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Immunology

Three-dimensional structure of β_2-microglobulin

(histocompatibility antigens/crystal structure/immunoglobulin domains)

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ABSTRACT **The three-dimensional structure of β_2-microglobulin, the light chain of the major histocompatibility complex class I antigens, has been determined by x-ray crystallography. An electron density map of the bovine protein was calculated at a nominal resolution of 2.9 Å by using the methods of multiple isomorphous replacement and electron density modification refinement. The molecule is approximately 45 × 25 × 20 Å in size. Almost half of the amino acid residues participate in two large β structures, one of four strands and the other of three, linked by a central disulfide bond. The molecule thus strongly resembles Ig constant domains in polypeptide chain folding and overall tertiary structure. Amino acid residues that are the same in the sequences of β_2-microglobulin and Ig constant domains are predominantly in the interior of the molecule, whereas residues conserved among β_2-microglobulins from different species are both in the interior and on the molecular surface. In the crystals studied, the molecule is clearly monomeric, consistent with the observation that β_2-microglobulin, unlike Ig constant domains, apparently does not form dimers *in vivo* but associates with the heavy chains of major histocompatibility complex antigens. Our results demonstrate that, at the level of detailed three-dimensional structure, the light chain of the major histocompatibility class I antigens belongs to a superfamily of structures related to the Ig constant domains.**

β_2-microglobulin (β_2m) was discovered in the urine of patients with chronic kidney dysfunction (1). It has since been found in a variety of physiological fluids as well as on the surfaces of nearly all cells as the light chain of the major histocompatibility complex (MHC) class I antigens of man (HLA) and other vertebrates (2–5). These antigens play central roles in two widely studied activities involving immune recognition by T cells: the rejection of foreign tissue grafts through direct recognition of foreign MHC antigens and the recognition of viral and other antigens in conjunction with self-MHC antigens (6–8). The MHC class I antigens display an extraordinary polymorphism that is the apparent basis for the diversity and specificity of these recognition events. The heavy chains of these antigens are integral membrane proteins, and their polymorphism is confined to their NH_2-terminal 180 amino acid residues, those farthest from the cell surface. In contrast, β_2m and the 90 extracellular residues closest to the membrane are highly conserved. Although the function of β_2m in these antigens is unknown, there is evidence that its presence is necessary for post-translational processing and insertion of HLA heavy chains into the membrane (9, 10). It also appears to stabilize the structure of the heavy chain in that its removal causes loss of alloantigenic sites on HLA (11, 12).

$\beta_2$ms from different species have similar chemical structures. Approximately 50% of the residues are identical in the five sequences that are known completely (13–17). $\beta_2$ms from different species apparently can replace one another in the quaternary structure of the MHC class I antigens (18–20), suggesting that the conservation of sequence reflects strong evolutionary pressure to conserve a functionally important conformation.

By amino acid sequence homology, β_2m belongs to a "superfamily" of proteins related to the Ig constant domains and believed to have evolved from a common ancestor (21). The observation that the chains of Ig contain regions homologous to one another in amino acid sequence led Edelman to suggest that these regions would be folded into distinct compact domains with similar three-dimensional structures (22). Such domains have subsequently been observed in all Igs whose three-dimensional structures have been determined (23). Recently, several other proteins have been shown to have all or part of their amino acid sequences homologous to those of Ig constant domains. These molecules include the T-cell differentiation antigen Thy-1 (24), the α and β chains of the T-cell antigen receptor (25–29), the MHC class I and II antigens (7, 30), and β_2m (13–17). The similarities in primary structure have led to the suggestion that the homologous portions of these molecules may resemble Ig domains in detailed three-dimensional structure as well. Chemical studies indicate that in the MHC class I antigen complex, β_2m associates noncovalently with the region of the heavy chain that is homologous to the Ig constant domains, the 90 extracellular residues adjacent to the membrane (31). In this case, the mode of association as well as the three-dimensional structure may resemble that of Ig constant domains.

Here we report the determination, at 2.9 Å nominal resolution, of the three-dimensional structure of β_2m. We show that the molecule closely resembles the constant domains of Ig with significant differences only in the polypeptide loops connecting the β structures. Most of the amino acid residues that are identical in the aligned sequences of β_2m and Ig constant domains have their side chains in the interior of the molecule, consistent with the common peptide folding. There is much more variation in the residues on the molecular surface, consistent with the different functional roles of these molecules.

MATERIALS AND METHODS

The preparation and crystallization of β_2m from bovine milk and colostrum have been reported previously (32, 33). The molecule crystallizes in the orthorhombic space group $P2_12_12_1$ with a = 77.27, b = 47.99, and c = 34.42 Å. Heavy-atom derivatives were prepared by soaking crystals in crystallization buffer (0.05 M phosphate/0.02% NaN_3, pH 7.80) in which heavy-atom reagents had been dissolved. If the reagent was insoluble in this buffer, crystals were transferred to a solution of 0.02 M Tris NO_3/0.02% NaN_3, pH 7.80, for at least 2 hours and then treated with heavy-atom reagents

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Abbreviations: β_2m, β_2-microglobulin; MHC, major histocompatibility complex; m.i.r., multiple isomorphous replacement; HLA, the major histocompatibility antigens of man.

Table 1. Data collection and reduction

Name	Concentration, mM	Soaking time, days	No. of crystals	Total observations	Unique reflections	R*	B_{der},† Å^2	ρ_{max},‡ Å^{-2}
Native	—	—	1	56,102	2892	0.0451	—	0.0288
$Hg(OAc)_2$§	0.1	8	3	32,478	3049	0.0637	−0.24	0.0256
$Pt(NH_3)_2(NO_2)_2$	1.0	7	3	31,494	2965	0.0463	−5.66	0.0240
HgI_4^{2-}	¶	12	3	40,078	2996	0.0487	1.31	0.0256

*$R = \Sigma[I(\mathbf{H}) - \bar{I}(\mathbf{H})]/\Sigma\bar{I}(\mathbf{H})$ for the averaging of symmetry-equivalent reflections, where $\bar{I}$ is the average intensity of reflection **H** and I is any measurement of that reflection.
†$B_{der} = B_{derivative} - B_{native}$, the difference between the isotropic temperature factors.
‡$\rho_{max} = (\sin^2\theta/\lambda^2)$ for the highest resolution data used in any calculation.
§The $Hg(OAc)_2$ derivative was prepared in Tris NO_3 buffer.
¶The preparation of the HgI_4^{2-} derivative is discussed in the text.

dissolved in the latter buffer. Approximately 90 compounds were tested before three usable derivatives, $Hg(OAc)_2$, $Pt(NH_3)_2(NO_2)_2$, and HgI_4^{2-}, were found.

The HgI_4^{2-} derivative was discovered in soaking experiments using $CH_2(HgI)_2$. In subsequent control experiments, it was found that this derivative was not formed when the soaking solution was shielded from room light. A high-resolution difference electron density map of the site of substitution, using multiple isomorphous replacement (m.i.r.) phases based on the other two derivatives, revealed a clearly tetrahedral moiety. This result suggested that the derivatizing substance was HgI_4^{2-}, formed by photodecomposition of $CH_2(HgI)_2$. This suggestion was confirmed by the observation that crystals treated with pure K_2HgI_4 have projection diffraction patterns and difference maps identical to those treated with $CH_2(HgI)_2$ and light.

Three-dimensional diffraction data were collected to a maximum resolution of 2.9 Å on 2° screenless oscillation photographs. Graphite monochromatized copper radiation from a rotating-anode generator operated at 40 kV, 60 mA was used. Except where noted, all computation was carried out by use of the ROCKS system of crystallographic computer programs (34). During film scanning, crystal slippage was assessed by comparing each photograph with a plot of the diffraction pattern predicted from the crystal parameters measured in alignment and early data photographs. When necessary, new orientation parameters were calculated from data obtained from the data photographs (35). Data reduction and scaling were performed as described (36). The native diffraction data were placed on an absolute scale and an isotropic temperature factor was estimated by using differential Wilson plot procedures, with the parameters of the refined structure of concanavalin A (37) as the reference. Heavy-atom derivative data were processed similarly, using the native protein as reference. Wilson plots of derivative intensity differences ($I_{der} - I_{nat}$) were used to assess the highest resolution at which derivative data could be considered isomorphous to native. Data collection and reduction are summarized in Table 1.

Heavy atoms were located by inspection of difference Patterson and difference electron density maps. Anomalous difference Patterson maps indicated that the $Hg(OAc)_2$ derivative provided useful anomalous dispersion data and these data were included in the m.i.r. phasing and used to establish the absolute hand of the protein. Heavy-atom parameters were refined by the method of Blow and Matthews (38) in which each derivative was refined separately, using m.i.r. phases calculated from the other two derivatives. After this refinement had converged, the parameters were refined in a final series of joint refinements. Anisotropic temperature parameters were included for the mercuric acetate and platinum derivatives because difference electron density maps showed nonspherical heavy-atom sites for these derivatives. The final assignment of heavy-atom sites was confirmed by calculating a difference map of each derivative using m.i.r. phases based on the other two derivatives. The overall figure-of-merit was 0.611 for the final heavy-atom parameters given in Table 2. The ratio of lack of closure to atomic scattering factor, E/f, was 0.78, 0.69, and 1.0 for the $Hg(OAc)_2$, $Pt(NH_3)_2(NO_2)_2$, and HgI_4^{2-} derivatives, respectively. The boundary of the molecule was clearly visible in a map calculated with these phases and much of the polypeptide chain could be interpreted with the aid of the published amino acid sequence (17).

After this preliminary interpretation, the protein phases were further refined by electron density modification methods. For these refinements, a molecular envelope was defined by interpretation of the m.i.r. map. This envelope

Table 2. Refined heavy-atom parameters

Atom	Occupancy	Fractional coordinates x	y	z	Thermal parameters*
Hg1†	0.550	0.0481	0.1336	0.1416	1.01, −1.32, 3.92, 2.40, −3.86, −2.23
Pt1	0.176	0.0334	0.1226	0.1948	1.77, −1.70, 15.22, 3.69, −3.45, −0.01
Pt2	0.261	0.1052	0.1292	0.1631	1.83, −1.71, 18.42, −0.49, −3.32, 6.30
Hg2†	0.242‡	0.1124	0.1905	0.2967	11.971
I1	0.242	0.0877	0.1469	0.2404	24.923§
I2	0.242	0.1445	0.1557	0.3079	24.923
I3	0.242	0.1051	0.2387	0.3270	24.923
I4	0.242	0.1016	0.1552	0.3164	24.923

*Single values are isotropic thermal parameters, B (Å^2). When six values are given, they are respectively the parameters (B_{11}, B_{22}, B_{33}, B_{12}, B_{13}, B_{23}) × 10^3 in the anisotropic temperature factor expression:

$$\exp[-(h^2B_{11} + k^2B_{22} + l^2B_{33} + hkB_{12} + hlB_{13} + klB_{23})].$$

†Hg1 is the site of $Hg(OAc)_2$ substitution; Hg2, of HgI_4^{2-} substitution.
‡The Hg and I sites of the HgI_4^{2-} derivative were constrained to have identical occupancies.
§The isotropic temperature factors of the I atoms were fixed at the values obtained in a Wilson plot of the isomorphous differences.

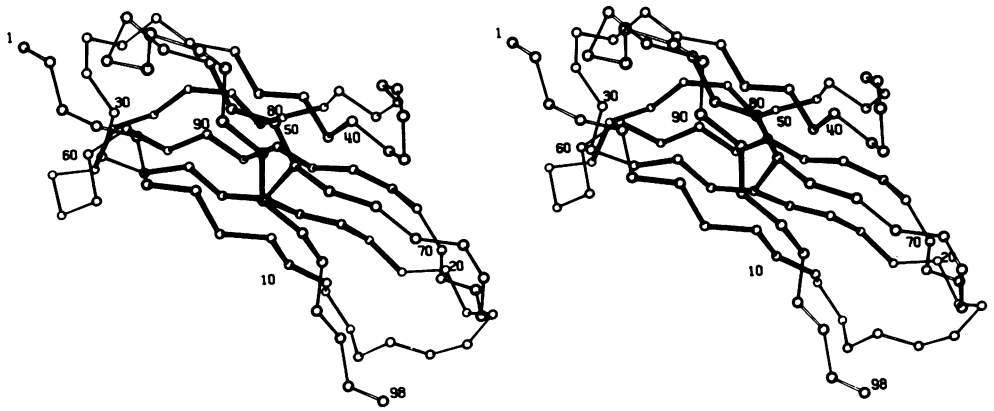

FIG. 1. Stereo drawing of the α-carbon backbone of β_2m. Peptide bonds are represented by single lines; peptide bonds in β structure and the disulfide bond are shown as bold lines. The view of the molecule is down the crystallographic y axis, with x horizontal and z vertical.

enclosed 42% of the volume of the unit cell, compared with a calculated protein volume fraction of 45% (33). In each of four cycles using this same envelope, densities outside the protein envelope, presumably representing solvent, were set to zero. At the same time, the average solvent density was subtracted from the protein densities inside the envelope. Remaining negative densities were set to 0.1 times their calculated value, leaving positive densities unchanged. New phases were calculated by back transformation of the modified map. Values for unrecorded native structure factors obtained in the course of this procedure were left in the phase sets at reduced weight. In the resulting electron density map, several regions that were difficult to interpret in the m.i.r. map became clearer, and a complete interpretation of the course of the polypeptide chain became possible. Atomic coordinates of the backbone atoms obtained from this map were improved and side chain atomic positions were assigned by using an interactive model-building program (39) on an Evans and Sutherland MPS graphics computer. Map densities are weak in the regions of residues 1–2, 41–45, and 95–98, and the interpretation there must be regarded as preliminary. Refinement of the coordinates is in progress. Coordinates of known Ig structures for comparison were obtained from the Brookhaven Protein Data Bank (40).

RESULTS AND DISCUSSION

The three-dimensional structure of β_2m is strikingly similar to the structures of the known Ig domains. The chain is folded into a typical "β-barrel" configuration dominated by two antiparallel pleated sheets, comprising four and three strands, respectively (Fig. 1). The four-stranded sheet contains residues 6–11, 28–21, 61–69, and 56–49; the three-stranded sheet contains residues 90–94, 82–77, and 36–40. The arrangement of and connectivity between the β strands are the same as in the known Ig constant domains and the disulfide bond connecting the sheets is in the same location. Thirty-five residues occur in the β structures of all known Ig domains (41), and 32 of them are in the β structures of β_2m in the current interpretation. Fig. 2 shows the main chains of β_2m and the C_H3 domain of human F_c aligned by least-squares fitting to bring the α-carbon atoms of their β structures into maximum agreement. There are some differences in the detailed folding around the loops near residues 20, 45, 60, and 70 and near the COOH terminus, but the overall coincidence is very strong. When the molecules are aligned in this manner, the average distance between β-structure α-carbon atoms is 0.9 Å. C_H1, C_H2, and C_L show comparable similarities, with their β-structure α-carbons differing from those of β_2m by 1.2, 1.0, and 1.0 Å. A similar comparison among Ig constant domains yields differences ranging from 0.6 to 1.1 Å.

Comparison of β_2m and the C_H3 domain reveals a general pattern of conservation of structurally significant features, although there are some intriguing differences. Twenty-three residues are both chemically identical and in the same three-dimensional location. Fifteen of these are either in or adjacent to the β structures, and 12 of these 15 have their side chains pointing into the region between the β sheets. Pro-32 is in the *cis* configuration; the polypeptide chain could not be

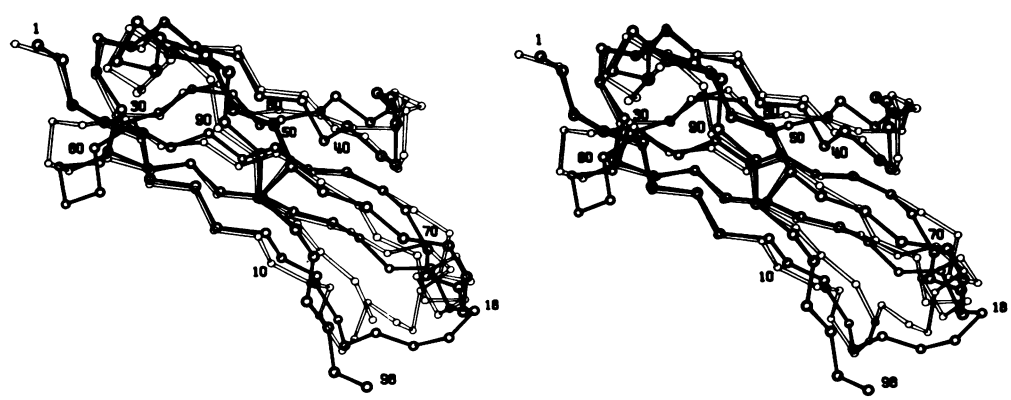

FIG. 2. Comparison of the polypeptide chains of β_2m and C_H3 of human F_c (42). The β_2m molecule (heavy lines, sequence numbers) is oriented as in Fig. 1. C_H3 (light lines, no sequence numbers) has been positioned by rigid body least-squares fitting to make its β-structure α-carbon atoms align with those of β_2m.

fitted to the electron density in this region if this residue was forced to be *trans*. The comparable residues in human C_H3 (42), C_H1 and C_L of Fab Kol (43), and C_H1 of Fab New (44) are also *cis* prolines. Apparently, the *cis* conformation is necessary to accommodate a sharp reversal of chain direction that occurs at this point. In contrast to these similarities, the β structures of β_2m show less conservation of sequence when compared to Ig constant domains than those domains show among one another. Of the 35 core β-structure residues, only 7 or 8 are identical when β_2m is compared to Ig constant domains, whereas 12–18 identities are obtained when constant domains are compared to each other. Finally, next to the disulfide bonds of all Ig domains is a tryptophan that occurs at the same relative sequence position. The comparable residue in bovine β_2m is Leu-39 and in the other known β_2m amino acid sequences it is either leucine or methionine.

Alignment of the amino acid sequences of $\beta_2$ms from different species with the three-dimensional structure presented here reveals a more extensive and qualitatively different pattern of conservation than the comparison with Ig constant domains. Of the 48 residues that are identical in the five completely known sequences, 36 are in or adjacent to the β structures. Of these, 17 have their side chains between the β sheets where they presumably are involved in the stabilization of a common tertiary structure. Interestingly, 32 residues on the external surface of the protein are also conserved. These conserved external side chains occur throughout the molecule, but there are obvious clusters of them on the face of the four-stranded β structure and on the loop of polypeptide comprising residues 12–21. The apparent conservation of these regions of the molecular surface suggests that they may have an important functional role.

In contrast to the similarity in tertiary structure, β_2m differs from Ig constant domains in quaternary structure. β_2m usually occurs as a free monomer or in association with MHC antigen heavy chains, whereas Ig constant domains are paired across 2-fold or quasi-2-fold axes of symmetry. In the crystal structure presented here, β_2m is clearly monomeric. There is one major intermolecular contact in these crystals, but it is less extensive than the C_H1–C_L and C_H3–C_H3 contacts in Ig. This interaction is between molecules related by the crystallographic 2-fold screw axis parallel to z (Fig. 3). This type of interdomain contact has not been seen previously in the known Ig structures. Contacts of this type may occur only in the crystalline state and only in the bovine protein, but it is also possible that β_2m may exhibit contacts

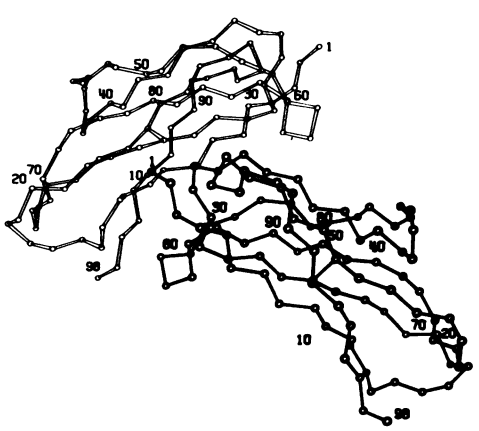

FIG. 3. Intermolecular contact along the crystallographic z axis. The end of one molecule (heavy lines) interacts with the edge of the four-stranded β structure and terminal loops of a second molecule (light open lines). The two molecules shown are not an isolated dimer; the pattern repeats throughout the crystal because of translational symmetry.

similar to this one with regions of MHC class I antigens or with other Ig-like structures on cytotoxic T cells. Precise characterization of the noncovalent interactions involved in these contacts must, of course, await the availability of the refined atomic coordinates.

The residues that participate in the C_H1–C_L and C_H3–C_H3 interfaces are very similar to one another, but they are generally not conserved in β_2m, consistent with the failure of this molecule to form dimers. Of 29 residues in contact in the C_H1–C_L interface, 11 are identical in C_H3–C_H3 and 5 are conservative changes (42–44). In contrast, only 1 of the C_H1–C_L contact residues (Glu-125 of C_L) is the same as the β_2m moiety in the comparable location (Glu-16). Five other residues show conservative changes, but the other 23 sites are different in the two proteins. The difference between β_2m and the constant domains is even more noticeable when interdomain salt links are compared: of the 8 residues in C_H1–C_L salt links, none is identical, or even charged, in β_2m. In conclusion, interactions between β_2m and other Ig-like molecules, including the heavy chains of MHC class I antigens, may involve the four-stranded β structure, but specific residues and interactions in such an assembly must be different from those observed previously.

Despite these differences in detail, evidence from solution studies and the structure described here are consistent with a mode of binding involving the four-stranded β structure. A monoclonal antibody is known to bind to Arg-45 of human β_2m both when the molecule is free and when it is complexed to the HLA heavy chain (45). The analogous residue in bovine β_2m is Lys-45, and this residue is in a loop at the upper right end of the molecule in Fig. 1. Binding of an antibody at this site would leave the four-stranded β sheet of β_2m free to interact with an Ig-like domain. It has also been observed that tyrosines 10, 26, and 63 of human β_2m are iodinated in the free molecule but not when it is complexed with HLA heavy chain (46). In the three-dimensional structure, these protected side chains are exposed on the surface of the four-stranded β structure where they would be in noncovalent contact with the HLA heavy chain if these molecules formed a complex similar to those formed by C_H1–C_L and C_H3–C_H3.

Although the structure of β_2m presented here is consistent with the notion that the molecule associates with MHC antigen heavy chains in a manner analogous to Ig constant domain pairing, such an association has not been proven. It remains possible that β_2m complexes through its four-stranded β sheet in a novel way or through another part of the molecule. An unambiguous resolution of this issue awaits the determination of the three-dimensional structure of a heavy chain–β_2m complex, or at least more extensive chemical studies.

To our knowledge, β_2m is the first component of the MHC antigen system whose three-dimensional structure has been determined. The MHC class I antigens, in complex with β_2m, participate in specific recognition and functional events involving both foreign antigens and receptors on cytotoxic T lymphocytes. A chemical and evolutionary link between the molecules involved in these processes and the Ig molecules has been established by studies of their genetic and amino acid sequences. The structure presented here extends this link to the level of detailed three-dimensional conformation. This structural information should provide a firmer basis for a more detailed understanding of the functional interactions of these important molecules.

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