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Physiopathology of Foreign Body Infections

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Abstract—*Foreign body infections share several properties: a high susceptibility to microorganisms which are usually of low pathogenicity (such as* S. epidermidis*) and with only some exceptions failure to respond to antimicrobial therapy without surgery. The common denominator for the three elements that play a role in the physiopathology of such infections (bacteria, neutrophils and different materials) is host protein deposited over the surface of the foreign body. Staphylococci and neutrophils selectively adhere to fibronectin and to a variable degree to laminin and fibrinogen. These proteins potentially modulate phagocyte function. With the progress of biotechnology and the increasing numbers of implantable prostheses, it will become critical to increase our understanding on how to prevent and treat foreign body infections.*

I. INTRODUCTION

FOREIGN BODIES are widely used in modern medicine. Examples include permanent devices such as cerebrospinal fluid shunts, intra-ocular lenses, pacemakers' wires and electrodes, prosthetic cardiac valves, prosthetic joints or removable invasive devices such as intravenous catheters.

With the development of biotechnology and novel medical approaches it is quite certain that the number of possible uses of foreign bodies in medicine will continue to increase. Independently of the nature of the foreign body, all these devices share common infectious diseases problems that can be summarized as follows (see also Table 1):

(a) A high *susceptibility* to infection; indeed small numbers of microorganisms, frequently of low pathogenicity (such as *S. epidermidis*), which usually would be eliminated by host's defenses, are capable of inducing a foreign body infection.

(b) A characteristic *microflora*: according to the sites of implantation and the nature of the material, there is a characteristic pattern of microorganisms. In most published studies dealing with various types of foreign body infection, there is a predominance of *S. epidermidis* and *S. aureus*.

(c) The *persistence* of the infection despite intensive and prolonged antibiotic therapy.

Several recent reports indicate that eradication of infection might be possible with antibiotics alone under specific conditions. This includes infections with highly susceptible microorganisms or particular foreign body infections such as peritoneal dialysis catheters or long-term intravenously implanted catheters (such as Hickman catheters). This might be explained, at least partially, by the high concentration of antibiotics which may be injected locally in these two types of infection. However, it is clear that for most cases the best way to eradicate the infection is to take out the foreign body.

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II. THE DEVELOPMENT OF AN ANIMAL MODEL TO STUDY THE PHYSIOPATHOLOGY OF FOREIGN BODY INFECTIONS

Over the last decade we have developed an animal model of foreign body infection [1]. Teflon tissue cages are implanted subcutaneously, and allow sampling of microorganisms, cells or fluid during infection. The foreign body infection mimics all the characteristics of the clinical situation: (a) a low inoculum of poorly virulent *S. aureus* always produces an infection; (b) the infection is almost impossible to cure with antibiotic therapy; (c) the number of local neutrophils is proportional and follows in a kinetic manner the local number of bacteria. In addition, this model allows the introduction into the cages of lamellae which may be sampled for microbiological quantification, characterization of the proteins deposed on their surface, and microscopical examination. Many of the studies described below were performed with the help of this foreign body model.

III. POSSIBLE PATHOGENIC FACTORS INVOLVED IN FOREIGN BODY INFECTION (Fig. 1)

It is clear that the infection occurs over a *surface* and the invading microorganisms are able to survive despite the local influx of large numbers of *polymorphonuclear leukocytes*. It is thus important to

Table 1. *Characteristics of foreign body infection*

1. Low inoculum leads always to infection
2. Predominant microorganisms: *S. epidermidis* > *S. aureus* > > gram-negative rods
3. Prophylactic therapy efficacious
4. Antimicrobial therapy often unsuccessful: cure achieved by taking out the foreign body

understand the biology of surfaces in particular: (a) the properties of *adherent neutrophils*; (b) the proteins of *adherent bacteria* and (c) the surface properties of the material and whether interaction with *proteins* deposited on the surface of the foreign body alters these properties. Thus we will try to analyze each one of these components separately.

a. The role of neutrophils in the physiopathology of foreign body infections

a.1. *The susceptibility of the foreign body to infection. The high susceptibility* of the foreign body to *S. aureus* infections led us to speculate that there might be a local phagocytic defect that resembles chronic granulomatous disease. This genetic defect is characterized by patients whose neutrophils are unable to mount a respiratory burst and thus unable to generate oxygen-dependent microbicidal components necessary to kill catalase-positive microorganisms, in particular *S. aureus* [2]. We collected neutrophils from the cages before infection and found that indeed the neutrophils were defective at various levels:

i. first, stimulation of these cells triggered only a weak respiratory burst and the generation of low amounts of superoxide anions;

ii. second, tissue cage neutrophils had lower content of bactericidal enzymes present in primary or secondary granules.

It was thus easy to understand the very poor bactericidal activity of tissue cage neutrophils. In comparison neutrophils collected from the peritoneal space or blood from the same animal could kill *S. aureus* in a much more efficient manner.

What are the mechanisms that create such deficient neutrophils? An answer to this question was provided by incubation of fresh neutrophils with the foreign body: this maneuver allowed us to show that this interaction activates neutrophils (adhesion, degranulation) and leads to the formation of deficient cells. Thus the presence of the foreign body activates the neutrophil by a mechanism similar to frustrated phagocytosis.

Finally, the fact that deficient neutrophils play a pathogenic role could be directly demonstrated by local transfusion of fresh neutrophils: this maneuver prevented the development of subsequent infection, despite local injection of bacteria. It is concluded that this local granulocyte deficiency probably explains the high susceptibility of the foreign body to infection.

a.2. *The persistence of infection.* In foreign body infections there is an apparent paradox because once the infectious process starts, there is an arrival of a large number of competent neutrophils but the infection process persists. We have unraveled at least two mechanisms that explain the persistence of the infection:

— the first is the observation that there is a local consumption of opsonins. Opsonins (complement, immunoglobulins) are necessary to coat bacteria and render them recognizable by specific receptors present in the surface of neutrophils. In the purulent exudate of the foreign body infection, neutrophils release large amounts of proteolytic enzymes such as elastase that degrade opsonins and thus create a privileged sanctuarium for the microorganisms [3];

— second, present work in our laboratory has allowed the development of a methodology for the assessment of *surface* phagocytosis. Such a quantification has allowed us to demonstrate that the bacterial killing by neutrophils over surfaces is very dependent on the nature of the protein monolayer covering the surface. Indeed neutrophils possess receptors on their surface to

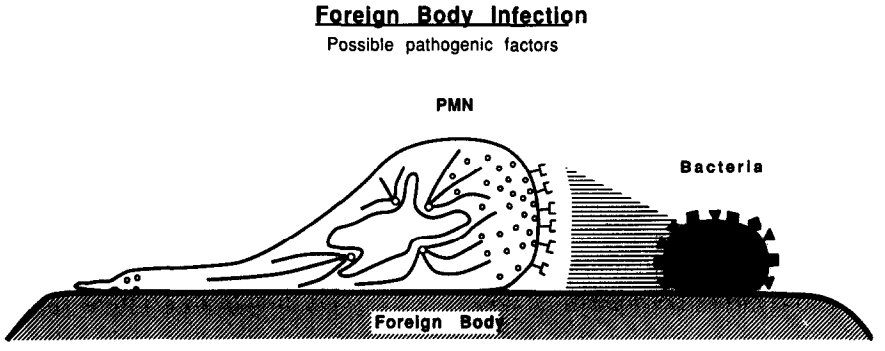

Fig. 1. *The three elements involved in the physiopathology of foreign body infections: bacteria, neutrophils (PMN) and surfaces. Their common denominator is the proteins that coat the foreign surfaces. Various proteins such as fibronectin allow cell and bacterial adherence and modulate the functions of neutrophils.*

a variety of extracellular matrix proteins such as fibronectin or laminin. These receptors may modulate cellular behavior. Preliminary experiments in our laboratory indicate that in fibronectin-coated surfaces the bactericidal activity of neutrophils is much more efficient than in albumin-coated surfaces. Thus the spatial heterogeneity of deposited proteins over the surface of the foreign body might explain local surviving bacteria in the presence of large numbers of neutrophils, i.e. bacteria might survive in regions where the proteins present in the extracellular matrix lead to a mass efficient phagocytosis.

b. Understanding the properties of a foreign surface that allows the establishment and persistance of microbial colonization

Clearly the nature of the material must allow deposition of different proteins on its surface and must contain irregularities where microorganisms may hide or be protected from phagocytes.

In order to approach the problem of understanding surface we have recently started to employ a novel technique, tunnel microscopy, in collaboration with Prof. Descouts, from the Physics School in Geneva. This high resolution microscopy has several advantages compared to previous techniques, including the fact that no fixation is required and that this method allows the observation of structures as small as single molecules. In preliminary experiments we have been able to characterize irregularities over the surface of the foreign bodies. Some of the materials tested allow deposition of fibronectin in a more permissive 'adherent state' for staphylococci than others. It remains to be observed by tunnel microscopy at a single molecular level whether different behavior of different materials might be explained by the manner the protein is deposited over the foreign surface. It will be very interesting in the future to test whether different foreign bodies may be coated with different extracellular matrix proteins and whether this will affect the survival of adherent microorganisms.

c. Characteristics of bacteria that allow adherence to the foreign body: the important role of fibronectin

Several reports have indicated that staphlococci possess in their surfaces 'adhesins' that allow adherence to several extracellular matrix proteins [3–7]. Among these, three have received over the last few years considerable attention; fibronectin, fibrinogen and lamilin. We have been able recently to demonstrate that fibronectin is one of the most important adhesive proteins for the initial adherence of staphylocci. Nude foreign body surfaces in the presence of sera or albumin promote bacterial adherence only very weakly. However, once the foreign body has been implanted, it very rapidly promotes adherence. The adherent promoting factor is of protein origin because it is trypsin sensitive. We investigated further to understand whether this could be due to local deposition of fibronectin.

Immunofluorescence with anti-fibronectin antibodies revealed that large amounts of this protein are deposited over the surface of the foreign body. In order to search whether fibronectin might be important for promotion of bacterial adherence to foreign bodies we used antifibronectin antibodies. In the presence of these antibodies adherence could be markedly decreased and various controls demonstrated that this process was selective. Finally, immunofluorescence staining both of bacteria and fibronectin allowed to demonstrate that the bacteria co-localized and were deposited over the fibrillar distribution of fibronectin.

IV. CLINICAL IMPLICATIONS; STUDIES ON INTRAVENOUS CATHETERS

a. Intravenous device infection by bacteremic staphylocci

A good way to search for a potential pathogenic role of proteins such as fibronectin, fibrinogen and lamilin deposited over the surface of the foreign body is to study the presence of receptors for such proteins in clinical staphylococcal isolates. We collected [7] bacteremic staphylococci secondary to an intravenous device infection. *S. aureus* isolates exhibited high adherence to fibronectin- or to fibrinogen-coated surfaces and a much weaker adherence to lamilin coated surfaces. The coagulase-negative isolates exhibited also a high adherence to fibronectin. However, only a small minority of *S. epidermidis* could adhere to fibrinogen and none to lamilin-coated surfaces. Thus mostly fibronectin, and maybe for some strains fibrinogen and lamilin, appear to play an important role in the initial adherence to foreign bodies of invading staphylococci.

b. Analysis of adherence proteins present over the surface of intravenous device catheter

It clearly becomes important to measure the concentration and the biological adherent promoting properties of fibronectin, fibrinogen or lamilin. P. Vaudaux in our laboratory has developed a variety of biological and immunological assays to assess the presence of these proteins over the surface of catheters. These studies on catheters *in vitro* allow us to demonstrate, similarly to the animal models, that uninserted catheters promote adherence very poorly, whereas they become very 'sticky' for the strains tested after insertion. The developed radioimmunoassays will allow now to quantify the presence of fibronectin and fibrinogen over the catheters and to investigate whether these proteins

might play a pathogenic role in this important clinical situation [8, 9].

V. CONCLUSIONS

Table 1 summarizes the major possible pathogenic factors of the three protagonists that participate in the establishment of the foreign body infection: neutrophils, bacteria and surfaces. The studies described here allow us to conclude that if one wants to understand the physiopathology of such infections it is important to study the biology of surfaces. Indeed due to the presence of specific surface receptors both phagocytic cells and microorganisms behave differently whether they are in suspension or over surfaces. The structure of the foreign body might lead to different functional behavior both of bacteria and cells, at least in part, due to different deposed proteins. Thus, the common denominator of the three elements involved in the start and persistence of the infection is the different molecules deposed over the surface of the foreign body.

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REFERENCES

1. Zimmerli W, Waldvogel FA, Vaudaux P, Nydegger UE. Pathogenesis of foreign body infection: description and characteristics of an animal model. *J Infect Dis* 1982, **146**, 487–497.
2. Zimmerli W, Lew PD, Waldvogel FA. Pathogenesis of foreign body infection. Evidence for a local granulocyte defect. *J Clin Invest* 1984, **73**, 1191–1200.
3. Lew PD, Vaudaux P, Zubler R *et al.* Decreased-heat labile opsonic activity and complement levels associated with the evidence of C3 breakdown products in infected pleural effusions. *J Clin Invest* 1979, **63**, 326–334.
4. Vaudaux P, Suzuki R, Waldvogel FA *et al.* Foreign body infection: role of fibronectin as a ligand for the adherence of *Staphylococcus aureus*. *J Infect Dis* 1984, **150**, 546–553.
5. Falcieri E, Vaudaux P, Huggler E, Lew PD, Waldvogel FA. Role of bacterial exopolymers and host factors on adherence and phagocytosis of *Staphylococcus aureus* in foreign body infection. *J Infect Dis* 1987, **155**, 524–531.
6. Vaudaux P, Lew D, Waldvogel FA. Host-dependent pathogenic factors in foreign body infection. A comparison between *Staphylococcus epidermidis* and *S. aureus*. *Zbl Bakt* 1987, Suppl 16, 183–193.
7. Herrmann M, Vaudaux PE, Pittet D *et al.* Fibronectin, fibrinogen and laminin act as mediators of adherence of clinical staphylococcal isolates to foreign material. *J Infect Dis* 1988, **158**, 693–701.
8. Vaudaux PE, Huggler E, Lerch PG *et al.* Role of human immunoglobulin G in serum-mediated inhibition of *Staphylococcus aureus* adherence to surface-bound fibronectin. *J Invest Surg* 1989, in press.
9. Vaudaux P, Pittet D, Haeberli A *et al.* Host factors selectively increase staphylococcal adherence on inserted catheters: a role for fibronectin and fibrinogen/fibrin. *J Infect Dis* 1989, in press.