

Pentraxin-Chromatin Interactions: Serum Amyloid P Component Specifically Displaces H1-Type Histones and Solubilizes Native Long Chromatin

By P. J. G. Butler,* Glenys A. Tennent, and M. B. Pepys

From the Immunological Medicine Unit, Department of Medicine, Royal Postgraduate Medical School, London W12 0NN; and the *Laboratory of Molecular Biology, Medical Research Council, Cambridge CB2 2QH, United Kingdom

Summary

Pure serum amyloid P component (SAP) and native long chromatin, mixed together at wt/wt ratios between 1:1 and 1:2 in the presence of physiological concentrations of NaCl and calcium, both remained in solution, whereas each alone precipitates rapidly under these conditions. This solubilization accompanies the binding of SAP to chromatin and the displacement of H1-type histones, which are essential for condensation and higher order folding of chromatin. Such binding of SAP to chromatin is remarkable since displacement of H1 and H5 by salt alone requires ~ 0.5 M NaCl. SAP also bound to nucleosome core particles forming soluble complexes with an apparent stoichiometry of 1:2, a result that is compatible with attachment of SAP at the nucleosome dyad, the site of H1 in intact chromatin. SAP thus undergoes a specific, avid interaction with chromatin that promotes its solubilization and may thereby contribute to the physiological handling of chromatin released from cells in vivo. In contrast, C-reactive protein (CRP) did not bind significantly to either chromatin or to core particles at physiological ionic strength. Incubation of chromatin with either normal serum, or acute phase human serum containing raised levels of CRP, did not induce complement activation regardless of the presence of added SAP or CRP, nor was any cleavage of DNA observed.

The pentraxins, C-reactive protein (CRP)¹ and serum amyloid P component (SAP) in man, are a stably conserved family of plasma proteins (1, 2). No deficiency or polymorphism of either CRP or SAP has yet been reported in man, suggesting that they have important physiological functions that are probably related to their capacity for calcium-dependent binding to particular specific ligands (1).

It has been reported that CRP binds to chromatin, then activates complement, leading to solubilization of the chromatin (3, 4), and that it may thus participate in scavenging chromatin from dead cells. However, we have found that in buffers of physiological ionic strength, human CRP does not bind significantly to chromatin or DNA (5). In contrast, SAP is the single protein in whole normal or acute phase human serum that undergoes calcium-dependent binding to DNA, and it also binds specifically to chromatin and nucleosome core particles in vitro (5). Furthermore, we have demonstrated SAP deposition in vivo on extracellular accumulations of chromatin in the skin lesions of certain patients with SLE (6).

Throughout this paper we use H1 to include H1-related histones, i.e., H1 subtypes and H5, which occur in avian erythrocyte chromatin.

¹ Abbreviations used in this paper: AU, absorbance units; CoF, cobra factor; CPS, pneumococcal somatic C-polysaccharide; CRP, C-reactive protein; SAP, serum amyloid P component.

In man, therefore, SAP, rather than CRP, may participate in vivo in the handling of chromatin released into the extracellular environment.

We now report that the binding of purified SAP to native long chromatin selectively displaces histone H1 and, at the same time, makes such chromatin soluble in buffered saline at physiological strength, in which it would otherwise precipitate completely.

Materials and Methods

Pentraxins. Human SAP and CRP (>99% pure) were isolated and assayed as previously described (7, 8). They were stored frozen at -70°C in solution in, respectively, 10 mM Tris, 140 mM NaCl, 10 mM EDTA, 0.1% (wt/vol) NaN_3 , pH 8.0 (TE buffer); and 10 mM Tris, 140 mM NaCl, 2 mM CaCl_2 , 0.1% (wt/vol) NaN_3 , pH 8.0 (TC buffer). SAP was dialyzed into 10 mM Tris, 140 mM NaCl, pH 8.0 (TN buffer), before use. All experiments with CRP and long chromatin were also repeated with CRP freshly isolated from acute phase serum within 24 h of venesection and used within 24 h.

Chromatin, Core Particles, and DNA. Native long chromatin, H1-stripped chromatin, nucleosome core particles, and free DNA were from chicken erythrocytes (9, 10) and were in solution in 0.1 mM EDTA. A₂₆₀ at 1 mg/ml was taken as 10 absorbance units (AU) for chromatin or cores and 20 AU for DNA.

PAGE. Reduced denatured protein samples and standards of chromatin and SAP were run in 4–30% gradient gels (Pharmacia Ltd., Milton Keynes, England), or in homogeneous 18% gels (11), and relative band densities were quantitatively scanned (12, 13).

Sucrose Density Gradient Ultracentrifugation. Linear sucrose gradients (10–40% or 10–30% [wt/vol]) were prepared by direct mixing and centrifuged at 5°C in a rotor (SW40; Beckman Instruments, Inc., Palo Alto, CA) at 37,000 rev/min for 16 h (for nucleosome cores) or 30,000 rev/min for 2.5 h (for long chromatin). Gradients were harvested in 1-ml fractions through a UV monitor. For binding of SAP to nucleosome cores, materials were dialyzed into TN buffer and mixed before addition of CaCl₂ to a final concentration of 2 mM and fractionation in TC buffer. Long chromatin (containing histones H1 and H5) precipitates at high ionic strengths and could not be dialyzed into TN buffer. Instead, chromatin and SAP were dialyzed into 10 mM Tris/Cl, 0.125 mM PMSF, 0.5 mM benzamidine, pH 8.0, before mixing, and further additions were then made before fractionation. Cores or chromatin were quantitated by A₂₆₀ or by estimation of histones in SDS-PAGE; SAP was estimated by SDS-PAGE and electroimmunoassay (7).

Complement Studies. Native long chromatin, H1-stripped chromatin, and free DNA, containing 50 μg DNA in each case, were incubated at 37°C for 5–60 min with 25–250 μg CRP or SAP in the presence of fresh normal serum at a final concentration of 1:2, 1:3, or 1:20, and 2 mM CaCl₂ and MgCl₂. Long chromatin, 10–100 μg, was also incubated with freshly taken acute phase serum from 11 individuals containing CRP at 12–128 mg/liter. Complement activation was sought by hemolytic complement assay and crossed immunoelectrophoresis (14) for C3. DNA cleavage was sought by electrophoresis in 2% agarose gels of DNA extracted (15) from the incubation mixtures. Positive controls for complement activation were incubation of serum with 5 μg pneumococcal C-polysaccharide (CPS) (16) in the presence of CRP, or with 15 μg cobra venom factor (*Naja naja*) (CoF) (17), and for DNA cleavage, incubation with micrococcal nuclease. Activation of complement by SAP alone was assessed by adding 50–1,000 μg/ml SAP to NHS and incubating at 37°C for 60 min. After centrifugation, C3 conversion in the supernatant and the quantity of SAP in each supernatant and pellet were measured.

Results

Solubilization of Native Long Chromatin by SAP. Native long chromatin is soluble only at extremely low ionic strength and in the absence of divalent cations (18). Purified, isolated human SAP also rapidly aggregates and precipitates in the presence of free calcium, as we have reported previously (19). However, remarkably, in mixtures of SAP with native long chromatin in a final solvent containing 150 mM NaCl, 10 mM Tris, and 2 mM CaCl₂, pH 8.0, both SAP and chromatin remained in solution (Fig. 1, Table 1). With different chromatin preparations, optimum mutual solubilization occurred at SAP to chromatin wt/wt ratios of between 1:1 and 1:2. With higher SAP/chromatin ratios, increasing amounts of SAP precipitated, as did some of the chromatin, although much more SAP remained in solution than in the absence of chromatin. In other experiments, not shown here, native chromatin that had been precipitated by addition of 150 mM NaCl and 2 mM NaCl₂ was resolubilized by subsequent addition of SAP. When SAP was added either to chromatin stripped of H1 or to free DNA, both of which are them-

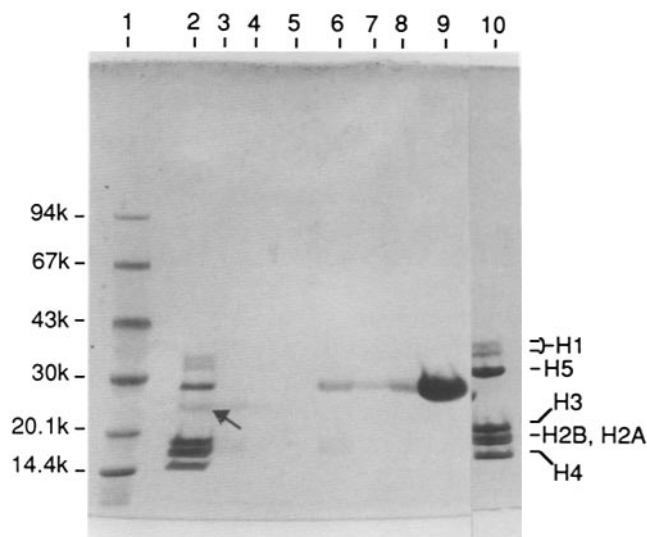


Figure 1. Reduced SDS 4–30% gradient PAGE of the sedimented precipitates after incubation of CRP (lanes 2–5) and SAP (lanes 6–9) with native long chromatin (lanes 2 and 6), H1-stripped chromatin (lanes 3 and 7), free native DNA (lanes 4 and 8), and TC buffer alone (lanes 5 and 9). Native long chromatin alone was run in lane 10, showing the normal full complement of histones, and marker proteins of known *M_r* in lane 1. In the presence of CRP (lane 2), the native long chromatin precipitated together with a trace amount of CRP (arrow). In the presence of SAP (lane 6), there was almost no precipitation of native long chromatin and only trace precipitation of SAP, compared with the massive precipitation of SAP alone (lane 9; and Table 1). Stripped chromatin (lane 7) and free DNA (lane 8) also kept almost all the SAP in solution (Table 1).

Table 1. Binding of SAP to Chromatin and DNA

Ligand	Pentraxin concentration in supernatant	
	CRP	SAP
	μg/ml	
Native long chromatin	106	111
H1-stripped chromatin	107	124
Free native DNA	103	112
None	118	19

20-μl volumes of ligands containing 50 μg of DNA in 0.1 mM EDTA were mixed with 20-μl volumes of CRP or SAP containing 50 μg of protein in TN buffer. TC buffer, 360 μl, was added to each tube, the contents were mixed, left at 20°C for 10 min, then centrifuged at 10,000 *g* for 5 min. The residual CRP or SAP in the supernatant is shown above. Comparable results were obtained in 10 other experiments, although the relative quantities of SAP and chromatin required for optimal mutual solubilization varied with different chromatin preparations.

selves soluble in TC, the SAP also remained in solution (Fig. 1, Table 1).

In contrast, CRP had no effect on precipitation of native chromatin, and only minimal depletion of CRP from the supernatant was demonstrable (Table 1). Precipitation of traces

Table 2. Human CRP Binds to Nucleosome Core Particles Only at Low Ionic Strength

Ionic strength	Offered	CRP		Core histones (SDS-PAGE)	
		Supernatant	Precipitate	Supernatant	Precipitate
<i>mM</i>			μg		
154	17.2	17.2	0	+	-
42	19.6	0.8	18.8	-	+

20- μl volumes of cores at 1 mg DNA per ml and of CRP at 1 mg/ml were mixed together in Tris-NaCl-calcium buffer with a final concentration of either 154 or 42 mM, and then centrifuged. The supernatants and pellets were assayed for CRP and for core histones. In control tubes without CRP, there was no precipitation of cores.

of CRP with chromatin (Fig. 1) is compatible with some binding of CRP to histones (20).

CRP Binds to Nucleosome Core Particles Only at Low Ionic Strength. Although CRP and nucleosome core particles coprecipitated almost completely at 42-mM ionic strength, no significant interaction was seen at physiological ionic strength, 154 mM (Table 2).

Binding of SAP to Nucleosome Core Particles. Sedimentation of core particles in sucrose gradients at physiological ionic strength was not significantly altered by the addition of CaCl_2 to 2 mM, while SAP, as expected, precipitated under these conditions. Cores alone sedimented as a single, approximately symmetric peak, $S_{20,w} \sim 11\text{S}$, by analytical ultracentrifugation. Addition of increasing amounts of SAP caused a more rapidly sedimenting "shoulder" to appear until, with an equal weight of SAP to nucleosome cores, a single faster sedimenting, approximately symmetric, peak was observed with tailing towards the core position (Fig. 2).

The formation of a complex that apparently sediments with a unique sedimentation coefficient suggests that there is stoichiometric binding of SAP to nucleosome cores. Despite scatter in the data, due to the inherently rather imprecise determination of the core concentration, the amount of SAP appeared to saturate around a value of ~ 0.6 mol SAP/mol core (Fig. 3), i.e., with approximately two cores bound to each decameric SAP molecule.

The nucleosome core has a dyad symmetry axis that passes between the two superhelical turns of DNA wound around the octamer of "core histones" (21). If the decamer of SAP (1) is composed of two layers of five subunits, bound to each other back-to-back, i.e., with dyad symmetry between subunits in the two layers, this result could occur by the binding of nucleosome cores around the "disk-like" SAP molecule with their dyads aligned with dyads of the SAP molecules between the two rings, and exclusion of binding to neighboring sites due to steric hindrance from the large cores.

We have attempted to visualize directly in the electron microscope the appearance of such SAP-core particle complexes in fractions from the sucrose density gradients. However, even after fixation with glutaraldehyde before centrifugation, the complexes seen have included a range of ratios. The stoichiometry observed may thus represent an equilibrium rather than a fixed ratio of cores to SAP molecules.

SAP Binds to Native Long Chromatin, Selectively Displacing H-1-type Histones. When a constant amount of native long chromatin was mixed with increasing amounts of SAP in 10 mM Tris/HCl, pH 8.0, and then brought to 140 mM NaCl and 2 mM CaCl_2 before sedimentation in sucrose density gradients, an increasing quantity of the chromatin remained in solution, in agreement with observations made

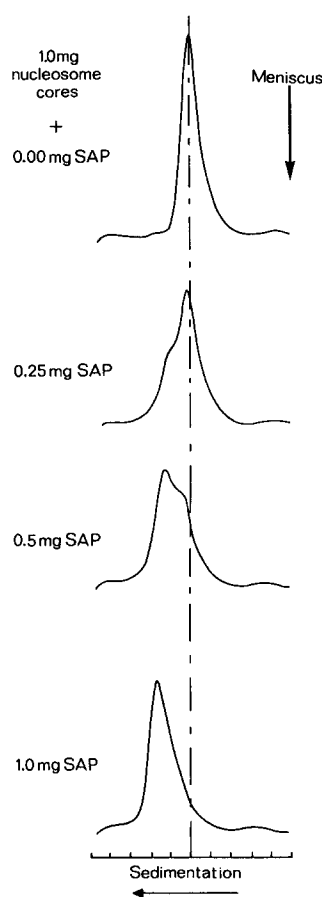


Figure 2. Gradient profiles for nucleosome core particles sedimented with SAP. Profiles are plotted as A_{254} , with sedimentation from right to left. Successive profiles are for 1-mg nucleosome cores, with increasing amounts of SAP as indicated. The broken vertical line indicates peak position for nucleosome cores alone (i.e., $S_{20,w} \sim 11\text{S}$).

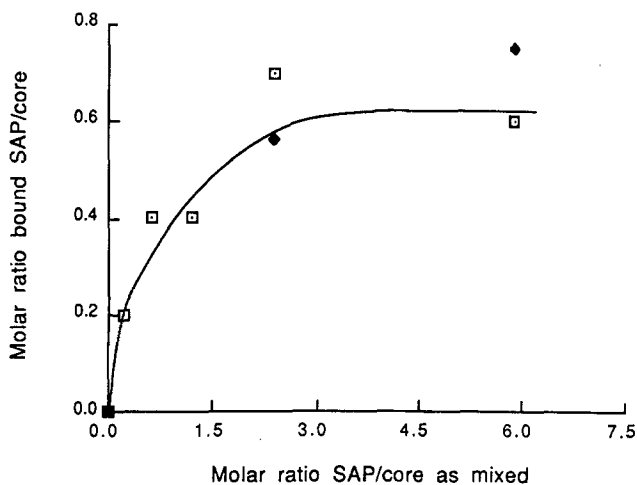


Figure 3. Dependence of molar ratio of SAP bound to nucleosome core upon ratio as mixed. Points are derived from two separate experiments. The curve is drawn for the likely binding isotherm and shows saturation of binding at higher initial ratios.

in the absence of sucrose (Table 1). Binding to chromatin was confirmed by demonstration of SAP in the chromatin peak. However, although the core histones, H2A, H2B, H3, and H4, were all present in this peak in ratios comparable with those seen in control chromatin not exposed to SAP, the H1-type histones were absent (Fig. 4 A).

This result is fully compatible with the finding that condensation of chromatin into its higher order structure, the 30-nm fiber, requires the presence of H1 (18), with loss of even <5% of the original H1 leading to a failure to fold normally (10). Formation of the 30-nm fiber precedes a further folding, and, before the highest level of folding is completed, precipitation occurs (22). Substitution of SAP for H5 and H1 in erythrocyte long chromatin would therefore be predicted to prevent this folding and condensation of the chromatin and its subsequent precipitation, as indeed we observed.

Binding of SAP to chromatin displacing H5 and H1 is remarkable since their displacement by salt alone requires ~ 0.5 M NaCl. The stability of SAP binding could reflect the multimeric nature of SAP, interacting with many repeated sites within long chromatin. Our result of around two nucleosome core particles binding per SAP molecule is fully compatible with this suggestion. The displacement of H1-type histones upon binding of SAP to long chromatin also indicates that this binding is probably occurring at that side of the nucleosome cores where the H1 is usually bound, i.e., the side where the DNA enters and leaves the core.

In a control experiment, SAP was mixed with long chromatin in the absence of CaCl_2 and, since no binding of SAP was expected under these conditions, no NaCl was added, since it would have precipitated the chromatin. Surprisingly, however, SAP became bound to the chromatin and displaced H5 and H1 in the usual way (Fig. 4 B). Furthermore, the same result was seen in the presence of 0.1 mM EDTA. Thus, unlike the binding of SAP to free DNA and nucleosome core particles (5), and indeed all other known binding reactions

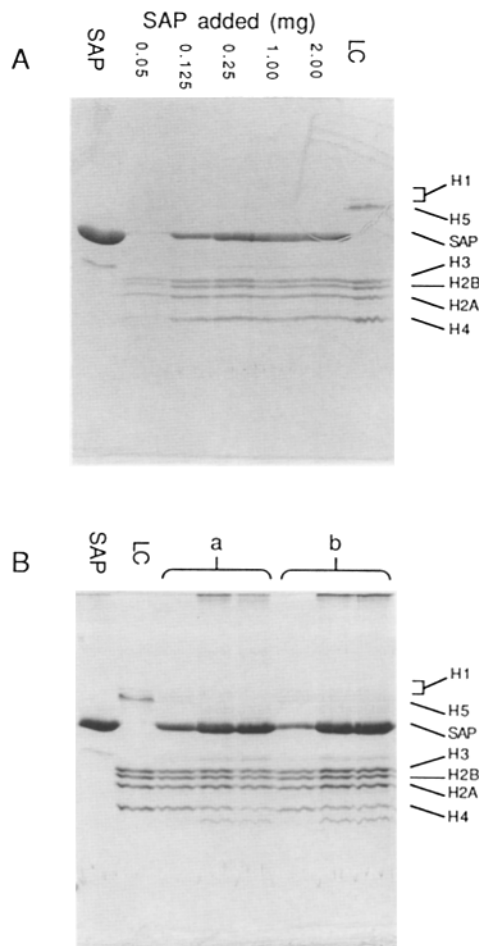


Figure 4. Histone and SAP compositions of major peaks in sucrose gradients for native long chromatin mixed with SAP and sedimented under various conditions. Samples from peaks were run in SDS 18%-PAGE, together with marker tracks of SAP and the original long chromatin (LC). (A) Samples sedimented in buffer with 140 mM NaCl, 2 mM CaCl_2 added after mixing 0.5 mg long chromatin with 0.05 mg SAP, 0.125 mg SAP, 0.25 mg SAP, 1.0 mg SAP, and 2.0 mg SAP. (B) 0.5 mg long chromatin mixed with 0.25 mg SAP and sedimented in buffers containing 10 mM Tris/Cl, pH 8.0, 0.125 mM PMSF, 0.5 mM benzamidine either alone (a) or with added 0.1 mM EDTA (b).

of SAP (1, 23), the binding of SAP to long chromatin can take place independently of the availability of free calcium ions, at least at low ionic strength (10 mM Tris/HCl), and is still strong enough to displace H1 and H5. While clearly not of physiological relevance, this observation indicates that charge interactions are important in SAP-chromatin binding.

Pentraxins, Chromatin, and Complement. Mixtures of CRP or SAP with chromatin or DNA did not activate complement significantly, nor did chromatin in fresh complement-sufficient acute phase serum containing its own CRP, in contrast to marked C3 cleavage induced by CPS in the presence of CRP. There was also no cleavage of DNA in any mixture, even when complement had been maximally activated by CoF.

In control experiments, CRP alone did not activate complement. However, supraphysiological amounts of SAP alone

produced dose-dependent C3 conversion related to the concentration-dependent and calcium-dependent aggregation of SAP itself. C3 activation occurred only when there was $>200 \mu\text{g/ml}$ of aggregated SAP. Chromatin or DNA inhibited this complement activation, presumably because binding of SAP to the ligands inhibited its self-aggregation (Table 1).

Discussion

We show here that soluble SAP binds nucleosome core particles with an apparent ratio of about two cores per decameric SAP molecule. Further work is required to establish whether this is genuine stoichiometry and, if so, whether it reflects binding of SAP to a particular site on the core or nonspecific steric effects. Intriguingly, residues 123–132 in both SAP and CRP are highly homologous with sequences in histones H1/H5 and H4, which may be a motif specifically recognizing the narrow minor groove of DNA at the nucleosome dyad (24). The crystallographic structure of human SAP (25) should provide more direct information on this point.

Although binding of SAP to cores is of interest in molecular terms, the interaction with native long chromatin is more likely to be of physiological relevance. SAP selectively displaces H1-type histones and prevents or reverses the precipitation of long chromatin that takes place at physiological ionic strength. Since a NaCl concentration $>0.5 \text{ M}$ is required to displace H1-type histones, the avidity of SAP for chromatin must be great. Binding of SAP, with its dramatic secondary consequence of solubilization, is thus likely to occur *in vivo* in physiological and pathophysiological micro-environments in which nuclei and/or chromatin fragments are released from, for example, maturing erythroblasts or dead cells. Experiments are in progress to elucidate the biological consequences of this phenomenon.

Our failure to find binding of CRP to chromatin and core particles may reflect, in part, the use of different ligands. The original work of Robey et al. (3) used rabbit CRP and chromatin preparations, the protein constituents of which were

critical for binding. CRP in physiological solvent conditions can bind to histones, immobilized by adherence to membranes or plastic surfaces (20), but the conformation of histones in such situations is unlikely to be the same as their native conformation in chromatin. However, more recently, CRP has been found to bind, not to chromatin, but specifically to the U1 small nuclear ribonucleoprotein (26). In testing for binding of CRP to core particles, Robey et al. (3) used a preparation that precipitated at 150-mM ionic strength, and its interaction with CRP was therefore tested by them in 30 mM saline (3). These are nonphysiological conditions in which, as we show here, human CRP coprecipitates even with bona fide core preparations that are, of course, completely soluble in isotonic saline. More extensive studies with rabbit CRP and comparable core particle preparations have shown calcium-dependent coprecipitation at NaCl concentrations $<85 \text{ mM}$, but no precipitation of either component in solutions containing $>85 \text{ mM NaCl}$ (R. Buck, J. O. Thomas, R. Thompson, personal communication).

We also did not observe any complement activation by mixtures of human CRP with chromatin or DNA, or by chromatin in whole fresh acute phase sera containing both complement and autologous CRP, in contrast to the marked complement consumption induced by CRP with its classical ligand, pneumococcal CPS (1). When crude nuclear fractions or whole nuclei were used, minor complement activation was seen in some experiments (data not shown), suggesting that the findings of Robey et al. (4) may have been due to the presence of other nuclear materials, such as phospholipids or the U1 ribonucleoprotein, to which CRP does bind (1, 26), or to other differences from the present chromatin preparations.

We report here for the first time the marked complement activation that is induced by addition of supraphysiological amounts of SAP to serum. This was associated with calcium-dependent aggregation of the SAP and was thus inhibited by chromatin or DNA. Neither the mechanism of complement activation nor the biological relevance, if any, of this phenomenon are yet known.

We thank Dr. Jean Thomas for discussions and access to unpublished results, Dr. J. T. Finch for EM, Dr. F. A. Robey for discussions, Mrs. Sandra Searles for technical assistance, and Beth Sontrop for expert preparation of the manuscript.

This work was supported by Medical Research Council Programme Grant 7900510 to M. B. Pepys and by the Arthritis and Rheumatism Council.

Address correspondence to M. B. Pepys, Immunological Medical Unit, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, England.

Received for publication 9 February 1990.

References

1. Pepys, M.B., and M.L. Baltz. 1983. Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid A protein. *Adv. Immunol.* 34:141.
2. Robey, F.A., and T.-Y. Liu. 1981. Limulin: a C-reactive protein from *Limulus polyphemus*. *J. Biol. Chem.* 256:969.
3. Robey, F.A., K.D. Jones, T. Tanaka, and T.-Y. Liu. 1984. Binding of C-reactive protein to chromatin and nucleosome core particles. A possible physiologic role of C-reactive protein. *J. Biol. Chem.* 259:7311.
4. Robey, F.A., K.D. Jones, and A.D. Steinberg. 1985. C-reactive protein mediates the solubilization of nuclear DNA by complement in vitro. *J. Exp. Med.* 161:1344.
5. Pepys, M.B., and P.J.G. Butler. 1987. Serum amyloid P component is the major calcium-dependent specific DNA binding protein of the serum. *Biochem. Biophys. Res. Comm.* 148:308.
6. Breathnach, S.M., H. Kofler, N. Sepp, J. Ashworth, D. Woodrow, M.B. Pepys, and H. Hintner. 1989. Serum amyloid P component binds to cell nuclei in vitro and to in vivo deposits of extracellular chromatin in systemic lupus erythematosus. *J. Exp. Med.* 170:1433.
7. de Beer, F.C., and M.B. Pepys. 1982. Isolation of human C-reactive protein and serum amyloid P component. *J. Immunol. Methods.* 50:17.
8. Pepys, M.B., A.C. Dash, R.E. Markham, H.C. Thomas, B.D. Williams, and A. Petrie. 1978. Comparative clinical study of protein SAP (amyloid P component) and C-reactive protein in serum. *Clin. Exp. Immunol.* 32:119.
9. Lutter, L.C. 1978. Kinetic analysis of deoxyribonuclease I cleavages in the nucleosome core: evidence for a DNA superhelix. *J. Mol. Biol.* 124:391.
10. Bates, D.L., P.J.G. Butler, E.C. Pearson, and J.O. Thomas. 1981. Stability of the higher-order structure of chicken-erythrocyte chromatin in solution. *Eur. J. Biochem.* 119:469.
11. Laemmli, U.K. 1970. Cleavage of structural proteins during the assembly of the head of bacteriophage T4. *Nature (Lond.)* 227:680.
12. Sulston, J., F. Mallett, R. Durbin, and T. Horsnell. 1989. Image analysis of restriction enzyme fingerprint autoradiograms. *Comput. Appl. Biosci.* 5:101.
13. Smith, J.M., and D.J. Thomas. 1990. Quantitative analysis of one dimensional gel-electrophoresis profiles. *Comput. Appl. Biosci.* In press.
14. Laurell, C.-B. 1965. Antigen-antibody crossed electrophoresis. *Anal. Biochem.* 10:358.
15. Maniatis, T., E.F. Fritsch, and J. Sambrook. 1982. Molecular Cloning: A Laboratory Manual. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY. 150-172; 458-459.
16. Gotschlich, E.C., and T.-Y. Liu. 1967. Structural and immunological studies on the pneumococcal C-polysaccharide. *J. Biol. Chem.* 242:463.
17. Pepys, M.B., C. Tompkins, and A.D. Smith. 1979. An improved method for the isolation from *Naja naja* venom of cobra factor (CoF) free of phospholipase A. *J. Immunol. Methods.* 30:105.
18. Butler, P.J.G. 1983. The folding of chromatin. *CRC Crit. Rev. Biochem.* 15:57.
19. Baltz, M.L., F.C. de Beer, A. Feinstein, and M.B. Pepys. 1982. Calcium-dependent aggregation of human serum amyloid P component. *Biochim. Biophys. Acta.* 701:229.
20. Du Clos, T.W., L.T. Zlock, and R.L. Rubin. 1988. Analysis of the binding of C-reactive protein to histones and chromatin. *J. Immunol.* 141:4266.
21. Richmond, T.J., J.T. Finch, B. Rushton, D. Rhodes, and A. Klug. 1984. Structure of the nucleosome core particle at 7Å resolution. *Nature (Lond.)* 311:532.
22. Widom, J. 1986. Physicochemical studies of the folding of the 100Å nucleosome filament into the 300Å filament. *J. Molec. Biol.* 190:411.
23. Pepys, M.B. 1988. Amyloidosis. In *Immunological Diseases*, Fourth Edition, Vol. 1. M. Samter, D.W. Talmage, M.M. Frank, K.F. Austen, and H.N. Claman, editors. Little, Brown, and Company, Boston. 631-674.
24. Turnell, W.G., S.C. Satchwell, and A.A. Travers. 1988. A decapeptide motif for binding to the minor groove of DNA. A proposal. *FEBS (Fed. Eur. Biochem. Soc.) Lett.* 232:263.
25. Wood, S.P., G. Oliva, B.P. O'Hara, H. White, T.L. Blundell, S.J. Perkins, I. Sardharwalla, and M.B. Pepys. 1988. A pentameric form of human serum amyloid P component: crystallization, X-ray diffraction and neutron scattering studies. *J. Mol. Biol.* 202:169.
26. Du Clos, T.W. 1989. C-reactive protein reacts with the U1 small nuclear ribonucleoprotein. *J. Immunol.* 143:2553.