Preventing Biofilm Formation and Encrustation on Urinary Implants: (Bio)molecular and Physical Research Approaches

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1 Introduction

Stents and catheters are used to facilitate urine drainage within the urinary system [1]. When such sterile implants are inserted into the urinary tract, ions, macromolecules and bacteria from urine, blood or underlying tissues accumulate on their surface. This often results in the formation of biofilm causing infections that can

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be responsible for discomfort and complications in patients [2]. Therefore, urinary tract implants may be considered as out-of-equilibrium systems where different phenomena acting at various times and length scales occur. This leads to their reshaping by deposition and encrustation of chemical and biological species on their surface and the formation of bacterial biofilms and mineral crystals. Due to the continuous nature of biological fluids, these phenomena are in perpetual dynamics and self-organization, which can complicate their study in the human body [3, 4]. Giving this complexity of the "system", a multidisciplinary input with different scientific approaches is needed to better understand and find solutions to this problem. In this chapter, we outline research strategies addressing biocompatibility, the use of antisense molecules, non-pathogenic bacteria and bacteriophages, and physical methods to prevent or inhibit biofilm formation and encrustation.

2 Biodegradable Metal Stents

Biodegradable metals are very appealing for urinary stent applications since they combine enhanced radial strength with a prolonged but controlled degradation time. Therefore, biodegradable metallic urinary stents (BMUS) constitute a promising research strategy overcoming some of the current stent limitations. The potential of biodegradable metals for urological applications was explored first by Lock et al., who investigated the efficacy of Magnesium–4%Yttrium (Mg–4Y), AZ31, and commercially pure Mg as antibacterial BMUS. They showed a significant decrease of *E. coli* viability in the presence of Mg alloys after 3 days compared with a commonly used commercially available polyurethane stent [5]. Zhang et al. explored the potential of the ZK60 Mg alloy and pure Mg for urinary applications in a rat model. ZK60 had a faster degradation rate than pure Mg and neither of the metals showed toxicity during the three weeks implantation time [6]. More recently, Tie et al. used a Mg alloy in a large animal model (*Guangxi Bama Minipig*) as a BMUS. The Mg alloy (ZJ31) presented a homogeneous degradation, excellent biocompatibility and antibacterial activity compared with stainless steel—a commonly used material for non-degradable metallic urinary stents [7].

Zinc (Zn) has a slower degradation time than Mg, with low tissue toxicity and good antibacterial activity. Champagne et al. compared pure Zn, Zn–0.5 Mg, Zn–1 Mg, Zn–0.5% aluminium (Zn–0.5Al), pure Mg and Mg–2Zn–1% manganese (Mg–2Zn1Mn), a commercially available Mg alloy. Zn-containing metals degraded more slowly, and more homogeneous corrosion was obtained for Zn–0.5Al [8].

Biodegradable metal stents in urology have only been explored by a few research groups to date, but these have shown good potential in terms of improved biocompatibility and antibacterial activity.

Mg has been studied the most, but Zn is another promising component. An alloy of both might combine the good biocompatibility and antibacterial properties of Mg with the slower degradation and increased homogeneity of Zn.

3   Molecular and Biological Approaches to Prevent Biofilm Formation and Encrustation

3.1   Antisense Molecules

Pathological protein synthesis, either as under- or overproduction, is a crucial part in many disease processes. Halting these abnormal syntheses might open the disease to effective therapies otherwise not available [9]. Antisense technology (AT) has been investigated for malignant, infectious, inflammatory and metabolic diseases [10]. It modulates protein synthesis by inhibiting gene expression through pairing an antisense nucleic acid sequence base with its complementary sense RNA strand. This stops translation into the target protein [9]. In addition, it can disturb other functions of RNA molecules such as splicing, folding, protein binding, microRNA activities, and RNA-mediated telomerase action [11]. AT is very target specific. For researchers, it is highly interesting since more and more underlying molecular pathways are getting identified for major diseases offering new opportunities to interfere in these. However, AT is not mature enough to overcome some inherent problems such as limited *in-vivo* stability, mode of application, and potential side effects [10]. AT may be used to address urinary implant contamination, infection, and biofilm formation (BF). Biofilms contain extracellular polysaccharides and nucleic acids. The presence of extracellular polysaccharides results in well-structured and strong biofilms [12], which in turn makes bacteria embedded within the biofilm up to 5000 times more antibiotic-resistant [13, 14]. Stopping the synthesis of extracellular polysaccharides can stop BF and/or weaken their bacteria-protective structure. AT would represent an early intervention whilst biofilm is still forming [15]. Especially in chronic infections with BF targeted by AT in its early stages, antibiotics can remain effective and remove or stop further biofilm activity [16].

Recently, it has been shown that the common urinary bacterium *Enterococcus faecalis* gene (efaA) is crucial in BF. Anti-sense *efaA* peptide nucleic acids could decrease it [17]. Research on AT to manipulate BF has only just begun. First the the genetic aspects governing bacterial BF processes need to be better understood [18]. Nevertheless, since one major drawback of urinary stents is the BF, antisense technology may be a promising approach to tackle this inherent stent problem in the future.

3.2   Non-Pathogenic Bacteria

Non-pathogenic bacteria can be used to reduce biofilm formation by pathogenic organisms using various mechanisms such as displacement, exclusion, and competition. In the displacement strategy, non-pathogenic cells or their metabolites disrupt the structure of a pre-formed pathogenic biofilm. Alternatively, pathogen exclusion

can occur by blocking adhesion sites, and competition for nutrients or growth factors can inhibit the development of pathogenic strains [19]. Additionally, non-pathogenic bacteria can also modulate the immune system affecting pathogenic cells.

Non-pathogenic bacteria are able to produce a range of compounds, including biosurfactants, bacteriocins and extracellular polymeric surfaces (EPS), that can be detrimental to the development of pathogenic organisms or affect their adhesion to a surface. It has been shown that the production of biosurfactants may interfere with the microbial adhesion of pathogens, including those that are found in the urinary tract [20]. Bacteriocins were also shown to be useful given their high potency, stability, and low toxicity [21–23]. EPS comprises a large group of high-molecular-weight polymers produced by different metabolic pathways in various organisms with proven antibiofilm properties [24]. The production of a vast array of molecules, including lactic acid, fatty acids, enzymes, and hydrogen peroxide, with the potential to control pathogenic biofilms, has also been identified in non-pathogenic cells [19].

Compared to other coating strategies, the use of non-pathogenic cells to coat medical devices may be advantageous because the coating is alive. This allows for the self-renewal of the anti-pathogenic activity, whereas conventional coatings eventually become covered by biomass which may reduce their effectiveness [25].

A number of hurdles have to be overcome for the broad application of non-pathogenic bacteria to protect the surface of urological stent implants. For example, although it has been shown that a certain degree of protection can be obtained for short time periods, the stability and activity of the coating for longer periods of time must be carefully assessed. If the protective effect relies on the viability of the non-pathogenic bacteria (for instance, to produce interfering molecules), this can be an issue. Also, if translocation of the non-pathogenic biofilm occurs (for instance, due to shear forces caused by urine flow), the coating efficacy can be compromised.

3.3   Bacteriophages

Viruses that use bacteria as their hosts are called bacteriophages. Whilst duplicating in the bacteria, they disrupt the metabolism of their hosts in several ways. Lytic bacteriophages destroy the host cell membranes and cells. Lysogenic bacteriophages use the functioning bacterium to multiply whilst letting it live. Lytic bacteriophages can therefore function as antibacterial agents. They are readily available, selective as to their hosts, and non-toxic for surrounding tissue cells. As a consequence, they have been discussed as a coating constituent for medical implants [26]. In early experiments, bladder catheters were pre-treated with lytic *Staphylococcus epidermidis bacteriophage 456*. This led to a significant decrease in intraluminal biofilm formation [27].

As with antibiotics, bacteria can become resistant to bacteriophages. This may be overcome using a mixture of several lytic viruses [28–30]. Silicone bladder catheters coated with hydrogel and pre-treated with such a mixture were indeed efficient

against multi-bacterial biofilms. It was proposed that such coating could tackle multi-bacterial biofilms by adapting the viral mixture [31].

Whilst the available evidence stems from experiments on bladder catheters only, the use of bacteriophages on urinary stents seems intuitive and promising. More importantly, since we live in an era of increasing and complex global bacterial resistance to antimicrobials, bacteriophages might represent an alternative approach in the future.

4 Physical Strategies to Prevent Biofilm Formation and Encrustation

4.1 Electrical Charges

The role of electrostatic charge is pivotal in bacterial adhesion. Most bacterial genera have a net negative charge as determined from quantification of their zeta-potential. Therefore, two types of engagement can be derived as antibacterial strategies, namely, material as repellent or as contact-killing agent. The first strategy implies that materials with high negative charge can be deployed as anti-bacterial stent material or coating to repel bacterial cells [32]. Heparin, having the highest negative charge density of known biological molecules [33], has been a popular candidate as stent coating material. However, its efficacy against biofilm formation has been controversial [33–35]. The second strategy relies on a positively charged surface and permeabilization of the bacterial cell membrane that leads to the leakage of intracellular material and eventual cell death. One approach involves grafting polyethyleneimine (PEI) [36] micro-brushes onto polyurethane stents followed by an alkylation process [37, 38]. The resulting micro-structure of PEI brushes with positive charges showed a reduction in both biofilm and encrustation development in *in vitro* and *in vivo* experiments [37]. Another choice of positively charged material is chitosan, which works as an antimicrobial against fungi, Gram-positive and Gram-negative bacteria through various modes of actions [39, 40]. A freeze-casting process was proposed to make entire ureteral stents from chitosan [41]. The best material and engagement strategy are yet to be concluded from further investigations.

4.2 Enhancing and Maintaining Ureteral Peristalsis

In physiological conditions, ureteral peristalsis moves the urine from the renal pelvis to the bladder. Although the insertion of ureteral stents can initially increase ureteral peristalsis, indwelling stents eventually lead to its cessation [42]. The mechanisms leading to aperistalsis in stented ureters are still unclear. A few models

[43] and experimental studies reported the possibility of artificially inducing ureteral peristalsis by: (1) electrical stimulation [44–46], (2) mechanical stimulation e.g. applying distension and/or (3) pharmacological treatment [45]. A possible strategy against encrustation and biofilm in stented ureters could be based on the 'flushing effect' of the ureteral peristalsis: if peristalsis can be preserved in stented ureters in the long term, the movements of the ureteral wall could eliminate encrustations and bacterial deposits from the stent surface. Haeberlin et al. demonstrated that peristalsis can be electrically induced in stented ureters. Catheters were inserted into *ex-vivo* ureters (the size of the catheters was comparable to conventional ureteral stents) and propagating contractions of the ureteral wall were observed after each electrical stimulation [46]. Since these experiments were only conducted in *ex-vivo* ureters in the short term (up to 3 h), *in-vivo* experiments are required to demonstrate the possibility of long-term preservation of the peristalsis by artificial electrical stimulation.

4.3   Ultrasound Waves

Ultrasound comprises longitudinal pressure waves with a frequency > 20 kHz. It represents a clinically viable modality of delivering mechanical stimulation within the body to achieve both therapeutic and diagnostic outcomes. It has also been demonstrated that ultrasound exposure can cause detachment of bacterial biofilms from different surface types and can promote the transport of antibiotics into planktonic or biofilm-forming bacterial cells [47]. Surface acoustic waves (SAW) are a type of sound waves that are transmitted along a surface, and the resulting vibrations have been identified as a factor reducing bacterial adhesion onto solid surfaces [48]. This approach has been adopted to counteract bacterial biofilm formation in bladder catheters, whereby an ultrasound transducer is coupled with the extracorporeal segment of the catheter. Upon activation, the transducer generates SAWs in the frequency range 100–300 kHz, resulting in surface oscillations with amplitudes of 0.2–2 nm that propagate over the catheter surface. In previous studies in a rabbit model, this method has been evaluated both *in vitro* and *in vivo* for inhibiting bacterial adhesion on Foley bladder catheters. It has been shown that SAW-activated catheters had a significantly lower biofilm load *in vitro,* and that this effect was greater when lower SAW intensities were employed (in the range 0.05–0.20 mW/cm^2). These findings were confirmed *in vivo*, where the average number of days until the development of a urinary tract infection was extended to 7.3 ± 1.3 days in the SAW-catheter group, compared to 1.5 ± 0.6 days in a non-treated, control group [49].

A commercially available SAW-activated catheter (UroShieldTM) has been developed by NanoVibronix Inc. (USA). Zillich et al. investigated its efficacy and safety through a randomized, double blinded clinical study on 22 patients, in which catheters were deployed for an average of 9 days. Patients having the UroShieldTM catheter reported less pain and bladder spasm, and showed a marked reduction in

biofilm formation [50]. More recently, a double blinded randomized controlled trial assessed 55 patients who had an indwelling urinary or suprapubic catheter for > 1-year, and had a treated urinary tract infection during 90 days prior to the commencement of the study. The large majority of patients having the SAW-activated UroShieldTM showed a significant reduction in bacterial load compared to the control group [51]. To the best of our knowledge, a similar approach has not yet been investigated for ureteric stents. Given the demonstrated efficacy of SAW on stent encrustation, this surely represents an interesting future research strategy. When developing such a strategy, there are some technical aspects to be considered. As we are dealing with fully intracorporeal devices, remote powering and control of the SAW activation, and a careful investigation into the propagation properties of the stent materials is needed. For the latter, geometrical features of a stent (e.g., presence of side holes) that may affect SAW propagation and the resulting surface displacement field must be considered, too.

4.4   Biosensors

One major problem of urinary stents and catheters is blockage by encrustation. If blockage occurs in a bladder catheter, it causes painful retention of urine and can provoke severe urinary tract infection and urosepsis. Often, the blockage results from urine infection with urease producing organisms, predominantly *Proteus mirabilis*. Urease generates ammonium which leads to an elevation of urinary pH. This leads to the precipitation of struvite and apatite, which then form a crystalline biofilm encrusting and blocking the urinary catheter. Biosensors are sensors that would alert patients and carers early of an ongoing encrustation and impending resulting blockage. A survey of the current literature shows that such sensors are mainly visual. A pH sensor based on a silicone-based strip incorporating a pH indicator (bromothymol blue) was integrated into an indwelling urinary catheter [52]. A change from yellow to blue indicating impending blockage occurred 19 days before the actual blockage in early human trials. Catheters can also be designed to integrate a pH dependent luminescent material [53]. A lanthanide (Eu) pH-responsive probe that can be incorporated in a hydrogel catheter coating was described. Upon elevation of pH in the presence of urease, the luminescence turns off. However, the system was not tested neither *in vivo* nor *in vitro*. Another approach to provide early warning of encrustation and blockage is to associate a 'trigger' layer, usually EUDRAGIT®S 100, on a hydrogel layer encapsulating a pH reporter or antibacterial agent [54, 55]. Upon elevation of the urinary pH, the upper layer dissolves, triggering the release of a pH indicator such as carboxyfluorescein or bacteriophages. Both approaches were tested in an *in vitro* bladder model, which provided a 12 h advanced warning of blockage and a 13–26 h advanced warning of delayed catheter blockage. The above are early and simple examples of pH-indicating visual biosensors. Because they are visual, they will only work on catheters where an extracorporeal part remains visible. However, the idea of biosensors to indicate early stent

encrustation is an appealing one. Fully intracorporeal stents could be equipped with micro- or nano-technological wireless sensors for the same purpose.

5 Conclusions

In this chapter, we presented a brief but comprehensive overview of future research strategies in the prevention of urinary device encrustation with an emphasis on biodegradability, molecular, microbiological and physical research approaches. The large and strongly associated field of stent coatings and tissue engineering is outlined elsewhere in this book.

There is still plenty of room for future investigations in the fields of material science, surface science, and biomedical engineering to improve and create the most effective urinary implants. In an era where material science, robotics and artificial intelligence have undergone great progress, futuristic ideas may become a reality. These ideas include the creation of multifunctional programmable intelligent urinary implants (core and surface) capable to adapt to the complex biological and physiological environment through sensing or by algorithms from artificial intelligence included in the implant. Urinary implants are at the crossroads of several scientific disciplines, and progress will only be achieved if scientists and physicians collaborate using basic and applied scientific approaches.

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