protease for 30 min at 37 °C in a 15% polyacrylamide gel as described (15). Exposure times of the fluorograph varied between 24 h and 3 weeks, as necessary. Lane 1, undigested AGP-1 synthesized by cell-free translation; lanes 2 and 4, digested AGP-1 synthesized by cell-free translation and by cultured hepatocytes, respectively; lanes 3 and 5, digested AGP-2 synthesized by cell-free translation and by cultured hepatocytes, respectively.

Fig. 5. Glycosylation of AGP-1 and AGP-2. A, polyadenylated liver RNA from a turpentine-treated C57BL/6J male was translated in a cell-free system in the presence of dog pancreas microsomes. The synthesized glycosylated proteins were isolated by chromatography on concanavalin A-Sepharose and separated by two-dimensional electrophoresis (12). Only the region of the gel containing the AGP intermediates is reproduced. Due to a partial modification of AGPs to more basic forms by an unknown reaction in the translation mixture (12), the intermediates appear as two vertical rows of spots. The positions of the AGP forms differing by a single N-glycan unit are indicated. B, nonglycosylated AGPs synthesized by hepatocytes. Primary hepatocytes in culture were treated for 2 h in 2 µg/ml of tunicamycin, which results in 95% inhibition of [14C]mannose incorporation (data not shown). These cells were labeled with [35S]methionine for 6 h in the continued presence of tunicamycin, and the secreted proteins in the culture medium were separated by two-dimensional gel electrophoresis. Only the section of the fluorogram containing AGP-1 and AGP-2 is reproduced. C, fully N-glycosylated AGPs synthesized by hepatocytes. Primary hepatocytes were labeled with [35S]methionine for 10 min. Total cellular glycoproteins were purified by chromatography on concanavalin A-Sepharose (5) and separated by two-dimensional gel electrophoresis. The same section of the fluorogram as in B is reproduced. D, partial endo-β-N-acetylglucosaminidase H digestions. Glycosylated and nonglycosylated forms of AGP-1 and AGP-2, prepared as described in B and C above, were cut out of preparative two-dimensional acrylamide gels and digested for 30 min at 37 °C with endo-β-N-acetylglucosaminidase H in an 11% polyacrylamide gel, as described (35). Lanes represent the following samples: lanes 1, 2, 3, 4, and 5, fully glycosylated AGP-1; 5, nonglycosylated AGP-1; 6–8, fully glycosylated AGP-2 with five N-glycan units; 9–10, fully glycosylated AGP-2 with six N-glycan units; 11, nonglycosylated AGP-2. Since the pattern of glycosylated proteins (see C) includes a series of spots which have similar molecular weights but slightly more acidic charge than AGP-2, they were included in the following lanes to demonstrate that they represent a nonrelated protein: 12, protein that is slightly more acidic than the AGP-2 with five N-glycans; 13, protein that is slightly more acidic than the AGP-2 with six N-glycans; 14, and 15 are undigested controls; lanes 2 and 7 contain 1 milliunit of enzyme; lane 3 contains 3 milliunits of enzyme; lanes 4, 8, 10, 12, and 13 contain 6 milliunits of enzyme. The figure represents a composite of fluorographic exposures of between 18 h and 2 weeks. The numbers on the left indicate molecular weights × 10^-5, estimated from co-electrophoresed molecular weight markers.

Genetic Variation in the Acute Phase Reactant mRNAs of Inbred Mice—In order to find genetic variation that may be useful in gaining new insights into the nature of the acute phase response, we have compared the acute phase reactant mRNAs in the livers of several inbred mouse strains. Two interesting structural variants were found. The strains express one of two charge forms of AGP-1. One form, denoted AGP-1-B, is expressed, for instance, in strain C3H/HeJ, while the other form, denoted AGP-1-A, is expressed in strains AKR/J and DE/Cv (Fig. 6). A variant form of SAA was found in strain DE/Cv. The latter expresses an acidic SAA, denoted SAA-A, while all other strains express a basic SAA, denoted SAA-B (Fig. 6). (C3H/HeJ × DE/Cv)F1, hybrids express both SAA-A and SAA-B as well as AGP-1-A and AGP-1-B (Fig. 6). Thus far, DE/Cv is the only inbred strain that has been analyzed and expresses SAA-A. The electrophoretic phenotypes for SAA and AGP-1 in several inbred strains are shown in Table I. Mobility differences were also apparent by two-dimensional gel analysis of native plasma proteins (data not shown).

All other acute phase reactant mRNA translation products indicated that AGP-1 contains five N-glycans while AGP-2 comprises a mixture of forms with five and six N-glycans (Fig. 5D).
are identical among laboratory strains, as assessed by two-dimensional gel electrophoresis. In addition, using the inflammation protocols described, we have found no evidence for quantitative variation among the mouse strains tested in the levels of any acute phase reactant mRNAs either in control or inflamed animals.

The existence of structural variation for AGP-1 and for SAA enables location, by linkage analysis, of the respective structural genes in the mouse genome. Such analysis can be readily accomplished with the use of recombinant inbred lines. These are sets of inbred strains generated by inbreeding the progenitor strains (18). Recombinant chromosomes containing various combinations of progenitor genes become fixed in homozygous form; thus, by comparing the segregation pattern of alleles of a variant gene, the gametes produced in this cross is shown in Table I; the results place the SAA structural gene approximately 13 centimorgans distal from the centromere from b. Interestingly, this location places Agp-1 very close to the Lps locus, which is involved in regulating all aspects of the acute phase response in mice (22). Experiments to more accurately map Agp-1 are currently in progress.

Since electrophoretic variation for SAA occurs only in strain DE/Cv, no appropriate recombinant inbred strains are available for mapping the SAA structural gene. However, to determine possible linkage of the SAA structural gene to Gpi-1, we made use of the backcross progeny derived from mating (C3H/HeJ × DE/Cv)F1 hybrid females to DE/Cv males. Of eight Agp-1b backcross animals, five were SAA-A/SAA-A and three were SAA-A/SAA-B; of eight Agp-1b animals, three were SAA-A/SAA-A and five were SAA-A/SAA-B. Thus, there is no evidence for any linkage between the SAA structural gene and Agp-1 on chromosome 4. Recent analysis of a polymorphism in genomic DNA corresponding to an SAA cDNA clone indicates that the SAA structural gene is linked to Gpi-1 on chromosome 7. At the suggestion of Dr. Ben Taylor, we have verified this assignment by measuring segregation of the SAA structural gene and two chromosome 7 genes, Gpi-1 and c, in the (C3H/HeJ × DE/Cv)F1 × DE/Cv backcross generation. In the 24 progeny that were examined, the SAA structural gene recombined with Gpi-1 in three animals and with c in seven animals. The distribution of gametes produced in this cross is shown in Table III; the results place the SAA structural gene approximately 13 ± 7 centimorgans distal to the centromere from Gpi-1, in good agreement with the results of Taylor and Rowe. This gene
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TABLE II

| Locus | AKXD strains |
|-------|--------------|
| Ly-m19 | A A D D D A A A A D D D A A A A D D D D D A D D |
| b | x x x x x x x x |
| Agp-1 | D D A D D A A A A D D D D D D A A A A D D |

TABLE III

Linkage of Saa to chromosome 7

Animals from the (C3H/HeJ x DE/Cv)F1, x DE/Cv backcross generation were typed for Gpi-1, c, and Saa. The various gamete types generated by the hybrid parent are listed along with the number of animals expressing each type. Strain C3H/HeJ is Gpi-1", Sa0b, and c", while strain DE/Cv is Gpi-1", Sa0b, and c". Region I is between Gpi-1 and Saa and Region II is between Saa and c.

DISCUSSION

A genetic approach to the study of the mammalian acute phase response offers the potential to identify and map structural genes encoding acute phase reactants and regulatory genes that may modulate the response. We have undertaken genetic studies in the mouse; the availability of a large number of inbred and wild-derived stocks showing extensive genetic variation (23) clearly makes the mouse an advantageous model for such studies.

We have focused our attention on translatable acute phase reactant mRNAs of the liver. By cell-free mRNA translation, we have defined the spectrum of acute phase mRNAs and could identify several mRNAs that are induced during the acute phase response as well as several that are repressed. In contrast to rat (10, 12), there are two AGP's in mouse. Since both were identified in the cell-free mRNA translation products, it is likely that they are encoded by separate mRNAs. To what extent AGP-1 and AGP-2 are structurally related is unknown. Their mRNAs must share considerable sequence homology, since both cross-react with a rat AGP cDNA probe (Fig. 2). Whether these mRNAs derive from separate or overlapping structural genes can be answered only by direct analysis of corresponding genomic sequences.

Interstrain variation in AGP-1 electrophoretic mobility was identified and used to map the corresponding structural gene, Agp-1, to chromosome 4. The genetic data allowed us to tentatively place Agp-1 very close to the Lps locus, although such placement must be verified by more extensive analysis which is in progress. Lps was identified previously on the basis of a diminished response to lipopolysaccharide in C3H/HeJ mice (22) and appears to regulate all aspects of the response, including lymphoid cell activation, hypothermia, and induction of both colony-stimulating factor and SAA levels in serum (25); in addition, we have recently noted the effect of the Lps locus on induction of mRNAs for all acute phase reactants detectable by the in vitro translation assay.1 Whatever the relationship between Agp-1 and Lps, it is clear that not all acute phase reactant structural genes are clustered on chromosome 4. Data on SAA place its structural gene, Saa, on chromosome 7; this agrees with the assignment made on the basis of a DNA polymorphism.2

Current experiments are focusing on M. spretus, which exhibits a very interesting array of variations. Novel forms of several acute phase reactants, including SAA, AGP-2, and haptoglobin, exist in this mouse. Thus, map locations of the respective structural genes can be determined. A putative

1 H. Baumann, W. A. Held, and F. G. Berger, unpublished observations.

2 M. J. Goeddel, D. E. Fries, and V. A. H. Dantsker, unpublished observations.
Fig. 7. Hepatic acute phase response in the wild mouse, *M. spretns*. Total liver RNA was extracted from a control *M. spretn* female (A), two turpentine-treated females (B and C), and a turpentine-treated female (C57/He/J × *M. spretrum*)F1 hybrid (D). The cell-free translation products were separated by two-dimensional gel electrophoresis. The fluorographs were exposed for 18 h. Arrows indicate the following proteins: Alb, albumin; apo-A-I, apolipoprotein A-I; Hp, haptoglobin; Hpx, hemopexin; MUP, major urinary protein. BPB, bromphenol blue.

Fig. 8. Electrophoretic polymorphism for SAA in *M. spretns*. Total liver RNA was extracted from three turpentine-treated *M. spretn* females and translated in the cell-free system. The cell-free translation products were separated by two-dimensional gel electrophoresis using a 12% polyacrylamide gel in the second dimension. Fluorographs were exposed for 24 h. Only the section containing SAA is reproduced. The SAA phenotype of each of the three individuals is indicated.

regulatory variation, which governs the induction specifically of AGP-1 mRNA, is found in *M. spretns*. The location and nature of the locus responsible for this alteration is under investigation and may lead to the identification and characterization of *cis-* or *trans-*acting factors responsible for modulating the acute phase response of specific genes.

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