The Conversion of Fibrinogen to Fibrin at the Surface of Curliated *Escherichia coli* Bacteria Leads to the Generation of Proinflammatory Fibrinopeptides*

Received for publication, March 12, 2003, and in revised form, June 1, 2003
Published, JBC Papers in Press, June 12, 2003, DOI 10.1074/jbc.M302522200

Kristin Persson‡, Wayne Russell, Matthias Mörgelin, and Heiko Herwald§
From the Department of Cell and Molecular Biology, Lund University, S-221 84 Lund, Sweden

The inflammatory response to bacterial infection is the result of a complex interplay between bacterial products and host effector systems, such as the immune and complement systems. Here we show that *Escherichia coli* bacteria expressing fibrous surface proteins, known as curli, assemble and activate factors of the human coagulation cascade at their surface. As a result of this interaction, fibrinogen is converted to fibrin and fibrinogen-derived peptides, termed fibrinopeptides, are generated. The molecular mechanisms behind the bacteria-induced formation of fibrinopeptides were investigated and shown to be triggered by the activation of the contact system, also known as the kallikrein/kinin system or the intrinsic pathway of coagulation. Samples containing fibrinopeptides generated by the interaction between bacteria and plasma were injected into animals and the inflammatory response was monitored. We found that this treatment provoked an infiltration of white blood cells, and the induction of the proinflammatory cytokine MCP-1 at the inflamed site. Our results therefore demonstrate that activation of the coagulation system at the bacterial surface contributes to the pathophysiology of bacterial infectious diseases.

Bacterial binding to eukaryotic cells, extracellular matrix proteins, or soluble components such as plasma proteins, is an important mechanism that allows the invading microorganism to establish, proliferate, and modulate the host response. In order to facilitate host specificity and tissue tropism, gram-negative bacteria produce a number of different surface organelles, which can be classified into non-fimbrial and fimbrial adhesins (for a review see Ref. 1). Most *Escherichia coli* and *Salmonella* strains carry a set of genes coding for a fimbrial organelle that is termed “curli” in *E. coli* (2) and “thin, aggregative fimbriae” in *Salmonella* (3). For simplification, these structures are collectively referred to as curli in this study. Electron microscopy has revealed that curli form thin, wavy, and highly aggregative coiled surface structures that are morphologically distinct from other types of fimbriae (2, 4). The finding that this organelle is preferentially expressed by enterohemorrhagic, enterotoxigenic, and sepsis strains, but not by enteroinvasive and enteropathogenic bacteria, implicates curli as an important virulence factor (5, 6).

Curli have a broad range of binding specificity. Like other fimbriae, curli fibers are involved in bacterial attachment to, and invasion of eukaryotic cells, which is promoted by the interaction between curli and fibronectin (7–9). Other ligands for curli are laminin, plasminogen, tissue plasminogen activator, MHC class I antigen, and fibrinogen, as well as low coagulation factors (5, 10–12). In *E. coli*, formation of curli organelles is regulated by two operons, *csgDEFG* and *csgBA*, which code for six proteins, termed CsgA to CsgG (for a review see Ref. 4). Recent studies have shown that CsgA carries two binding-sites for the different ligands, located at the N- and C-terminal part of the molecule (13). In solution, purified CsgA assembles into amyloids that are indistinguishable from curli fibers, indicating that CsgA is the major subunit in curli (14). Further characterization of the organelle has demonstrated that CsgB acts as a nucleator and CsgG as an outer membrane-located lipoprotein, whereas CsgD is a transcription regulator that belongs to the LuxR/UhpA family. The functions of CsgE and CsgF are still unknown (4).

The role of curli-expressing bacteria in infectious diseases has been demonstrated in different *in vitro* and *in vivo* studies. When injected into animals, curli-expressing bacteria disrupt the coagulation cascade by modulating the contact system and trigger inflammatory reactions by activating inducible nitric oxide synthase (12, 15, 16). Moreover, it has been observed that *E. coli* bacteria expressing curli and a mutant strain secreting soluble CsgA stimulate a human macrophage cell line to produce proinflammatory cytokines (17). In the same study it was also shown that serum samples from convalescent patients with sepsis, but not sera from healthy controls contain antibodies against CsgA, indicating that curli are expressed during the course of disease (17).

Fibrinogen plays an important role in blood clotting, fibrinolysis, cellular and matrix interactions, and wound healing (18). In addition to these functions fibrinogen also acts as a powerful initiator of inflammation, which is in part caused by its interaction with integrins expressed on neutrophils, monocytes, macrophages, and several subsets of lymphocytes (19). Amplification of the inflammatory response may also result from the formation of fibrin by thrombin and/or its subsequent degradation by plasmin. This leads to the generation of proinflammatory fibrinopeptides and fibrin degradation products, respectively. While fibrinopeptides, in particular fibrinopeptide B, are potent neutrophil chemotactants (20–22), fibrin degradation products trigger the release of monocyte/macrophage-derived cytokines (23).
The present study was undertaken to investigate whether curli-expressing bacteria can induce the formation of a fibrin network around the bacterium, leading to the release of fibrinopeptides. In addition, experiments were performed to determine if inhibition of the contact system in vitro and in vivo could revert some of the complications caused by bacterial-induced activation of this system.

EXPERIMENTAL PROCEDURES

Bacterial Strains and Culture Media—The E. coli K12 strain YMel was used in this study (24). A mutant strain YMel-1 was generated by insertional mutagenesis of the CsgA gene in YMel (5). Bacteria were grown on colonization factor antigen agar (25) at 28 °C for 48 h, washed, and applied to a miniaturized plate reader (FD-1; Melamed, Herzelia, Israel) at 2°C. For microscale experiments, bacteria were resuspended in buffer D. Samples were fixed for 1 h before the addition of 100 µl of 105 cpm/ml radioactively labeled protein for 1 h at room temperature. The bacteria were centrifuged at 8000 × g for 15 min, the supernatants were removed, and the remaining radioactivity in the pellet was counted.

Binding Assays—Bacteria resuspended in buffer D, were adjusted to concentrations of 2 × 109, 1 × 109, 2 × 108, and 2 × 107 cells/ml. Binding assays were performed as previously described (15). Briefly, 200 µl of bacterial suspensions were incubated with 25 µl (8 × 105 cpm/ml) radioactively labeled protein for 1 h at room temperature. For the competition assays the radiolabeled protein (25 µl; 8 × 105 cpm/ml) was mixed with various concentrations of the unlabeled competitor (fibrinogen or fibrin) before the addition of 200 µl of bacteria (2 × 106 cfu/ml). Samples were washed with 1 ml of buffer B, followed by centrifugation at 1500 × g for 15 min. The supernatants were removed, and the remaining radioactivity in the pellet was counted.

Bacterially Triggered Generation of Fibrinopeptides—YMel and YMel-1 bacteria were washed and adjusted to 2 × 109 bacteria/ml in buffer C. Equal volumes (0.5 ml) of bacteria and plasma were incubated for 30 min at room temperature in the presence or absence of 50 µg/ml H-o-Pro-Arg-CMK (final concentration). The samples were then washed three times in buffer C and resuspended in 0.25 ml chromogenic substrate S-2238 (4.0 mg/ml in 0.1 m sodium cacodylate buffer, pH 7.4). The bacteria were resuspended in buffer D. Samples were fixed for 1 h at room temperature and then overnight at 4 °C in 2.5% glutaraldehyde in 0.15 m sodium cacodylate, pH 7.4 (cylucodylate buffer). Afterward, they were washed with cylucodylate buffer and postfixed for 1 h at room temperature in 1% osmium tetroxide in cacodylate buffer, dehydrated in a graded series of ethanol, and then embedded in Epon 812 using agar as an intermediate solvent. Specimens were sectioned with a diamond knife into 50-nm thick ultrathin sections on an LKB ultramicrotome. The ultrathin sections were stained with uranyl acetate and lead citrate. Specimens were observed in a Jeol JEM 1230 electron microscope operated at 80 kV accelerating voltage. Images were recorded with a Gatan Multiscan 791 CCD camera.

Chromogenic Substrate Assay—YMel bacteria were washed and adjusted to 2 × 109 bacteria/ml in buffer C. Equal volumes (0.5 ml) of bacteria and plasma were incubated for 30 min at room temperature in the presence or absence of 50 µg/ml H-o-Pro-Arg-CMK (final concentration). The samples were then washed three times in buffer D and after the final centrifugation step the bacteria were resuspended in buffer D. Samples were fixed for 1 h at room temperature and then overnight at 4 °C in 2.5% glutaraldehyde in 0.15 m sodium cacodylate, pH 7.4 (cylucodylate buffer). Afterward, they were washed with cylucodylate buffer and postfixed for 1 h at room temperature in 1% osmium tetroxide in cylucodylate buffer, dehydrated in a graded series of ethanol, and then embedded in Epon 812 using agar as an intermediate solvent. Specimens were sectioned with a diamond knife into 50-nm thick ultrathin sections on an LKB ultramicrotome. The ultrathin sections were stained with uranyl acetate and lead citrate. Specimens were observed in a Jeol JEM 1230 electron microscope operated at 80 kV accelerating voltage. Images were recorded with a Gatan Multiscan 791 CCD camera.

Bacterially Triggered Generation of Fibrinopeptides—YMel and YMel-1 bacteria were washed and adjusted to 2 × 109 bacteria/ml in buffer C. Equal volumes (0.5 ml) of bacteria and citrate-treated plasma were incubated for 30 min at 37 °C on a rotator in the presence or absence of 50 µg/ml H-o-Pro-Arg-CMK (final concentration). The bacteria were then centrifuged at 3000 × g for 2 min, and the supernatants were measured using the Zymatrat PPA (Diagnostic Enzyme, Andésy, France) according to the manufacturer’s instructions.

Determination of Bradykinin—YMel and YMel-1 bacteria were washed and adjusted to 2 × 109 cells/ml in buffer C. Bacteria were then treated as described above (see “Bacterially triggered generation of fibrinopeptides”). After removal of the bacteria by centrifugation, the plasma supernatants were ultrafiltered using an intermediate ultracentrifuge (cut off 3000 Dalton; Millipore, Bedford, MA) and the bradykinin concentrations in the filtrates were determined by the Mark-A kit (Dainippon Pharmaceutical Co., Osaka, Japan) as described (30).

Animal Experiments—Eight-week-old female Balb/c mice (Taconic M&B A/S, Ry, Denmark) were used in the experiments. Animals were housed in a controlled environment at an ambient temperature of 20 °C on a 12 h:12 h light/dark cycle. Food and water were provided ad libitum. The regional ethical committee for animal experimentation approved the animal experiments (permit number M251–01). Subcutaneous air

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Footnotes:
1 The abbreviations used are: LPS, lipopolysaccharide; EM, electron microscopy; WBC, white blood cell; MCF, monocytic chemotactic protein; nPTT, activated partial thromboplastin time; TCT, thrombin clotting time.
pouch was formed as previously described (31) when animals were under anesthesia (Forene®). Briefly, 100 µl of test substances were injected together with 0.9 ml of air into the dorsal region of the mouse. Low molecular weight filtrates were obtained by incubating plasma with bacteria in the absence (LMWF-Inh) or presence (LMWF-Inh/H-11001) of 50 µg/ml H-D-Pro-Phe-Arg-CMK (final concentration) as described above (see “Bacterially triggered generation of fibrinopeptides”). Control substances were bradykinin (2,4 ng/ml), H-D-Pro-Phe-Arg-CMK (50 µg/ml), a mixture of FPA and FPB (0.5 µg/ml of each peptide), LPS (0.5 µg/ml), and vehicle alone (buffer A). After 72 h, the mice were sacrificed and the inflammatory exudates in the air pouches were recovered by lavaging the pouch with 1 ml of sterile buffer A. The lavage fluid was quickly aspirated and centrifuged at 500 × g for 10 min. The supernatants were removed and frozen immediately for later determination of the MCP-1 concentration by the OptEIA™ Mouse MCP-1 Set (BD Biosciences Pharmingen, San Diego, CA) according to manufacturer’s instructions. The pelleted cells were resuspended in sterile buffer A and counted.

RESULTS

Curli-expressing E. coli Bacteria Bind Fibrinogen and Monomeric Fibrin—The conversion of fibrinogen to fibrin is a critical step in infectious diseases that may lead to severe complications such as the formation of microclots, which can deposit in various organs. In order to study the influence of pathogenic bacteria on fibrin network formation, the binding of a curli-expressing E. coli strain (YMel) to fibrinogen and monomeric fibrin was investigated. The isogenic mutant strain YMel-1 that lacks curli was used as a control. Fig. 1A shows that 125I-fibrinogen and 125I-fibrin bound to YMel bacteria equally well. The binding was blocked in the presence of a molar excess of unlabelled fibrinogen or fibrin, respectively (Fig. 1B). By contrast, no binding to YMel-1 was observed. To further characterize this interaction at the molecular level, we sought to map fibrinogen/fibrin binding sites in curli. Thus, seven overlapping synthetic peptides covering the CsgA curli subunit (13) were applied to membranes and probed with radiolabelled fibrinogen or fibrin. As previously reported (13), fibrinogen bound to peptides NNS24 and VDQ26 (Fig. 2B), which are located at the N- and C-terminal region of the CsgA molecule, respectively (Fig. 2A). Fibrin was also found to interact with peptides NNS24 and VDQ26 (Fig. 2C). All other peptides showed little or no affinity for fibrinogen or fibrin. Of note, the binding of 125I-fibrinogen to peptides NNS24 and VDQ26 was inhibited by the addition of unlabelled fibrinogen. The determined half-maximal inhibitory concentrations (IC50) are 2.93 ± 1.63 nmol for the interaction with NNS24 and 2.49 ± 1.38 nmol for the interaction with VDQ26.

To visualize the interaction between fibrinogen and curli-derived peptides negative staining and electron microscopy was employed. Fig. 3 shows that peptides NNS24 and VDQ26,
labeled with colloidal gold, bound avidly to fibrinogen. A
statistical evaluation (some 300 molecules in each case) of
the binding properties of the different peptides revealed
that 22% of the added gold-labeled NNS24 peptide and 39%
of the gold-labeled VDQ26 peptide were associated with
fibrinogen. In contrast, only 7% of the control peptide KFQ22
bound fibrinogen. It appeared that NNS24 interacts preferen-
tially with the central globular D-domains of fibrinogen (77% of
the bound gold-labeled NNS24 was associated with the D
domain), while VDQ26 has more affinity for terminal globular
E-domains (79% of the bound gold-labeled peptide was asso-
ciated with the E domain). In contrast, control peptide KFQ22
had only limited affinity for the globular, but not the extended
domains of fibrinogen (43 and 57% of the total bound gold-
labeled peptide was associated with the D and E domains,
respectively). Taken together the presented data demon-
strate that curli fibers have a high affinity to fibrinogen and
fibrin, which is mediated by two regions in the CsgA molecule
and the D and E globular domains of fibrinogen.

Curliated Bacteria Interfere with Fibrin Polymerization—
Based on the results obtained from the binding studies, we
wondered whether the interaction between fibrinogen and
curliated bacteria could influence the ability of normal human
plasma to clot. Thus, the effect of these bacteria on fibrin
polymerization time was studied by measuring the fibrin
polymerization time (TCT). Fig. 4A shows that addition of
YMel bacteria to plasma provoked a prolongation of the clotting
time, whereas incubation with YMel-1 resulted in values
that were in the same range as the plasma control. The
effect of YMel bacteria on the TCT was dose-dependent (data
not shown). As these results implicate that the interaction
between curli and fibrinogen is at least partially responsible for
this effect, purified fibrinogen (3 mg/ml; the physiological con-
centration in plasma) was incubated with bacteria and then
subjected to the TCT assay. As seen in experiments using
normal plasma, the incubation of YMel bacteria with purified
fibrinogen impaired the clotting times, whereas YMel-1 had no
effect. Thus, the data demonstrate that the interaction between
curli fibers and fibrinogen contributes to the observed clotting
abnormalities.

Curli-induced Clotting Disturbances Are Prevented by Con-
tact System Inhibition—Previous studies have shown that the
assembly and activation of the contact system at the surface
of curli-expressing bacteria triggers not only the release of bra-
dykinin from the bacterium, it also influences normal clotting
(12, 15). Therefore, experiments were performed to address the
question of how contact activation triggers the coagulation
system on bacteria. To identify the role of bacteria-induced
contact activation, an inhibitor of FXII and PK (H-D-Pro-Phe-
Arg-CMK) (32) was used. Fig. 5A shows that when increasing
concentrations of H-D-Pro-Phe-Arg-CMK were added to human
plasma in the absence of bacteria, there was approximately a
19-fold prolongation of the aPTT. The finding that H-D-Pro-
Phe-Arg-CMK had only a marginal effect on the TCT (1.5-
fold), suggests the inhibitor is specific for the intrinsic pathway
of coagulation. To confirm these results, the effect of H-D-Pro-
Phe-Arg-CMK on the amidolytic activity of purified activated
thrombin, FX, and kallikrein was analyzed using chromogenic
substrate assays. The determined half-maximal inhibitory con-
concentrations (IC\textsubscript{50}) are $4.9 \times 10^{-6}$ M, $1.35 \times 10^{-6}$ M, and $1.77 \times 10^{-8}$ M for thrombin, FX, and kallikrein, respectively, demonstrating that the inhibitor preferentially blocks the activity of PK. We next investigated whether contact activation at the bacterial surface leads to an activation of other coagulation factors involved in the initiation of clot formation. Incubation of YMel bacteria with plasma led to an increased FXII/PK activity at the bacterial surface, as indicated by the hydrolysis of a FXII/PK-specific substrate (Fig. 5B). Similar results were obtained when the enzymatic activities of FXI, FX, and thrombin were investigated (Fig. 5B). However, in the presence of H-D-Pro-Phe-Arg-CMK the activities of all factors tested were comparable to control levels. Taken together, the data implicate that activation of coagulation factors at the bacterial surface is triggered by contact activation and that administration of a contact system inhibitor down-regulates this effect.

The interaction of YMel bacteria with the coagulation system was further analyzed by transmission electron microscopy. Fig. 5C depicts thin sections of YMel bacteria preincubated in plasma in the absence or presence of H-D-Pro-Phe-Arg-CMK. The images show that in the absence of the inhibitor, bacteria are surrounded with fibrin fibrils. However, fibrin polymerization was not detected when H-D-Pro-Phe-Arg-CMK was administered. This suggests that contact system driven activation of the coagulation system leads to a conversion of fibrinogen to fibrin at, or in close proximity to the bacterial surface. YMel-1 bacteria had no effect on fibrin fibril formation (data not shown).

As the conversion of fibrinogen to fibrin leads to the generation of FPA and FPB (18), we determined the concentrations of FPA in plasma that was treated with YMel or YMel-1 bacteria in the presence or absence of H-D-Pro-Phe-Arg-CMK. As seen in Fig. 5D, the addition of YMel bacteria to plasma in the absence of H-D-Pro-Phe-Arg-CMK resulted in increased FPA levels (43.2 $\pm$ 9.4 ng/ml). The FPA content was 25-times lower (1.7 $\pm$ 0.4 ng/ml), when experiments were performed in the presence of the inhibitor. The addition of YMel-1 bacteria to plasma resulted in FPA levels that were similar to the control. In summary, the data demonstrate that the interaction between curliated bacteria and plasma triggers the formation of a fibrin network around the bacteria followed by the release of fibrinopeptides. This mechanism is driven by the contact activation at the bacterial surface and administration of a contact system inhibitor blocks the effect.

Bacteria-induced Fibrinopeptides Trigger an Inflammatory Response in Mice—In a series of animal experiments the effects of the low molecular weight fractions generated after curliated bacteria were incubated with plasma, were tested in an airpouch model. Human plasma was incubated with YMel bacteria in the absence or presence of H-D-Pro-Phe-Arg-CMK. Bac-
Fibrinopeptides have been shown to play an important role in infectious diseases. For instance, FPB is a potent chemotactic agent for neutrophils, macrophages, and fibroblasts (20–22), and FPA concentrations in sepsis patients with disseminated intravascular coagulation (DIC) are more elevated than in patients without DIC (33). In severe bacterial infections where DIC is an underlying complication, derangements of the coagulation and fibrinolytic systems constitute a serious clinical problem with high mortality rates (for a review see Ref. 34). DIC is a syndrome characterized by systemic intravascular activation of coagulation, leading to widespread deposition of fibrin in the circulation and various organs. This is followed by secondary bleeding, which may occur because of the consumption of clotting factors and coagulation inhibitors (35). It is generally believed that tissue factor (TF) exposed to the circulation is mainly responsible for the systemic initiation of coagulation in these severe forms of infectious disease, TF exposure to the bloodstream occurs either after damage of the endothelial barrier or following stimulation of monocytes and/or endothelial cells by bacterial products or proinflammatory cytokines (for a review see Ref. 36). However, coagulation disorders during bacterial infection can also be induced locally, as exemplified by the ability of some bacterial species, such as E. coli, Salmonella, Staphylococcus aureus, and Streptococcus pyogenes, to assemble and activate the contact system (also known as the kallikrein/kinin system or intrinsic pathway of coagulation) at their surface (12, 15, 37–39). This mechanism leads to a hypocoagulative state as well as to the generation of proinflammatory kinins. In the case of a massive activation, infected animals suffer from serious complications, including infiltration of red blood cells and fibrin deposition in the lungs (12, 15). Of note, the pulmonary lesions were prevented when the infected animals were treated with the same contact system inhibitor as used in the present study (12).

E. coli is one of the bacterial species most frequently isolated from sepsis patients with DIC (40) and it has been shown that curli expression is significantly increased in sepsis strains (6). These findings suggest that curli are important virulence factors and previous studies showing that curli-expressing bacteria cause severe damage in animal models of sepsis underline this assumption (12, 15–17). The present investigation was therefore undertaken to elucidate the interaction between curli fibers and the coagulation system at the molecular level. Our in vitro results demonstrate that fibrinogen is converted to fibrin at the surface of curli-expressing bacteria and that this leads to the release of fibrinopeptides. The generation of fibrinopeptides is regulated by E. coli-induced contact activation as demonstrated by experiments showing that this mechanism is completely blocked by the application of a contact system inhibitor. As mentioned above, fibrinopeptides are important chemottractants (20, 21) and increased fibrinopeptide levels have been
reported in various clinical disorders including DIC (41). We therefore analyzed the effect of these peptides in an animal model, where mice were injected with fibrinopeptide-containing samples generated from plasma samples treated with curliated bacteria. These experiments demonstrate that the release of fibrinopeptides from fibrinogen bound to curli contributes to the inflammatory response, as seen by the recruitment of WBC to the inflamed site and the induction of the proinflammatory cytokine MCP-1. As observed in the in vitro studies, a downregulation of the inflammatory response resulted when mice were injected with plasma samples treated with curliated bacteria in the presence of a contact system inhibitor. These findings also indicate that the observed symptoms are caused by bacteria-triggered contact activation. Thus, taken together the present study shows that contact activation triggered by bacteria leads to the induction of proinflammatory reactions that can be reverted by administration of a contact system inhibitor.

Life-threatening conditions from bacterial infections are still a major clinical problem and despite improved intensive care treatment the mortality rates remain high. Although a huge effort has been made by many pharmaceutical companies to develop new drugs, only a few clinical trials, for instance the treatment of severe sepsis with activated protein C, have produced promising results (42). The results reported here suggest that the activation of the contact system during bacterial infection contributes to the progression of the disease, and our findings implicate that inhibitors of the contact system could represent potential drug candidates.

Acknowledgments—We thank Monica Heidenholm and Maria Baumgartner for excellent technical assistance, Patrik Nyberg for help with the animal experiments, Rita Wallén and Eric Hallberg, Cell and Organism Biology, Lund University, for support with electron microscopy, and Lars Björck for fruitful discussions.

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J. Biol. Chem. 2003, 278:31884-31890.
doi: 10.1074/jbc.M302522200 originally published online June 12, 2003

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