Proteus mirabilis biofilms and catheter-associated urinary tract infections

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Proteus mirabilis inhabits the environment and causes a number of infections including those of the skin, respiratory tract, wounds and urinary tract. These organisms express virulence factors associated with adhesion, motility, immunovarion, nutrient acquisition, host damage, as well as biofilm formation. P. mirabilis produces biofilms in diverse habitats with those formed in the human host playing a key role in indwelling device infections. The most studied P. mirabilis biofilms are those formed when the organism is grown in urine, resulting in unique features including the presence of swimmer cells and struvite and hydroxyapatite crystals upon growth in urine. Factors relevant to P. mirabilis biofilm formation include adhesion factors, proteins involved in LPS production, transporters, transcription factors, two component systems, communication factors and enzymes. P. mirabilis biofilm research will lead to a better understanding of the disease process and will subsequently lead to the development of new prevention, and treatment options.

Introduction

Proteus, Gram-negative bacilli that thrive in soil, water and the intestinal tracts of mammals, are capable of swarming or swimming in a coordinated manner, on solid surfaces. Several species of Proteus bacteria are known to colonize and infect the human host but the one most frequently linked with causing human disease is Proteus mirabilis. These bacteria are the causative agents of a variety of opportunistic nosocomial infections including those of the respiratory tract, eye, ear, nose, skin, burns, throat and wounds.1,2 P. mirabilis are more commonly associated with urinary tract infections (UTIs) in those individuals with structural or functional abnormalities, especially ascending infections in patients undergoing urinary catheterization.3,4 These organisms are capable of colonizing and causing disease due to their arsenal of virulence factors including fimbriae (mannose resistant/Proteus-like fimbriae (MR/P), mannose resistant/Klebsiella-like fimbriae (MR/K), uroepithelial cell adhesion/nonagglutinating fimbriae (UCA/NAF) and P. mirabilis fimbriae (PMF)), flagellar motility, immunovarion factors (degradative enzymes such as proteases, ureases, hemolysins), struvite and hydroxyapatite crystal formation, iron acquisition protein homologs and the ability to form biofilms.5

Proteus mirabilis in vitro Biofilms

Proteus has been shown to produce biofilms in diverse environments from aquatic conditions to indwelling devices [vascular access ports/hemasites, scleral buckles, ureteral stents, urethral catheters and trachoesophageal voice prostheses (Provox2)].7,11 P. mirabilis can produce biofilms on nonliving surfaces including polystyrene, glass, latex and silicone and on biological surfaces. These organisms have been found in both pure and polymicrobial biofilms.10 The structure of P. mirabilis biofilms grown in laboratory broth (Luria-Bertani) and urine (artificial and pooled human urine) has been analyzed using confocal scanning laser microscopy and 3-D imaging.4,15 Differences observed in the basic structure of these biofilms were media-dependent. Proteus mirabilis biofilms that developed in Luria-Bertani broth and pooled human urine appeared as typical mushroom-like structures with nutrient channels forming 21 to 24 h post-inoculation.14,15 However, P. mirabilis biofilms formed in artificial urine appeared as flat structures without channels after 24 h post-inoculation with swimmer cells observed protruding out of these biofilms.14 Jones et al. suggest that the formation of swimmer cells could represent a method by which P. mirabilis can disperse from the mature biofilm to seed new surfaces.14 In addition, when grown in artificial and pooled human urine, struvite crystals have been observed in biofilms produced by these organisms.14 Flagellar motility also has a role in surface perception and, as a result, biofilm formation. A functioning flagellum is critical

Abbreviations: CAUTIs, catheter-associated UTIs; CPSs, capsule polysaccharides; EDTA, tetra sodium ethylenediaminetetraacetic acid; EPS, extracellular polysaccharide; IgA, immunoglobulin A; LPS, lipopolysaccharide; MR/K, mannose resistant/Klebsiella-like fimbriae; MR/P, mannose resistant/Proteus-like fimbriae; P. mirabilis, Proteus mirabilis; PMF, P. mirabilis fimbriae; RsmA, repressor of secondary metabolites; UTIs, urinary tract infections; UCA/NAF, uroepithelial cell adhesion/nonagglutinating fimbriae
Also, the majority of patients with recurrent due to the blockage of catheters caused by biofilm encrustation. Especially problematic during catheter-associated UTIs (CAUTIs) colonization of replacement catheters with these organisms.19 Encrustation (62%) developed bladder stones, which led to the occurrence of all urinary tract stones. 18 Crystalline biofilms are especially problematic during the pathogenesis process. These structures assist in the establishment of colonization and crystallization by Proteus to catheter surfaces, the rough surfaces on the rims of the catheter eyeholes, as observed on Foley catheters, are prone to colonization and crystallization by P. mirabilis due to their extreme irregularity.23 These irregularities lead to blockages that occur generally at the eyelet or in the balloon region of the lumen. Scanning electron microscopy revealed that within 2 h post-inoculation, P. mirabilis cells were trapped within the crevices in the jagged eyelet surfaces.23 At 4 h, microcolonies had established in the surface depressions, and by 6 h, with the increase in urinary pH, crystals had started to develop in the biofilm.22 Therefore, impeding the rise of urinary pH and subsequent crystallization could be critical in preventing biofilm formation on indwelling devices inserted in the urinary tracts of patients infected with P. mirabilis.

### Table 1. Virulence factors of Proteus mirabilis that have a potential role in biofilm formation

| Virulence Factors | Proposed Role | Reference |
|-------------------|---------------|-----------|
| Mannose-resistant Proteus-like (MR/P) fimbriae | Adhesion, mutants defective in biofilm formation | 25 |
| UDP-glucuronic acid decarboxylase PmrI | LPS modification, mutants defective in biofilm formation | 27 |
| Inner-core LPS biosynthetic WaaE | Inner-core LPS biosynthetic protein, mutants decrease in biofilm formation | 37 |
| Pst transporter | High-affinity phosphate transporter, mutants defective in biofilm formation | 15 |
| RsbA | Membrane sensor of a two component system that enhance EPS* production in the presence of certain fats | 25 |
| Cis-2-decenolic acid | Homolog of Pseudomonas cell communication factor, role in dispersal and inhibit biofilm development | 30 |
| RsmA | RNA binding protein, possible regulation of biofilm formation | 63 |
| Urease | Nickel metalloenzyme, Local increase in pH to facilitate crystal formation, Mutants attenuated in CBA mouse model | 36 |
| Capsule | Aggregate precipitating components into stones | 39 |

*EPS, Extracellular polysaccharide.

for sensing and/or responding to the surface signal and flagellar mutants (including various flhD, flfGFLMPQ, flhA and flgKL genes) involved in surface perception that may cause defects in biofilm formation as with other bacterial species. In addition, the status of flagellar motors acts as a sensor for P. mirabilis to signal to the cell to undergo swarmer cell differentiation at the appropriate time, where inhibition of rotation promotes differentiation.16

### Proteus mirabilis in vivo Biofilms: Pathogenesis from Colonization to Mature Biofilm

Once P. mirabilis comes in contact with either a nonliving or host surface, the process of colonization begins. After the initial colonization, P. mirabilis form distinctive biofilm structures during the pathogenesis process. These structures assist in the persistence of P. mirabilis in the host by protecting these organisms from the host immune system and treatment by antibiotics.17 One of the more frequently studied biofilms produced by P. mirabilis are those biofilms that form within the urinary tract, in particular those initiated on urinary catheter surfaces. Bacterially derived stones, a characteristic of the biofilms developed during P. mirabilis-associated UTIs, account for up to 30% of all urinary tract stones.18 Crystalline biofilms are especially problematic during catheter-associated UTIs (CAUTIs) due to the blockage of catheters caused by biofilm encrustation. Also, the majority of patients with recurrent P. mirabilis catheter encrustation (62%) developed bladder stones, which led to the colonization of replacement catheters with these organisms.19

The crystalline biofilms associated with these catheters in vivo show the presence of two main types of crystals, struvite and apatite. Long rectangular crystals made of magnesium ammonium phosphate are termed struvite while microcrystalline structures made of a hydroxylated calcium phosphate (where the phosphate is often replaced by carbonate) are termed apatite.20 In addition, a conditioning layer of crystal formation rich in calcium and phosphate is found on catheters, even those impregnated with antimicrobial agents such as silver.20,21 Bacteria are in intimate association with this crystal layer, protected from the antimicrobial effects of impregnated compounds.20,21

Both physical and chemical factors play a role in the initiation and development of the crystalline biofilms observed during P. mirabilis colonization. The pH of urine can be essential for bacteria attachment to polymer surfaces as macroscopic aggregates of cells and crystals of calcium and magnesium phosphate form in alkaline urine, settle on the polymer surface and initiate crystalline biofilm development.22 Therefore, impeding the rise of urinary pH and subsequent crystallization could be critical in preventing biofilm formation on indwelling devices inserted in the urinary tracts of patients infected with P. mirabilis.

Besides the importance of urinary pH for attachment of Proteus to catheter surfaces, the rough surfaces on the rims of the catheter eyeholes, as observed on Foley catheters, are prone to colonization and crystallization by P. mirabilis due to their extreme irregularity.23 These irregularities lead to blockages that occur generally at the eyelet or in the balloon region of the lumen. Scanning electron microscopy revealed that within 2 h post-inoculation, P. mirabilis cells were trapped within the crevices in the jagged eyelet surfaces.23 At 4 h, microcolonies had established in the surface depressions, and by 6 h, with the increase in urinary pH, crystals had started to develop in the biofilm.22 After 20 h, an extensive mature crystalline biofilm was formed and was dispersed down the lumen of the catheter.23

Research has potentially linked a number of virulence factors to P. mirabilis biofilm formation (Table 1) and a summary of the events that may occur during biofilm formation are found in Figure 1. These factors include adhesion factors, proteins involved in LPS production, transporters, transcription factors, two component systems, cell communication factors and enzymes. MR/P fimbriae, whose expression undergoes phase variation, have been shown to play a role in colonization of these organisms in the mouse model.24 These fimbriae have been observed to be produced by the majority of cells in the CBA mouse model of ascending UTI.25 Mutants that constitutively expressed MR/P fimbriae (MR/P ON), produced significantly more and...
The role of swarming during *P. mirabilis* biofilm formation is still not completely understood. As mentioned previously, research has shown that swarming is repressed as extracellular matrix production is increased. Jones et al. demonstrated that mutants deficient in swarming and swimming were capable of forming biofilms and blocked catheters more quickly than the wild-type strain in the catheterized bladder model. It is conceivable that swarming must be repressed in order for these organisms to remain attached to surfaces to initiate formation of the biofilm.

Two major factors known to be involved in urinary crystal formation and hence, crystalline biofilm formation by *P. mirabilis* are bacterial urease and capsule polysaccharides or CPSs. Urease, a multimeric nickel metalloenzyme, contributes to the development of urinary stones due to urease-mediated hydrolysis of urea to ammonia and carbon dioxide that alkalinizes the local environment. This increase in urinary pH causes the formation of struvite crystal formation. To perpetuate the infection, these organisms must detach or disperse from the initial site of infection to seed adjacent sites of the urinary tract.
strain after two days post-inoculation and caused no urolithiasis during infection.36

Besides bacterial urease, capsules are thought to hasten struvite crystal growth33,37 observed during UTIs and CAUTIs associated with P. mirabilis by aggregating precipitated urinary components into crystalline stones.38 Proteus CPSs tend to be acidic due to struvite formation than other CPS types, as examined by particle 49565 added to artificial urine at a pH of 7.5 to 8.0 induced more

P. mirabilis a water control (blocked ranging from 18 to 27 h). 45,46 In a study P. mirabilis reduced of crystalline biofilms from san impregnated silicone and latex-based catheters were free or extract. 50 Several groups have examined the effect P. mirabilis by Chew et al. ureteral stents eluted with triclosan had reduced

P. mirabilis Currently, much of the research on P. mirabilis biofilms focuses on the formation of and the potential methods of eradication of these biofilms on various indwelling device surface materials (silicone, plastics). Of the 18 currently available urethral catheters tested, all were susceptible to P. mirabilis biofilm encrustation and blockage.40 Encrustation occurred in indwelling urethral catheters by a clinical strain of P. mirabilis ranging from 17.7 h (silver-coated latex) to 47 h (all silicone) when studied in the laboratory model of the catheterized bladder using pooled human urine.41 Swarming organisms, such as P. mirabilis, have been shown experimentally to be better able to migrate over Foley catheter surfaces, in particular those with hydrogel coatings.32 In addition, P. mirabilis is capable to assisting nonmotile bacteria, such as Staphylococcus aureus, to be transported over catheters.32

Based on the study by Chang et al. adherence and biofilm formation of P. mirabilis to surfaces may be facilitated by the presence of pre-existing biofilms as biofilm formation on gentamicin-containing polymethyl methacrylate increases upon preincubation with autoclaved killed or live Staphylococcus epidermidis biofilms.43

A number of compounds have been tested for their effectiveness against P. mirabilis crystalline biofilms on catheter materials including triclosan,44-46 nalidixic acid,47 tetra sodium EDTA (EDTA),48 urease inhibitors,49 quorum sensing inhibitors,49 and Ibicella lutea extract.50 Several groups have examined the effect of the commonly used antimicrobial compound triclosan on P. mirabilis biofilm development. It has been shown that triclosan impregnated silicone and latex-based catheters were free or reduced of crystalline biofilms from P. mirabilis as compared with a water control (blocked ranging from 18 to 27 h).45,46 In a study by Chew et al. ureteral stents eluted with triclosan had reduced P. mirabilis biofilm formation when suspended in artificial urine.44

However, it must be noted that P. mirabilis strains have varying susceptibility to triclosan and thus can be selected for upon the use of this biocide.51 This is also true of antibiotic impregnated catheters. While the use of antibiotics have shown improved efficacy, the widespread use of antibiotics and the issues of resistance development cannot be ignored.

Silicone catheter retention balloons treated with a solution of nalidixic acid has been shown to significantly extend the lifespan of the catheter by reducing catheter encrustation.37 Alternatively, EDTA-treated silicone catheters took significantly longer to cause blockages by encrustation (45 h in saline vs. 67 h in daily EDTA treatments, p = 0.047) as examined scanning electron microscopy.48 Urease inhibitors, such as fluoroamide, have also shown some efficacy since they reduce pH and reduce calcium and magnesium salt deposits on silicone catheters and the resulting biofilm formation as examined by scanning electron microscopy.49 Quorum sensing antagonists, p-nitrophenyl glycerol and tannic acid, have been shown to inhibit the quorum sensing system and subsequently inhibit P. mirabilis biofilm formation in artificial urine.49 Although not specifically tested in human urinary catheters, other quorum sensing antagonists such as synthetic furanone compounds like (5Z)-4-bromo-5-(bromomethylene)-3-butyl-2(5H)-furanone that can be derivatives of those produced by marine alga Delisea pulchra have shown excellent efficacy.52 Encrustation and catheter blockage can also be reduced by increasing a patient’s fluid intake with citrate-containing drinks.52 Novel anti-biofilm natural products can result in the reduced ability of P. mirabilis to develop biofilms, such as one study where glass and polystyrene surfaces were treated with Ibicella lutea extract, a South American indigenous plant, as demonstrated by spectrophotometry.50 In the many studies using silver as an antimicrobial coating in clinical studies, a moderate benefit has been noted,53 most likely due to the low rate of silver ions elution and the protective effects of crystal layer development over the catheter luminal surface that may shield bacteria from the silver antimicrobial effects.20,21 However, this limited benefit may be improved by the incorporation of nanosilver, nanometer sized silver particles, to increase the surface area and silver dissolution in the surrounding liquid.54 As with other modalities, large scale clinical testing is somewhat limited so the efficacy is unknown.

Catheter materials with various coatings have been examined for the development of P. mirabilis biofilms. Hydrogel coating (based on polyvinylpyrrolidone) has been shown to accelerate biofilm formation on silicone as compared with uncoated silicone via the laboratory model of catheterized bladder.55 An anti-fouling coating of marine mussel adhesive protein, which resembles polyethylene glycol [mPEG-DOPA(3)], has potential to resist conditioning film formation on silicone disks incubated in pooled human urine and uropathogen attachment in human urine as examined by scanning electron microscopy.56 However, the efficacy of these coating would need to be tested in randomized and large scale clinical studies to judge the validity of these surfaces.57

In a study by Stickler et al. test drainage and artificial catheterized bladder systems remained sterile for 10 d with the use of a silver-releasing device located in the draining tube.58 This demonstrates that urinary catheters were protected from ascending bacteria, including P. mirabilis, from contaminated urine-drainage bags as shown by scanning electron microscopy and chemical analysis.58 Introducing an electric current through silver electrodes attached to catheters was demonstrated to significantly decrease encrustation by P. mirabilis biofilms.59 Cellulose acetate/bromothymol blue sensors in urine collection bags detected the presence of P. mirabilis biofilm encrustation approximately 12 d
prior to catheter blockages.60,61 With the addition of lytic bacteriophages, *P. mirabilis* biofilm formation including the mechanism by which these organisms produce these structures. Since crystalline biofilms are known to develop during CAUTIs associated with *P. mirabilis* and are responsible for some of the more severe sequelae experienced, performing more extensive studies focused on biofilm formation could lead to the identification of important proteins involved with this process. This would lead to a better understanding of the general process of biofilm development and could indicate potential targets for prevention and treatment of these types of infections.

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