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The sequence of human retinal S-antigen reveals similarities with α-transducin

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The complete amino acid sequence of human retinal S-antigen (48 kDa protein), a retinal protein involved in the visual process has been determined by cDNA sequencing. The largest cDNA was 1590 base pairs (bp) and it contained an entire coding sequence. The similarity of nucleotide sequence between the human and bovine is approximately 80%. The predicted amino acid sequence indicates that human S-antigen has 405 residues and its molecular mass is 45050 Da. The amino acid sequence homology between human and bovine is 81%. There is no overall sequence similarity between S-antigen and other proteins listed in the National Biomedical Research Foundation (NBRF) protein data base. However, local regions of sequence homology with α-transducin (Tα) are apparent including the putative rhodopsin binding and phosphoryl binding sites. In addition, human S-antigen has sequences identical to bovine uveitopathogenic sites, indicating that some types of human uveitis may in part be related to the animal model of experimental autoimmune uveitis (EAU).

S-antigen; 48-kDa protein; Human cDNA; Amino acid sequence; Uveitis; Visual process

1. INTRODUCTION

Vision begins with the conversion of light energy into an electrical impulse (phototransduction) [1,2]. This is accomplished by the outer segments of the photoreceptor cells of the retina. Initial absorption of light converts rhodopsin into an active form (R*) which interacts with and activates hundreds of transducin (Td) molecules [3–5]. The activated Td interacts with phosphodiesterase (PDE), each molecule of which hydrolyzes thousands of molecules of cyclic guanosine monophosphate (cGMP) [5–7]. The decrease of cGMP concentration blocks the entry of sodium ions by closing Na^+ channels [8–10]. Thus, light energy is amplified to generate a membrane potential. This electrical signal is processed into a neuronal signal by other retinal cells. The rhodopsin bleached by light is then phosphorylated by rhodopsin kinase at multiple serines and threonines near the carboxyl terminus [11]. S-antigen binds to the R* and R*P to play a negative regulatory role in the visual process [12–14]. As a contrasting hypothesis, S-antigen does not bind to R*P but directly inactivates PDE [15,16]. Many similar proteins have been shown to be involved in the visual system, the adenyl cyclase system and hormone receptor signal transduction [17]. Therefore, it is possible that the adenyl cyclase system has a protein similar to S-antigen which plays a role in negative regulation. However, only in the photoreceptor cells in retina and pinealocytes in pineal gland, has S-antigen been detected by immunocytochemistry [18].

S-antigen is also a highly antigenic protein

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Abbreviations: NBRF, National Biomedical Research Foundation; EAU, experimental autoimmune uveitis; R*, photoactivated rhodopsin; R*P, phosphorylated photoactivated rhodopsin; CD, circular dichroism; Td, transducin; PDE, phosphodiesterase; cGMP, cyclic guanosine monophosphate

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responsible for the induction of experimental autoimmune uveitis (EAU) [19,20]. Recently the structure of bovine S-antigen [21–23] and sites responsible for EAU have been characterized [24]. In order to understand the functional role of S-antigen in phototransduction and in the induction of human uveitis, it is important to determine the structure of human S-antigen. Here, we report the amino acid sequence of human S-antigen and discuss its role in the visual process and in human disease.

2. MATERIALS AND METHODS

Human retinal library (generous gift from Dr J. Nathans, Genentech) was screened with ^{32}P-labelled 5′ noncoding sequence of a bovine S-antigen cDNA probe (331 bp long) as described [22,23]. Initially, 1×10^5 plaques were screened giving 1×10^3 positive plaques. Most of the clones seem to have nearly full-size cDNA insert. Nine cDNA inserts were subcloned into bluescribe plasmid (Stratagene, San Diego, CA) and amplified.

Restriction enzyme analysis was performed with *Eco*RI, *Bam*HI, *Hae*III, *Bgl*II, *Kpn*I, *Sac*I, *Xho*I and *Pst*I enzymes (International Biotechnologies Inc., New Haven, CT). DNA sequences were obtained by the dideoxy chain termination method [25] modified for [^{35}S]ATP (Amersham Inc., Arlington Heights, IL) [21]. Specific oligonucleotide primer probes (15 or 20 mer) were made on an automated DNA synthesizer (Model 380B, Applied Biosystem, Inc., Foster City, CA).

3. RESULTS AND DISCUSSION

Several positive plaques for human S-antigen cDNAs were obtained from a human retina cDNA library by hybridization with bovine S-antigen cDNA probes [21–23]. Nine of them contained the full coding sequence of S-antigen and had the same restriction sites for *Bgl*II, *Eco*RI, *Kpn*I, *Sac*I and *Xho*I (not shown). Three cDNAs out of nine clones had different *Hae*III sites in the coding sequence indicating that S-antigen may be polymorphic, since the cDNA library was constructed from multiple retinas [26]. The largest cDNA insert, 1590 bp was sequenced (fig.1). This cDNA insert has a poly-A tail at the 3′ end but lacks 100–150 bp at the 5′ end. The bovine and mouse mRNA size is approximately 1600–1700 nucleotides (nt). The sequence similarity between human and bovine DNA is approximately 80% (fig.2). However, similarity in the non-coding sequence is less than 30%, while in the coding sequence it is 86%. Both human and bovine cDNAs have a long 5′ noncoding sequence (300~400 nt)

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GGGATCTAGCGAGGATGCCCCCTACAAATTCCCCACATCACGTAGGCCAGGAGCCTCAGC
      10        20        30        40        50        60
GCTGCCCCTTCAGGCTCATCTGGCAAGACGGTACCAGCTTGCTCAGAACAGGGGCTGGCT
      70        80        90       100       110       120
ATTCATCATCTCAGAGCATAGAGACGCTCTCCTTGCCACCCGGCCCTTCCCACCTGGTTG
     130       140       150       160       170       180
                                                M A A S G K T   7
GTGACAATCACAAGGTGTAGAAGTTGCCAGCGACAGATAAGATGGCAGCCAGCGGGAAGA
     190       200       210       220       230       240
  S K S E P N H V I F K K I S R D K S V T  27
CCAGCAAGTCCGAACCGAACCATGTTATCTTCAAGAAGATCTCCCGGGACAAATCGGTGA
     250       260       270       280       290       300
  I Y L G N R D Y I D H V S Q V Q P V D G  47
CCATCTACCTGGGGAACAGAGACTACATAGACCATGTCAGCCAAGTCCAGCCTGTGGATG
     310       320       330       340       350       360
  V V L V D P D L V K G K K V Y V T L T C  67
GTGTCGTGTTGGTTGATCCTGATCTTGTGAAGGGAAAGAAAGTGTATGTCACTCTGACCT
     370       380       390       400       410       420
  A F R Y G Q E D V D V I G L T F R R D L  87
GCGCCTTCCGCTATGGCCAAGAGGACGTTGACGTGATCGGCTTGACCTTCCGCAGGGACC
     430       440       450       460       470       480
  Y F S R V Q V Y P P V G A A S T P T K L 107
TGTACTTCTCCCGGGTCCAGGTGTATCCTCCTGTGGGGGCCGCGAGCACCCCCACAAAAC
     490       500       510       520       530       540
  Q E S L L K K L G S N T Y P F L L T F P 127
TGCAAGAGAGCCTGCTTAAAAAGCTGGGGAGCAACACGTACCCCTTTCTCGTGAGTTTC
     550       560       570       580       590       600
  D Y L P C S V M L Q P A P Q D S G K S C 147
CTGACTACTTGCCCTGTTCAGTGATGTTGCAGCCAGCTCCACAAGATTCAGGGAAGTCCT
     610       620       630       640       650       660
  G V D F E V K A F A T D S T D A E E D K 167
GTGGGGTTGACTTTGAGGTCAAAGCATTCGCCACAGACAGCACCGATGCCGAAGAGGACA
     670       680       690       700       710       720
  I P K K S S V R Y L I R S V Q H A P L E 187
AAATCCCCAAGAAGAGCTCCGTGCGATATCTGATCCGTAGTGTACAGCATGCCCCACTTG
     730       740       750       760       770       780
  M G P Q P R A E A T W Q F F M S D K P L 207
AGATGGGTCCCCAGCCCCAGCTGAGGCGACCTCCCAGTTCTTCATGTCTCACAAGCCCC
     790       800       810       820       830       840
  H L A V S L N R E I Y F H G E P I P V T 227
TGCACCTTGCGGTCTCTCTCAACAGAGAGATCTATTTCCATGGGGAGCCCATCCCTGTGA
     850       860       870       880       890       900
  V T V T N N T E K T V K K I K A C V E Q 247
CCGTGACTGTCACCAATAACACAGAGAAGACCGTGAAGAAGATTAAAGCATGCGTGGAAC
     910       920       930       940       950       960
  V A N V V L Y S S D Y Y V K P V A M E E 267
AGGTGGCCAATGTGGTTCTCTACTCGAGTGATTATTACGTCAAGCCCGTGGCTATGGAGG
     970       980       990      1000      1010      1020
  A Q E K V P P N S T L T K T L T L L P L 287
AAGCGCAAGAAAAAGTGCCACCAAACACCACTTTGACCAAGACGTTGACGCTGCTCCCCT
    1030      1040      1050      1060      1070      1080
  L A N N R E R R G I A L D G K I K H E D 307
TGCTGGCTAACAATCGAGAAAGGAGAGGCATTGCCCTGGATGGGAAAATCAAGCACGAGG
    1090      1100      1110      1120      1130      1140
  T N L A S S T I I K E G I D R T V L G I 327
ACACAAACCTTGCCTCCAGCACCATCATTAAGGAGGGCATAGACCGGACCGTCCTGGGAA
    1150      1160      1170      1180      1190      1200
  L V S Y Q I K V K L T V S G F L G E L T 347
TCCTGGTGTCTTACCAGATCAAGGTGAAGCTCACAGTGTCAGGCTTTCTGGGAGAGCTCA
    1210      1220      1230      1240      1250      1260
  S S E V A T E V P F R L M H P Q P E D P 367
CCTCGAGTGAAGTCGCCACTGAGGTCCCATTCCGCCTGATGCACCCTCAGCCTGAGGACC
    1270      1280      1290      1300      1310      1320
  A K E S I Q D A N L V F E E F A R H N L 387
CAGCTAAGCAAAGTATTCAGGATGCAAATTTAGTTTTTGAGGAGTTTGCTCGCCATAATC
    1330      1340      1350      1360      1370      1380
  K D A G E A E E G K R D K N D A D E      405
TGAAAGATGCAGGAGAAGCTGAGGAGGGGAAGAGAGACAAGAATGACGCTGATGAGTGAA
    1390      1400      1410      1420      1430      1440
GATGTCGGCTCAGGATGCCGGAAAATGACCTGTAGTTACCAGTGCAACGAGCAAAGCCCC
    1450      1460      1470      1480      1490      1500
ACAGTTTAGTCCTTTGGAGTTATGCTGCGTATGAAAGGATGAGTCTTCTTCCGAGAAATA
    1510      1520      1530      1540      1550      1560
AAGCTTGTTTGTTCTCCCCTGGAAAAAAAA
    1570      1580      1590
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Fig.1. The sequence of cDNA clone for human S-antigen. The upper line shows predicted amino acid sequence and lower line shows nucleotide sequence. Numbers on the right indicate amino acid residues and subscripts of nucleotides indicate nucleotide residues from 5′ end. The underlined nucleotides preceding the S-antigen sequences denote the first methionine codon and in frame termination codon.

	Phosphoryl Binding Site												Guanine Binding Site				
Consensus Sequence	**Gly Ala**	x	x	x	x	**Gly**	**Lys**		**Asp**	x	x	**Gly**		**Asn**	**Lys**	x	**Asp**
Human S-Ag	**Ala**	Pro	Gln	Asp	Ser	**Gly**	**Lys**	(139-145)	**Asp**	Val	Ile	**Gly**	(77-80)	Ser	**Lys**	Ser	Glu (8-11)
	Gly	Ile	Ala	Leu	Asp	**Gly**	**Lys**	(296-302)									
Bovine S-Ag	**Ala**	Pro	Gln	Asp	Val	**Gly**	**Lys**	(135-141)	**Asp**	Val	Met	**Gly**	(73-76)	**Asn**	**Lys**	Pro	Ala (4-7)
	Gly	Ile	Ala	Leu	Asp	**Gly**	**Lys**	(292-298)									

Fig.2. Homologies of human and bovine S-antigen to the consensus sequence of GTP/GDP binding sites. The numbers in parentheses represent the amino acid residues. Consensus spacing of consensus sequences are either 40–80 or 130–170 amino acid residues between the first and second elements and 40–80 amino acid residues between the second and third sequence elements. X indicates any amino acid residues.

and a relatively short 3′ noncoding sequence (~150 nt).

The initiation codon at base 222 is in a sequence which conforms well to the Kozak consensus sequence (TAACATG compared with CANCATG) [27]. The open reading frame between 222 and 1436 appears to contain the entire coding sequence for S-antigen, a protein consisting of 405 amino acids with a calculated molecular mass of 45050 Da. The sequence identity at the protein level between human and bovine is 81%.

Another small open reading frame between 15 and 200 which could encode 60 amino acid residues is observed and it has no similarity with any sequence in the NBRF database. Bovine S-antigen cDNA has a similar open reading frame in the 5′ noncoding sequence. There is also no significant nucleotide or amino acid sequence similarity between the small open reading frames in human and bovine 5′ noncoding sequences. Such short open reading frames in the 5′ noncoding region have been reported in other cDNAs [28,29] and they appear to have influence on their translation [30].

Although the function of S-antigen in the phototransduction process is not well understood, a possible relationship with GTP binding proteins exists. S-antigen and GTP-binding proteins have some interesting local sequence similarities. GTP binding proteins including proto-oncogenes referred to as ras proteins, bacterial elongation factors (EF-Tu and EF-G), α-tubulin, adenylate kinase, signal-transducing G-proteins and Tα contain highly conserved functional sequences [31]. The striking feature is at the GTP binding site, including a consensus sequence composed of three elements, Gly/Ala-X-X-X-X-Gly-Lys, Asp-X-X-Gly and Asn-Lys-X-Asp with conserved spacing. Human and bovine S-antigens have four such sequences as shown in fig.2, but in the reverse orientation. They have phosphoryl binding consensus sites Ala-X-X-X-X-Gly-Lys and Asp-X-X-Gly with the right consensus spacing. In addition, both S-antigens have Gly-X-X-X-X-Gly-Lys elements at 295–301 (human) and 292–298 (bovine) without consensus spacing. These three sites may form binding pockets for phosphates [32].

In contrast to the phosphoryl binding sites, there is no obvious candidate for guanine binding sites in the S-antigen sequence [31]. The closest homology in bovine is An-Lys-Pro-Ala with the right spacing. Thus, S-antigen may not bind to GTP. When Asp of Asn-Lys-X-Asp is replaced by Asn as Asn-Lys-X-Asn in the ras mutant protein, the affinity for GTP is lowered by a factor of 100 [33]. Addi-

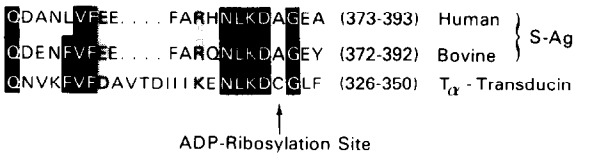

Fig.3. Homologies of human, mouse and bovine S-antigen sequences to Tα sequence. Dark boxes indicate the identical amino acid residues and half shade boxes indicate conserved amino acid residues. Bovine sequence was published [21–23]. S-antigen was not ADP-ribosylated by pertussis toxin [23]. The numbers in parentheses represent the amino acid residues.

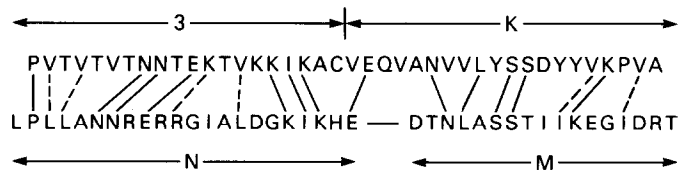

Fig.4. Sequence similarity of human S-antigen peptides M and N to k and 3. Peptides M, N, K and 3 of bovine S-antigen are uteitogenic sites for experimental animals [24,44]. Solid lines between sequences indicate the identical amino acid residues and dotted lines indicate conserved amino acid residues. (I = V = L, K = R).

tionally, in the same protein, a Lys or Tyr replacement of the Asp in Asn-Lys-X-Asp abolishes GTP-binding activity [34]. We did not observe binding of the ATP to S-antigen (not shown), which is consistent with other results [12–14]. Thus, it is reasonable to speculate that R*P binds to putative phosphoryl pocket of S-antigen.

The second interesting regional similarity of S-antigen is with a site near the carboxyl terminus of Tα where pertussis toxin catalyzes ADP-ribosylation [35] as shown in fig.3. Modification of α-transducin by pertussis toxin results in marked reduction of the light dependent GTPase activity as well as the light stimulation of PDE [36]. This suggests that the carboxyl terminus of Tα plays a critical role in the interaction with R*. We speculate that S-antigen and Tα bind to R* at the same site.

Thus, the structure of S-antigen is consistent with the observation of Kuhn et al. [12–14] that it interacts with R* at the same site as Tα in a competitive manner [12]. Initial S-antigen and R* binding may be very weak, as reported previously [12–14]. However, when rhodopsin is phosphorylated with rhodopsin kinase, secondary binding may take place: S-antigen phosphoryl pockets may bind to the phosphate groups of R*P leading to tighter binding than R*/Tα thereby quenching the capacity of Tα to activate PDE. The Tα binding site on rhodopsin is estimated to be at the carboxyl terminus, residues 317–339[37] or loop V[38], which is close to the multiple phosphorylation sites [11]. Furthermore, carboxyl terminus amino acid residues (approximately 10) were cleaved from the phosphorylated rhodopsin by proteinase. This rhodopsin increases PDE activity higher than the original level [39]. This result suggests that the carboxyl terminus does not interact with Tα. The phosphorylation of rhodopsin is an important process for inactivation of the phototransduction cascade.

S-antigen is also present in the pineal gland where there is no detectable rhodopsin [40]. We speculate that S-antigen binds to phosphorylated β-adrenergic receptors since the β-adrenergic receptor has some sequence similarity to rhodopsin and is also known to be inactivated by phosphorylation [41]. A recent report indicates that S-antigen indeed inhibits the β-adrenergic signal transduction cascade [42].

Recently, the immunopathogenic sites of bovine S-antigen, peptides M, N, K and 3 for the induction of EAU in the Lewis rat have been characterized [24]. Human S-antigen is also capable of inducing EAU in experimental animals including Lewis rats, guinea pigs and monkeys (in preparation) with similar pathology [43]. Interestingly, human S-antigen has an identical sequence to bovine S-antigen M and N peptides (306–317), furthermore it has sequence similarity between peptides M and N and peptides K and 3 (fig.4). The multiple repeated structures may play an important role in the induction of EAU. These findings would indicate that EAU induced by peptides M and N could have clinical relevance to some types of human uveitis. As mentioned previously, however, human S-antigen seems to be polymorphic, perhaps indicating that the susceptibility to disease is in part due to the heterogeneity of the S-antigen structure in each individual.

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