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# Binding of Fibronectin to *Staphylococcus* Strains

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Fibronectin, a major protein component of plasma and loose connective tissue has previously been shown to bind to several strains of *Staphylococcus aureus*. We examined a large number of strains of different species of *Staphylococcus* with respect to their ability to bind fibronectin. The relative numbers of strains defined as fibronectin-binders among the different species were as follows: *S. aureus* (22 of 23), *S. haemolyticus* (5 of 5), *S. warneri* (8 of 11), *S. hyicus* (5 of 6), *S. hominis* (13 of 17), *S. saprophyticus* (11 of 20), *S. epidermidis* (4 of 7), and *S. simulans* (8 of 10). Only three species showed a predominance of nonbinders over binders: *S. capitis* (4 of 14), *S. xylosus* (0 of 4), and *S. cohnii* (3 of 11). These data indicate that staphylococcal species isolated from soft tissue infections frequently have the ability to bind fibronectin and suggest that the ability to bind to this protein may contribute to the virulence of coagulase-positive and coagulase-negative staphylococci.

Fibronectin is a glycoprotein present in substantial amounts in blood (0.3 mg/ml of plasma) and in the extracellular matrix of loose connective tissues (21). Since the original observation that heat-killed, formalin-treated *Staphylococcus aureus* cells are able to bind fibronectin (12), several papers have appeared describing the interaction of fibronectin with bacteria. *S. epidermidis* and streptococci of serological groups A, C, and G have also been reported to bind fibronectin (26, 27). The biological significance of the binding of bacteria to fibronectin is not clear. Saba et al. (23) have shown that plasma fibronectin may act as an opsonin mediating the phagocytosis of gelatin-coated particles, and it was suggested that the protein plays a similar role in the clearance of *S. aureus*. This hypothesis was seemingly supported by the observation of Proctor et al. (Clin. Res. 27:650A, 1979) that incubation of staphylococci with polymorphonuclear leukocytes resulted in an enhanced chemiluminescence response when the assay was performed in the presence of fibronectin. Verbrugh et al. (27) found the opsonic activity of fibronectin (i.e., the ability to mediate ingestion of bacteria by phagocytes) to be very low. An explanation of this apparent paradox was recently provided by Proctor et al. (19, 20) who showed that fibronectin promoted the attachment of bacteria to neutrophils (which caused the enhanced chemiluminescence response), but ingestion of bacteria did not occur unless classical opsonins (i.e., immunoglobulin G (IgG) or complement or both) were present.

The binding of bacteria to fibronectin may represent a mechanism of tissue adherence. Fibronectin immobilized in blood clots and the connective tissue matrix may serve as a substratum (site) for bacterial attachment and colonization. This hypothesis suggests that fibronectin binding is of advantage to the bacteria at least in some types of infection.

The genus *Staphylococcus* contains species whose pathogenicity ranges from very virulent (*S. aureus*) to rather avirulent. The latter are rarely isolated from human infections (*S. xylosus*). Available data on fibronectin binding refer only to a few strains of *S. aureus* and *S. epidermidis*. This fact prompted our study on the binding of fibronectin to a large collection of strains of staphylococci belonging to different species. The strains examined included fresh clinical isolates and 29 laboratory strains.

## MATERIALS AND METHODS

**Chemicals.** Fibronectin was isolated from human plasma (28) and radiolabeled with [$^{125}$I]iodine by the chloramine T method (7). The specific activity of the labeled protein was $6 \times 10^6$ cpm/μg. Chicken egg albumin, bovine serum albumin, and human IgG were purchased from Sigma Chemical Co., St. Louis, Mo. Percoll was purchased from Pharmacia Fine Chemicals, Uppsala, Sweden, and Trypticase soy broth was purchased from BBL Microbiology Systems, Cockeysville, Md.

**Bacterial strains.** Strains were obtained from a collection of strains at the Department of Bacteriology, College of Veterinary Medicine, Uppsala, Sweden, or were kindly supplied by K. H. Schleifer, Technical University, Munich, Germany; W. E. Kloos, North Carolina State University, Raleigh, N.C.; R. R. Marples, Central Public Health Laboratory, London, England; and M. Kocur, Czechoslovak Collection of Microorganisms, Brno, Czechoslovakia. Clinical isolates, mainly from wound infections, septicemia, and urinary tract infections, were isolated at the Stockholm County Council Central Microbiological Laboratory, Stockholm, Sweden. Strains of *S. aureus* were classified on the basis of the tube coagulase test, using human- and rabbit-citrated plasmas and the test for thermostable DNase. Coagulase-negative strains of staphylococci were identified to the species level on the basis of the following tests: hemolysis, nitrate reduction, aerobic acid production from beta-D-(−)-fructose, D-(+)-xylose, D-(+)-arabinose, D-(−)-ribose, maltose, alpha-lactose, sucrose, D-(+)-trehalose, D-mannitol, and xylitol (10). Susceptibility to novobiocin and lysostaphin, phosphatase activity, and anaerobic growth in the presence of thioglycolate were also tested. Identification of strains belonging to the species *S. hyicus* was performed by the method of Devriese et al. (3).

Bacteria were stored on deep agar. Before use they were subcultured on blood agar plates (37°C) and subsequently grown in Trypticase soy broth at 37°C for 18 h with constant shaking. Bacteria were washed once in phosphate-buffered saline (PBS) (0.13 M NaCl, 0.2% $NaN_3$, 0.02 M sodium phosphate buffer [pH 7.4]) and heated at 88°C for 20 min. The concentration of bacteria was calculated from a previously prepared standard curve relating absorbance at 600 nm to the number of bacteria counted in a Petroff-Hausser chamber. Bacterial suspensions stored at 4°C for several weeks retained fibronectin-binding ability.

**Quantitation of $^{125}$I-labeled fibronectin binding to bacteria.** Binding of $^{125}$I-labeled fibronectin to bacteria was quantified as described previously (22). Bacteria ($10^9$ cells) and $^{125}$I-labeled fibronectin ($7.5 \times 10^4$ cpm, corresponding to $1.3 \times 10^{-2}$ μg of fibronectin) were incubated at 20°C in a total volume of 0.5 ml of PBS containing 0.1% chicken egg albumin for 3.5 h unless otherwise stated. Subsequently, 100 μl of the incubation mixture was carefully added to 0.5 ml of PBS layered on top of 3 ml of Percoll in PBS (density, 1.020 g/ml). The tubes were centrifuged at 1,350 × *g* for 15 min during which bacteria sedimented through the media and formed a pellet at the tip of the tube. Supernatants were aspirated, and radioactivity associated with the pellets was determined in a gamma counter.

**Quantitation of $^{125}$I-labeled IgG binding to bacteria.** The method used essentially followed the procedure described previously (22). Briefly, staphylococci ($2 \times 10^9$ cells) were incubated with $3 \times 10^4$ cpm of $^{125}$I-labeled human IgG (specific activity, $1.2 \times 10^7$ cpm/μg) in 300 μl of incubation buffer (0.5% deoxycholate, 0.1% Nonidet P-40, 0.1% bovine serum albumin, 0.15% NaCl, 0.03% $NaN_3$, 0.01 M sodium phosphate [pH 7.4]). The tubes were incubated for 15 min at 20°C with vigorous shaking. The incubation was stopped by the addition of 1 ml of wash buffer (0.25% deoxycholate, 0.1% Nonidet P-40, 0.15% NaCl, 0.1 M Tris-hydrochloride [pH 7.4]). Bacteria were pelleted by centrifugation at 1,350 × *g* for 15 min. The supernatant was poured off, the pellet was washed twice with the wash buffer, and radioactivity associated with the pellet was quantitated.

In both assays, background values, i.e., radioactivity recovered after centrifugation of incubation mixtures containing no bacteria, were subtracted. The data presented are the average of at least two experiments, each with duplicate samples. All of the incubations were performed in polystyrene tubes (Sarstedt, Princeton, N.J.) preincubated overnight with a 0.1% solution of bovine serum albumin in PBS to minimize nonspecific binding of bacteria and proteins to the walls of the tubes.

## RESULTS

**Development of a standard assay.** Preliminary experiments with strains of different species (data not shown) indicated that the amounts of $^{125}$I-labeled fibronectin bound to freshly prepared, live bacteria did not significantly differ from those bound to heat-treated bacteria. Incubation of bacteria at 88°C for 20 min killed the cells, and this procedure was adopted to avoid possible degradation of bacterial receptors and fibronectin by proteases or lysis of cells by autolytic enzymes secreted by live bacteria.

The binding of $^{125}$I-labeled fibronectin to bacteria was found to be specific, in the sense that addition of an excess of unlabeled fibronectin blocked the binding of the radiolabeled derivative to the staphylococci. Binding of fibronectin to selected strains was a time-dependent process (Fig. 1). The kinetics of binding to three strains of *S. aureus* (two reference strains and one clinical isolate) and two coagulase-negative strains were similar. In all cases, the binding reaction was completed within 2 h. After this incubation period, the amount of $^{125}$I-labeled protein bound to the bacteria reached a plateau. Incubations were routinely carried out for 3.5 h in the subsequent experiments to allow maximal binding of $^{125}$I-labeled fibronectin to the bacteria. The amounts of fibronectin bound to different strains were expressed relative to the amount bound by *S. aureus* Cowan 1. As experimental conditions could vary from one occasion to another (e.g., depending on the specific activity of the added protein), the binding of $^{125}$I-labeled fibronectin to the reference strain Cowan 1 was determined in each experiment. The binding of fibronectin to *S. aureus* Cowan 1 had previously been characterized (22). When cells of this strain were incubated under standard conditions as described above, the amount of radioactivity bound by $2 \times 10^8$ cells, i.e., cells present in a 100-μl sample of the 0.5 ml incubation mixture, was 1,280 ± 212 cpm (mean ± standard error of the mean).

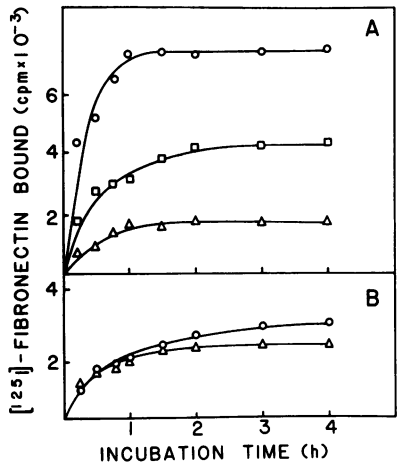


FIG. 1. Time course of fibronectin binding to selected strains of staphylococci. (A) *S. aureus* strains: ○, Newman; △, Cowan 1; and □, S 15475 (clinical isolate). (B) coagulase-negative strains: ○, *S. capitis* LK 499 and △, *S. warneri* 0 366 (clinical isolate). Bacteria were incubated with labeled fibronectin as described in the text. The data refer to the amount of $^{125}$I-labeled fibronectin bound by $2 \times 10^8$ heat-treated bacteria. Background values are subtracted.

**Fibronectin binding by laboratory strains of *S. aureus*.** When strains of coagulase-positive staphylococci were incubated with $^{125}$I-labeled fibronectin, the amount of protein that bound to the bacteria varied considerably among different strains (Table 1). One strain (Smith 5R) bound less than 5%, whereas another (Newman) bound more than 350% of the amount of $^{125}$I-labeled fibronectin bound by the reference strain Cowan 1. Two strains known to produce high amounts of extracellular toxins and enzymes and low amounts of cell-associated protein A (strains Wood 46 and V8) bound low amounts of fibronectin.

Unencapsulated *S. aureus* M bound as much fibronectin as the reference strain, whereas its encapsulated variant was classified as a nonbinder. However, in another pair of strains (*S. aureus* Smith), the encapsulated "diffuse" strain bound almost as much fibronectin as the "compact" variant lacking capsule. Microscopic observations confirmed the presence of capsule in both the M encapsulated and the Smith diffuse strains.

**Comparison of binding of $^{125}$I-labeled fibronectin and $^{125}$I-labeled IgG to different strains of staphylococci.** A correlation between IgG and fibronectin binding to different strains of *S. aureus* was recently suggested (4). In our study, selected strains of *S. aureus* and some coagulase-negative strains were compared with respect to fibronectin binding. The results of these studies (Table 2) show no direct correlation between IgG and fibronectin binding to bacteria; e.g., whereas strain Newman bound almost four times as much fibronectin as the reference strain Cowan 1, the amount of IgG bound to the two strains was essentially the same. Also, *S. aureus* Foggi bound the same high amount of IgG but very low amounts of fibronectin. Among the *S. aureus* strains tested, none were found that bound high amounts of fibronectin but low amounts of IgG (compare reference 4). All coagulase-negative strains examined lacked IgG receptors, although some of them (exemplified in Table 2 by *S. haemolyticus* 211) bound substantial amounts of fibronectin.

**Binding of fibronectin to clinical isolates of staphylococci.** Clinical isolates of ten different

TABLE 1. Binding of fibronectin by *S. aureus* laboratory strains

| *S. aureus* strain | Relative amt of $^{125}$I-labeled fibronectin bound[a] |
|---|---|
| Newman | 384.1 |
| Plommet | 196.6 |
| Copenhagen | 178.2 |
| H5 | 166.3 |
| 524 I | 144.3 |
| 3528 | 131.5 |
| R I | 121.6 |
| 124 | 121.3 |
| 234 | 119.6 |
| 7915 | 118.4 |
| 524 II | 117.6 |
| Walker | 107.9 |
| M unencapsulated | 103.2 |
| Cowan 1 | 100.0 |
| 284 | 80.0 |
| Newman D 2 C | 76.8 |
| U 500 (methicillin resistant) | 76.8 |
| Smith compact | 74.6 |
| M 18 | 65.9 |
| Lakkerty | 65.5 |
| Smith diffuse | 57.7 |
| Pele | 52.2 |
| Wood 46 | 26.4 |
| V8 | 21.2 |
| 89 | 20.5 |
| 269 | 14.4 |
| Foggi | 13.9 |
| M capsulated | 5.8 |
| Smith 5R | 2.3 |

[a] Bacteria were grown at the same conditions, centrifuged, washed, and heat treated. The number of bacteria per incubation was adjusted to the same level. The amount of $^{125}$I-labeled fibronectin bound to *S. aureus* Cowan 1 was set as 100%. As the extent of ligand varied from one experimental occasion to another, data are presented as relative binding.

TABLE 2. Comparison of binding of fibronectin and human IgG to selected staphylococcal strains (laboratory strains and fresh clinical isolates)[a]

| Strain | Relative %[a] of binding of | |
|---|---|---|
| | Fibronectin | Human IgG |
| S. aureus | | |
| Cowan 1 | 100 | 100 |
| Newman | 384.1 | 98.1 |
| Plommet | 196.6 | 102.7 |
| Copenhagen | 178.2 | 93.6 |
| H 5 | 166.6 | 81.3 |
| M unencapsulated | 103.2 | 97.4 |
| V8 | 21.2 | 42.3 |
| 269 | 14.4 | 9.4 |
| Foggi | 13.9 | 94.3 |
| M encapsulated | 5.8 | 90.0 |
| S. haemolyticus 211 | 114.8 | 2.7 |
| S. hominis 23 | 22.9 | 1.2 |
| S. saprophyticus 223 | 2.3 | 1.9 |

[a] Binding of $^{125}$I-labeled fibronectin and human IgG was compared for selected strains of *S. aureus* and coagulase-negative staphylococci. The amount of each protein bound is expressed as a percentage of the amount of protein bound to *S. aureus* Cowan 1.

coagulase-negative species and of *S. aureus* were examined for fibronectin binding (Fig. 2). The numbers of available strains were limited for some species which are rarely isolated from clinical specimens. The extent of fibronectin binding varied greatly among the individual strains of different species. The ability of bacteria to bind fibronectin was not a property found for all strains of specific species although some species, e.g., *S. aureus*, *S. haemolyticus*, and *S. warneri*, had a high proportion of good fibronectin binders. However, these species also contained strains that were classified as nonbinders. Most of the strains of *S. capitis*, *S. xylosus* and *S. cohnii* bound little or no fibronectin, and strains belonging to other species usually bound intermediate or low amounts of fibronectin.

## DISCUSSION

In the present investigation we examined the ability of strains belonging to different species of the genus *Staphylococcus* to bind fibronectin. Different strains bound variable amounts of fibronectin. Among the 10 species examined, there was no single species in which strains were uniformly positive or negative in terms of binding. Therefore the ability of a given strain to bind fibronectin is not a useful property for taxonomic classification. However, the screening of strains isolated from patients with wound infections, septicemia, and urinary tract infections clearly suggests that fibronectin binding is more common among strains of certain species.

In a study of coagulase-negative staphylococci isolated from the urinary tract, wound, and other infections, Nord et al. (16) and Dornbusch et al. (5) reported *S. epidermidis* to be the most frequently isolated species, followed by *S. saprophyticus* (urinary tract), *S. haemolyticus*, *S. hominis*, *S. cohnii*, and *S. warneri*. Similar results were reported in recent studies (6, 13, 15, 16, 25). Two of the species, namely *S. haemolyticus* and *S. warneri* were found to include strains that bound substantial amounts of fibronectin. The same is also true of strains of *S. hyicus*, which are known to produce infections in animals (2, 3, 17). On the other hand, strains of *S. epidermidis* bound only intermediate to low amounts, and strains of *S. cohnii* bound little or no fibronectin. It appears likely that the ability to bind fibronectin does not differentiate species of the genus *Staphylococcus* into two categories, i.e., virulent binders and avirulent nonbinders, although

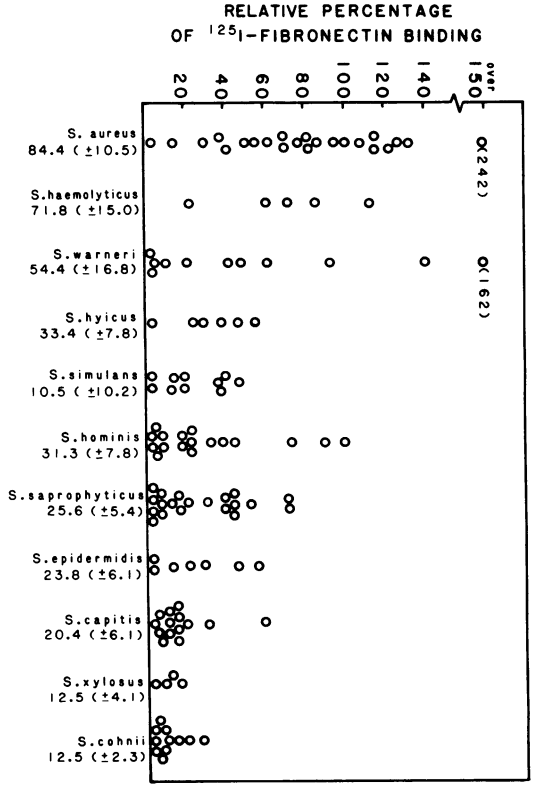


FIG. 2. Binding of fibronectin to staphylococcal strains of 11 different species. Data are presented as percentages of $^{125}$I-labeled fibronectin bound relative to *S. aureus* Cowan 1. Each circle indicates one strain. Mean values of the binding capacity of strains of each group are shown as well as the standard error (in parentheses).

this should be confirmed in experimental infection models in which the virulence of different strains can be compared.

In a recent report, Myhre and Kuusela (14) classified all examined strains of *S. epidermidis* and *S. saphrophyticus* as fibronectin nonbinders, whereas we found fibronectin-binding strains belonging to these species in our collection. It should, in this context, be pointed out that the capacity of fibronectin binding depends on the conditions used for culturing bacteria (see below) and that the fibronectin binding capacity varies greatly from one strain to another within the same species.

It is presently not known whether the amounts of fibronectin bound to different strains reflect the number of receptors present on the surface of the bacteria. The availability of the receptors for the large fibronectin molecule may differ from one strain to another. The presence of capsule may be one of the factors interfering with the access of fibronectin to the underlying receptors (8). Along this line, we found that encapsulated *S. aureus* M did not bind $^{125}$I-labeled fibronectin, whereas the unencapsulated variant bound substantial amounts of the protein. Similar results have previously been reported by Verbrugh et al. (27). In another pair of strains (*S. aureus* Smith) the difference was not so striking since the amount of $^{125}$I-labeled fibronectin bound to the encapsulated strain was 77% of that bound to the strain lacking capsule. It is possible that the masking effect of the capsule may vary from one strain to another depending on the thickness of the capsular material and its location relative to fibronectin receptors. The amount of fibronectin bound by staphylococci may be influenced by factors such as phase of growth of bacteria at harvest as well as type and pH of the media (19). The influence of these factors was not tested in our study, and bacteria were always harvested at late logarithmic phase of growth in Trypticase soy broth.

Doran and Raynor (4) suggested that fibronectin and IgG compete for the same receptor, namely protein A. This finding was recently disputed by Verbrugh et al. (27). The results of our study suggest that no correlation exists between the ability of various strains to bind fibronectin and IgG. Binding of fibronectin occurred to many strains of coagulase-negative staphylococci which usually are considered to be lacking IgG receptors, although it has been claimed that *S. hyicus* strains possess IgG receptors (i.e., protein A-like structures) (16). Our data indicate that strains of *S. hyicus* did not bind more fibronectin than did strains of other coagulase-negative species. The suggested identity of fibronectin receptors and protein A appears to be ruled out by our findings of strains that bound high amounts of IgG and little or no fibronectin and vice versa.

Strains of *S. intermedius*, *S. sciuri* (9, 11, 18), and the more recently identified *S. caseolyticus* (24) were not included in this study, nor were strains of *Micrococci*. Strains of *Micrococcus luteus*, a species considered to be nonvirulent were earlier reported to bind fibronectin (Proctor et al., Clin. Res. 27:650A).

Binding of bacteria to fibronectin exposed on the surface of epithelial cells may be one of the mechanisms of adherence. Other mechanisms, involving interactions based on the charge or the hydrophobicity of the bacteria or both as well as additional specific interactions between bacterial cell wall components (e.g., teichoic acid) (1) and appropriate receptors in the host tissue may also be involved in bacterial tissue adherence.

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