A Protein with Characteristics of Factor H Is Present on Rodent Platelets and Functions as the Immune Adherence Receptor*

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The complement system has three pathways containing over 30 plasma and membrane-bound proteins that play a key role in immune defense (1). These proteins cause the rapid destruction of invading microorganisms and mediate the solubilization and clearance of immune complexes. Immune complexes bearing the activated complement component C3b bind to cells with specific membrane receptors, which transport them to the mononuclear phagocyte system in the liver and spleen. This phenomenon is called immune adherence (IA)2 (2, 3) and is responsible for the disposal of immune complexes from the body (4, 5). The in vitro correlate of this is rosetting of IAR-bearing cells with C3b-containing particles (3, 6).

The IAR of primates is CR1, which is present on erythrocytes (7). In addition to erythrocytes, CR1 is also present on blood cells, including monocytes, lymphocytes, neutrophils, and eosinophils and resident cells such as podocytes in the renal glomerulus, follicular dendritic cells in lymphoid organs and astrocytes in the brain (8–10). CR1 is a member of the regulators of complement activation gene cluster located on chromosome 1q32, all of which have ligand specificity for activation products of C3 and/or C4 and contain repetitive units known as short consensus repeats (SCRs) (11, 12). In contrast, IA function in non-primates, including rodents, is not served by erythrocytes, but rather by platelets bearing an undefined IAR (13, 14).

Several attempts have been made to identify this non-primate IAR. Mouse platelets form rosettes with C3b-containing erythrocytes, which can be disrupted by incubating cells with factor I (15), implying that the IAR provides factor I cofactor activity. The obvious candidate for this is mouse CR1; yet, CR1 is clearly absent from mouse platelets, as well as erythrocytes and unstimulated neutrophils (16). A 150-kDa C3b/C4-binding protein isolated from rabbit platelets was absent on rabbit erythrocytes, but was not characterized further (17). In our previous studies (18, 19), we identified rodent platelet proteins that bound C3 fragments and hence were candidates similar to the IAR. However, at that time, we could only characterize them on the basis of their size and reactivities with available antibodies to mouse CR1 and CR2.

The purpose of this study was to identify the rodent platelet IAR. By functional, biochemical, immunological, and molecular biological approaches, we conclusively show rodent platelets can produce and bear a protein with characteristics of factor H, a member of the regulators of complement activation family. This platelet-associated factor H functions as the IAR.

EXPERIMENTAL PROCEDURES

\textbf{Antibodies (Abs)—}Goat anti-human factor H was purchased from QuiHel (San Diego, CA), and cross-reacts with mouse and rat factor H (see below), which is not surprising given that factor H is highly conserved among species (20). Sheep Abs were raised to rat rCrry (21) and rDAP (22) (a gift of Dr. B. Paul Morgan, University of Wales College of Medicine, Cardiff). Rabbit anti-mouse rCrry was supplied by Dr. V. Michael Hohers (23) (University of Colorado Health Sciences Center, Denver). A goat anti-rat thrombocyte Ab was purchased from Accurate

FITC, fluorescein isothiocyanate; GPI, glycosylphosphatidylinositol; IF, immunofluorescence; PBS, phosphate-buffered saline; PIPLC, phosphatidylinositol-specific phospholipase C; SCR, short consensus repeat; TBST, Tris-buffered saline with 0.5% Tween 20; PAGE, polyacrylamide gel electrophoresis; RACE, rapid amplification of cDNA ends; RT-PCR, reverse transcription-polymerase chain reaction; µL/CMS/MS, microcapillary reverse-phase HPLC nanoelectrospray tandem mass spectrometry.
Factor H on Rodent Platelets

Scientific (Westfield, NY). Although rodent platelets are known to not bear Fc receptors (24), all experiments were performed with F(ab’)2 Ab fragments, which were prepared by standard techniques (25).

C3 Purification—The purification of rat and mouse C3 from plasma have been described previously (19, 26). In brief, rat C3 was purified by a 5–11% pepsin precipitation followed by Mono Q anion exchange chromatography (Amersham Pharmacia Biotech). A similar technique was used to purify mouse C3, except that a 5–10% polyethylene precipitation was used, and following Mono Q chromatography, size exclusion chromatography on Sephacryl S-300 HR was performed. The preparations were noted as pure with SDS-PAGE.

Amino Acid Sequencing—Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut Oubut O
mental Procedures,
light microscopy. Magnification,
containing EC423b bound to IAR-containing platelets was visualized by
analyzed by
/H9262
also recovered by C3b affinity chromatography.
of intrachain disulfide bonds. In addition, a 115-kDa band was
this protein migrated at 175-kDa, consistent with the presence
of intrachain disulfide bonds. In addition, a 115-kDa band was recovered. Under reducing conditions,
To isolate C3b-binding proteins
—
from Rat Platelet Membranes
... examines A). As a positive control, rat
platelets (Fig. 4
lanes 1
plasma factor H was run in parallel
Therefore, rat platelets have a 150-kDa C3b-binding protein with bio-
eluted rat platelet membranes were subjected to C3b affinity chromatog-
ysis after the following treatments: 1) high salt washing; 2)
pretreatment with PIPLC, and 3) pretreatment with neur-
amidase. High salt washing did not remove factor H from the
surface of platelets, nor, as predicted, did it remove the type I
membrane protein, Crry (not shown). PIPLC treatment did not
eliminate Crry (not shown) or factor H (Fig. 5
D
platelet surface, whereas DAF, attached to the platelet surface
eliminate Crry (not shown) or factor H (Fig. 5
D
from the
E
platelet surface, nor, as predicted, did it remove the type I
membrane protein, Crry, present on the surface of
Platelets Plasma
TABLE I
Amino acid sequences obtained from tryptic peptides derived from the
platelet 150-kDa C3b-binding protein and rat plasma factor H
Platelets Plasma
CLPVTELENGR CLPVTELENGR
LAVGSQFEFGAK LAVGSQFEFGAK
WQLPR WQLPR
TLGTVK TLGTVK
WTQLPKCVATDQ WTQLPKCVATDQ

FIG. 3. Rat platelet C3b-binding proteins are recognized by
anti-factor H Abs. Rat platelet C3b-binding proteins were electrophoresed under non-reducing conditions and subjected to Western blotting with anti-human factor H Abs (lane 1). As a positive control, rat plasma factor H was treated identically (lane 2).

FIG. 2. Isolation of rat platelet C3b-binding proteins. Solubi-

ized rat platelet membranes were subjected to C3b affinity chromatog-
raphy. Proteins bound to the C3b column were eluted and subjected to non-reducing SDS-PAGE followed by staining with Coomassie Blue.

FIG. 1. EC423b rosette with platelets from CR1/−/− (A) and
wild-type (B) mice. EC423b, prepared as described under “Exper-
imental Procedures,” were incubated with platelets from CR1/−/− (A) or
wild-type (B) mice for 20 min at 37°C, and the appearance of rosettes
containing EC423b bound to IAR-containing platelets was visualized by
light microscopy. Magnification, × 200.
platelets (lane 1) and liver (lane 2). By sequence analysis, the rat platelet and liver sequences were identical, and 90% similar to the known sequence of mouse factor H encompassing amino acids 802–958 (20); the predicted translated protein product was 85% identical to mouse factor H as shown in Table II. Using this PCR product as probe in Northern analyses, RNA from platelets, kidney, and liver had identically sized RNA transcripts of 5.5, 3.4, and 1.8 kilobases (Fig. 7).

By 3′RACE of RNA isolated from rat platelets, a product of the predicted size of 699 base pairs was amplified. The nucleotide sequence of this product was identical to the known sequence of mouse liver factor H, except for one base at residue 4169 in the 3′-untranslated region. These results indicate rat platelets have the inherent capacity to produce factor H protein, which is predicted to be a soluble protein. Thus, any alterations accounting for its capacity to bind to the platelet membrane are likely to occur after protein translation.

**Factor H Functions as the Rodent IAR**—Platelets from normal rats and mice formed rosettes with EC423b cells (Fig. 8, A and C). Preincubation with anti-factor H F(ab′)₂ Abs inhibited rosette formation in platelets of both species (Fig. 8, B and E). As a negative control, antibodies to Crry, a complement regulator on the rodent platelet surface, were used. Platelets pretreated with anti-Crry F(ab′)₂ clearly rosetted with EC423b (Fig. 8D). Rosette formation was eliminated when platelets were preincubated with neuraminidase (Fig. 8F). Thus, factor H on the rodent platelet surface is the functional IAR.

**DISCUSSION**

The IA reaction was defined by Nelson (2, 3) as the interaction between cells and complement-coated particles. Immune complexes bearing the activated complement component, C3b, bind to cells containing IAR, which then transport them to the mononuclear phagocyte system for their disposal. In primates, IA function clearly is served by CR1 on erythrocytes. In contrast, the immune complex clearance mechanism in non-primates, including rodents, is carried out by platelets rather than erythrocytes (13, 35). The mouse complement receptors CR1 and CR2 were identified on the basis of similarity to their human counterparts. However, notable differences are that: 1)
they are derived from alternatively spliced transcripts of the same gene, Cr2 (27, 36), 2) they have similar but not identical ligand binding characteristics compared with humans (37), and, 3) neither of the proteins are present on platelets, erythrocytes, or unstimulated neutrophils (16), confirming that CR1 does not function as the rodent IAR. We showed that rosetting occurred, as an in vitro assay for the IA reaction, with platelets isolated from CR1−/− mice. Therefore, the IAR in rodents has gone unidentified.

In this study, we purified a 150-kDa single chain protein from platelets by C3b affinity chromatography. Its characteristics by SDS-PAGE are similar to the C3b-binding protein isolated from rabbit platelets by the Atkinson laboratory (17). The 150-kDa C3b-binding platelet protein and factor H isolated from rat plasma were identical in the regions where the peptide sequences were obtained, which were localized to two areas spanning 23.3% of the length of the protein and encompassing SCR#1–3 and 14 as identified by mass spectrometry in the 115-kDa protein (39). It is more likely that this 115-kDa protein is either a breakdown product in the preparation of solubilized platelet membranes or a spliced gene product, which occurs frequently in the regulators of complement activation gene family (36, 40).

Factor H displays several similarities with the human IAR, CR1. Both are large glycoproteins possessing only N-linked carbohydrate moieties (41, 42). Both belong to the regulators of complement activation family, which also includes CR2, DAF, and membrane cofactor protein (11, 12). Genes of this family are encoded on the long arm of chromosome 1q32 in humans (43) and a conserved linkage group in mouse chromosome 1 (44). These proteins share a tandemly repeated SCR motif of ~60 amino acids, containing a conserved amino acid framework around four invariant cysteines, which form two disulfide bonds. Like CR1, factor H is a versatile protein with several different functions. It inhibits the formation and accelerates the decay of C3 convertases, serves as a cofactor for factor I (45), displays chemotactic activity for monocytes (46), and possibly participates in interactions with extracellular matrix and leukocytes (47).

Any candidate for the rodent IAR must be present on the surface of platelets. By flow cytometry and IF, factor H was present on the platelet membrane. Neither technique detected factor H on rat erythrocytes. This is an important control, as erythrocytes do not participate in IA in non-primates (6, 13), and it also indicates not all circulating blood cells contain factor H. Flow cytometry further indicated that when rodent platelets were washed with high salt, factor H was not removed, providing evidence that factor H did not just passively adsorb from plasma onto the platelet membranes. Neuraminidase treatment of platelets reduced factor H, suggesting that factor H is bound to the platelet membrane by sialic acid residues, whereas Crry, a type I membrane protein, remained unaltered. PIPLC treatment caused a substantial decrease in DAF, a GPI-linked protein on the platelets but no change in factor H or Crry, indicating that factor H is not GPI-linked to the platelets.

There are numerous examples of factor H binding to the surface of a variety of cells, including nucleated cells (48, 49), viruses (50), bacteria (30, 51–53), and parasites (54). In the majority of cases, this is mediated via interactions of several sites on factor H with sialic acid residues on the host cell (30, 55, 56), although protein-protein interactions have also been shown to be important.

### Table II

| SCR#14 | L | T | T | L | H |
|--------|---|---|---|---|---|
| SCR#15 | EKIPCGQPPKIEHGSIKSPRSSEER-DLIESSSYEHGTTSYSVDDGFRISERRENDTVQMGKWSLPRGV | T | N | D | I |
| SCR#16 | GIPCGPPSIPPLGIVSHELESYYQGEEVTYNCSQSEGFGIDGPAFI | L | T | L | H | T |

**Fig. 6.** Platelets bear mRNA for factor H. RT-PCR analysis using primers spanning bases 2556–3028 of mouse factor H, showing that rat platelets (lane 1) contain RNA of the predicted size and comparable with that identified in rat liver (lane 2).

**Fig. 7.** Rat platelets contain factor H mRNA. Northern analyses show that rat platelets (lane 1) have factor H mRNA of comparable size to that identified in rat kidney (lane 2) and liver (lane 3). The positions of ribosomal RNA in the gel are indicated with arrows.
described (57). For the most part, the binding of factor H has conferred a resistance to complement activation, presumably through its capacity to decay C3 convertases as well as act as a factor I cofactor (39). Factor H mediates these actions through its affinity for C3b (58, 59), although specific binding to C3b is not a demonstrated feature of most of these interactions. As with other molecules with low affinity interactions, clustering of molecules can considerably increase binding avidity (60).

The PCR product obtained from rat platelet RNA differed from mouse liver factor H by only 15% at the protein sequence level. Furthermore, by 3'-RACE, nucleotide sequences corresponding to SCRs 19–20 and into the 3'-untranslated region were identical to that from mouse liver factor H. Northern analysis recognized factor H transcripts of similar lengths in rat liver, kidney, and platelets. Such differently sized transcripts have also been observed for human factor H mRNA, which is compatible with alternative mRNA splicing (61). In humans, the smaller 1.8 kilobase factor H mRNA transcript gives rise to the 45-kDa factor H-like protein 1 (39, 61). Despite the presence of a similarly sized transcript in platelets, we did not observe a 45-kDa C3b-binding protein from platelets in this study. Native factor H has three potential binding sites for both C3 and sialic acid, whereas factor H-like protein 1 has only one of each (39). As such, factor H would have superior binding capabilities for both sialic acid residues on the platelet surface and C3b in immune complexes.

The PCR and Northern analysis data clearly demonstrate the intrinsic ability of platelets to synthesize factor H. Factor H has been known to be associated with human platelets (62). This platelet-associated factor H resides in a granules, is functionally active, and is released upon complement activation or other stimuli (63, 64). Our data show that rodent platelets are different from their human counterparts as they contain factor H on their surface. In this regard, they are similar to U937 monocyctic cells, which synthesize and bear factor H on their plasma membrane while not secreting it as a soluble protein (65).

In summary, we have isolated a 150-kDa C3b-binding protein from rat platelets. By biochemical and immunochromical criteria, the protein has characteristics of factor H and resides on the surface of platelets, which also have the inherent capacity to produce this protein. When the function of factor H is blocked on rodent platelets with neutralizing Abs, rosetting with EC423b is prevented, establishing factor H as the rodent IAR. Further studies of platelet-associated factor H will help elucidate mechanisms of immune complex clearance and inflammatory cell accumulation in various rodent models of immune complex-mediated diseases. These animal models are particularly useful in this era where genetic manipulations of individual genes are possible. The generation of factor H-deficient mice will allow dissection of the role of the IAR in vivo.

Fig. 8. Factor H is the functional IAR of rodent platelets. Rossetting of rat (A, B) and mouse (C, D) platelets with EC423b was determined following pretreatment with preimmune F(ab')2 (A, C), anti-Crry F(ab')2 (D), anti-factor H F(ab')2 (B, E), or neuraminidase (F). Rossetting with EC423b (A, C) was inhibited with anti-factor H Abs (B, E) or neuraminidase pretreatment (F), but not with anti-Crry Abs (D). Magnification: A–B, × 400; C–E, × 200.

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