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Applications of protein-resistant polymer and hydrogel coatings on biosensors and biomaterials

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Abstract

Nonspecific protein adsorption at interfaces is a significant issue in the development of robust biosensors and implantable biomaterials. The reduction of nonspecific protein adsorption plays a key role in improving the compatibility and efficiency of biomaterials. Modifying surfaces to achieve this goal is currently a complicated process, while the primary approach used is through chemical modification of the surface through polymer coatings. Meanwhile, anti-fouling hydrogel coating on solid substrates is a relative new technique in membrane surface modification. This review describes the comprehensive knowledge and recent research efforts on protein-resistant polymer and hydrogel coatings on the surface of biosensors, and biomaterials such as contact lenses and porous membranes. The basic concepts and mechanisms for the design and performance of polymer and hydrogel coating layers are introduced in terms of both biosensors and biomaterials. Polymer-based protein-resistant approaches for various types of basic materials are then summarized and discussed.

Interactions between protein and biomaterials

When the surface of an implanted biomaterial (synthetic or natural) comes into contact with a biological fluid, such as blood, a cascade of interdependent events takes place and several signals are generated [1]. Protein adsorption onto the surface is considered the most important factor in the interaction between the biological fluid and the biomaterial. Many factors affect the extent of protein adsorption, including electrostatic interactions, water-mediated hydrophobic and hydration forces (Figure 1) [2-5].

Nonspecific protein adsorption is a dynamic process that occurs very quickly, typically only seconds after the fluid meets the surface of the material, which generates an adsorbed layer, [6] and triggers a cascade of biological events [7,8]. For *in vivo* implants, this adsorbed layer activates an irrevocable host defense mechanism, which is known as the foreign body reaction, which finally results in the production of a fibrous a vascular capsule that isolates the material from its surroundings. This prevents further physical, chemical or physiological interaction with its surroundings [6]. In the case of *in vivo* implants, protein fouling not only reduces the efficacy of devices, but also results in thrombosis and other negative side effects [9]. Negative effects of protein fouling also take place in *in vitro* applications, since the adsorbed layer may clog the pores or inhibit specific binding of molecules to these devices [10,11]. For example, nonspecific adsorption of proteins significantly reduces the sensitivity of *in vitro* diagnostic assays, especially in the case of immunological assays [12]. In addition, proteins in the adsorbed layer undergo a slow denaturation process (Figure 2), which typically induces immunological responses *in vivo* or leading to failure in terms of specific sensing [13].

The reduction of nonspecific protein adsorption plays a key role in improving the compatibility and efficiency of biomaterials. The primary approach used is through chemical modification of the surface through polymer coatings (Figure 3). Such coating provide a 'stealth' effect, [14] which is attributed to the high level of hydration of the hydrophilic polymer backbones,

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steric repulsion, and reduction of the surface energy of the biomaterial [6,15-17]. Among these factors, hydration forces have been suggested as the key in determining whether a surface will promote or reduce protein adsorption [18]. Following this rule, various types of polymer coatings were designed as the protein-resistant layer to cover a 'bioinert' material. These coatings include polypeptides, [19] poly(ethylene glycol), [20] polyglycerol (PG), [21] polysaccharides, [22] polyoxazoline, [23] poly(propylene sulfoxide), [24] poly(phosphoester), [14] polyvinylpyrrolidone [25] and zwitterionic polymers such as phosphorylcholine and sulfobetaine or carboxybetaine polymers [26-28]. These coated surfaces resist non-specific binding of proteins, and are widely used in implants and devices *in vivo* such as catheters, prosthetic devices, contact lenses, drug delivery vehicles, as well as in immunoassays such as Enzyme-Linked Immunosorbent Assay (ELISA) and patterned cell culture materials for *in vitro* applications [12,29].

In summary, understanding and controlling protein adsorption on biomaterial surfaces is essential to preparing bioinert surfaces and improve the efficacy of biomaterials.

Protein-resistant coatings for in vivo and in vitro biosensors

Biosensors are important tools for research in molecular biology, for medical diagnostics, environmental monitoring and food safety, allowing real-time observation and rapid detection of chemical and biological molecules and their interactions [30]. The success of a biosensor is based on sufficiently high and controlled binding capacity of target biomolecules, and also the activity of the immobilized biomolecules should be stable. One of the main problems with sensors, is loss of sensitivity due to biofouling, namely due to adhesion of proteins and other biological materials on the surface of the sensor. Biofouling (and its negative effects) has been observed in both *in vitro* (non-invasive) and *in vivo* (invasive) biosensors [31,32] and it is widely regarded as the main cause of sensor failure [33,34]. Potential interference can be caused by nonspecific adsorption of biomolecules from the sample or the environment to the surface [35]. *In vitro* protein fouling studies have shown that biofouling on the membrane and the electrode would lead to decreased sensor signal [33,36].

To mitigate these problems, the sensor surface should have a low-fouling tendency, which is generally provided by using the bioinert polymers mentioned above [26,28,37]. Several approaches have been used to develop coatings that both enable a high degree of resistance to nonspecific adsorption and assist the immobilization of recognition molecules [38-41]. The immobilization of recognition molecules, which are often called bioreceptors, is usually done on carefully prepared low-fouling surfaces.

A common strategy used in biosensing is the addition of inert proteins including Bovine Serum Albumin (BSA) and casein, which can reduce the fouling rates by minimizing any hydrophobic and/or electrostatic attractions between the complex surface and the functionalized surface [4,11,42]. However, blocking with BSA sometimes leads to a substantial reduction of activity of the immobilized biomolecules/bioreceptor and decreased biorecognition activity thereby resulting in false negative results [43,44]. Instead, polymer coatings with active sites for binding active biomolecules have been developed for the application of highly sensitive biosensors.

PEG based polymers are most commonly used in passivation of biosensor surfaces [45]. For example, a protein-resistant POEGMA brushes coated surface was functionalized with biotin and allowed further specific binding of streptavidin both on Surface Plasmon Resonance (SPR) and Quartz Crystal Microbalance (QCM) biosensors (Figure 4) [46]. The resulting films showed enhanced signal-to-noise ratio (~10-fold enhancement) for the biospecific binding of streptavidin compared to biotinylated SAM without Poly(methacrylic acid) oligomeric glycol esters (POEGMA), when fibrinogen and lysozyme were set as the interfering species. A similar approach is to use the activated end group of POEGMA on the surface to bond functionalized protein with Diels–Alder "click" reaction [47].

As a potential replacement of Polyethylene Glycol (PEG) based polymers, zwitterionic ultra-low-fouling poly (carboxybetaine acrylamide) (pCBAA) brushes were successfully used in immobilizing bioreceptors (in this case antibodies) on an Surface Plasmon Resonance (SPR) sensor (Figure 5) [48,49]. This type of sensor was capable of detecting specific analytes in blood plasma without detectable signals of fouling molecules. Further studies from the same group used functionalized zwitterionic polymers to build up ω-dopamine-pCBAA grafted silicon resonator, [50] SiO_2-coated SPR sensor, [51] and catechol-pCBAA grafted gold SPR sensors [52,53].

Unlike the flat basic materials used in aforementioned equipment-based biosensors, some point-of-care biosensors are built up on inexpensive porous materials such as paper and nitrocellulose membranes. Development of these types of paper-based devices for diagnostics and biosensing has attracted a great deal of interest as they provide portable, low-cost, low-volume, disposable, and simple analytical devices for bioassays and environmental analysis [54]. Recently, bioactive paper or lab-on-paper devices have been developed as a practical platform for assays in many different areas such as diagnostics, food and water testing, and military applications [55-57]. These paper-based sensing devices can be applied not only in point-of-care testing but also in field analysis. This technology is already having an impact in low-cost testing and is expected to be used globally and in particular in resource-limited settings, in the near future.

While there are several proof-of-concept studies showing the potential of paper-based analytical devices, the adsorption and non-specific binding of proteins on paper surface is a serious problem for regular paper surfaces which may largely influence the accuracy of sensors [58,59]. The passivation of porous materials remains challenging as compared to the flat surfaces. As a basic requirement for the design and preparation of paper-based biosensor, anti-fouling properties must be built into the surface [60]. For this purpose, they are usually provided by modification with aforementioned hydrophilic polymerssuch as PEG analogues or zwitterionic polymers. For example, poly(carboxybetaine) (PCB) coated cellulose paper could significantly reduce the adsorption of human fibrinogen as compared with that of the unmodified control, and achieverapid and sensitive glucose detection from undiluted human serum and specific antigen detection via covalently immobilized antibodies (Figure 6) [61].

Protein-resistant coatings for contact lenses

Soft contact lenses made with hydrogels have been widely used for vision correction over more than 50 years [62]. These lenses always suffer from challenges related to the deposition of

proteins from the tear fluid onto the lenses, such as lysozyme, human serum albumin and globulin, [63-67] and subsequent formation of a coating layer of protein on the surface will serve as a precursor for microbial colonization and will induce the formation of biofilms. Therefore, protein adsorption on contact lenses is correlated to microbial cell attachment and some severe issues for the wearer [68-70]. In addition, a strong correlation has been found between the deposited lysozyme from the tear film onto the lenses and discomfort experience by the wearer [71].

Synthetic polymers associated with low protein adsorption, including poly(ethylene glycol) (PEG) [72] and 2-Methacryloyloxyethyl Phosphorylcholine (MPC), [73,74] and polymers with hydration improvement effects, such as poly(vinyl alcohol) (PVA), [75,76] have been entrapped within the bulk of the lens and improved the comfort of long term wear. Due to the protein-resistance-promoting properties of hyaluronic acid (HA), [77-79] a natural polysaccharide present in the tear film, various methods have been reported to incorporate HA into the bulk of the lens. Cross linking is the most commonly used method to introduce HA into the bulk hydrogel network, with HA incorporation demonstrated directly with the main lens material(s) (e.g. via photopolymerization of methacrylated photocrosslinkable HA with 2-hydroxyethyl methacrylate (HEMA) [80]), within a secondary interpenetrating network (e.g. polyethyleneimine crosslinked HA within an independently crosslinked HEMA network [79]), or via physical entrapment of a higher molecular weight HA-based cluster or nanogel (e.g. conjugation of HA to polypropylenimine tetramine dendrimers that improve HA immobilization within the lens) [77,78,81,82]. All of these approaches lowered the lysozyme and/or human serum albumin adsorption as compared to the native gels and have great potential to be developed into daily used contact lenses.

Protein-resistant hydrogel coatings on porous materials

As mentioned in the previous section, various types of hydrogels are protein repellent and the hydrogels coated on the cell culturing biointerfaces have great potential in reducing protein adsorption and controlling cell adhesion. Hydrogels have also been used in coating porous materials such as filtration membranes and tissue engineering implants in order to reduce fouling from the proteins and other components such as cells from the blood serum/plasma.

Membrane biofouling is a process that starts immediately upon contact of the surface with the fluid containing proteins, cells, particles and other components. They adhere to the surfaces in the pores of the membrane [83]. The most common method to improve membrane anti-fouling properties is by hydrophilic coating of the surfaces through physical adsorption, crosslinking, and sulfonation, or surface grafting through UV photo irradiation, plasma, high energy irradiation and “living”/controlled polymerisation [84].

Anti-fouling hydrogel coating on porous solid substrates is a relative new technique in membrane surface modification. PEG-based hydrogel has been coated on polyamide nanofiltration membranes, and such modified membranes shows an improved fouling resistance compared to pristine membranes [85]. A bifunctional hydrogel-coated film exhibiting both protein fouling resistance and antimicrobial activities was prepared by the copolymerization of poly(ethylene glycol) diacrylate (PEGDA) and a functional monomer containing ammonium salt (RNH_3Cl) on Polysulfones (PSF) membranes [86]. A hydrophilic hyperbranched poly(amido amine) (PAMAM) was successfully bonded onto the active polyamide reverse osmosis-membrane by chemical coupling [87]. Membranes modified with aqueous PAMAM solution showed very low protein adsorption compared to unmodified samples or samples modified with methanolic PAMAM solution. A poly(vinyl alcohol) (PVA) based polymer was synthesized and subsequently applied to modify a poly(vinylidene fluoride) (PVDF) membrane to both enhance the hydrophilicity and provide fouling resistance.

Free standing films containing hydrogel coating are prepared by a combination process of polymerization and crosslinking. For example, a Polyhedral Oligomeric Silsesquioxane (POSS) derivative containing UV-curable methacrylate groups (methacryl-POSS) was used as a multifunctional cross-linker to form thin and durable hydrogel films with poly(ethylene glycol) methacrylate (PEGMA) as a hydrophilic comonomer [88]. Free standing films prepared by crosslinking PEG matrix on ultra-fine cellulose nanofibers exhibited excellent anti-fouling properties, which were confirmed by short-term and long-term fouling tests using a BSA solution [89]. Another free-standing membrane was synthesized through polymerization of acrylamide in the presence of sodium alginate using N,N’-methylene-bisacrylamide as the covalent crosslinker and $CaCl_2$ as the ionic crosslinker, and exhibited low fouling properties against yeast suspension and BSA solution [90]. Crosslinked PEGDA hydrogels as a free-standing ultrafiltration membrane film could absorb significant amounts of water, and the results from static protein adhesion experiments showed that more hydrophilic surfaces, obtained from higher prepolymerization water content or with longer PEGDA chains, generally exhibit less Bovine Serum Albumin (BSA) accumulation [91].

In addition, there are a few trials that used hydrogel coatings on tissue engineering implant materials to reduce the protein and cell fouling from the body fluid and tissue *in vivo*. Polyvinylpyrrolidone (PVP) hydrogel coating bonded to a Polyurethane (PU) substrate improved the surface hemocompatibility of blood-contacting medical devices as shown by a reduced abruption of serum-derived fibrinogen and number of platelet aggregates formed during the contact of the material with blood over a long period (35 days) [92]. In another approach, ECM hydrogel coated polypropylene mesh device was shown to decrease the long-term host tissue response to the device when compared to the uncoated mesh devices due to a decreased collagen deposition at day 180 [93]. Table 1 summarised different coatings mentioned for the biomaterials.

Conclusion

Although there are many researches on protein-resistant coatings, all listed above are just part of them. Actually, we know that the key roles in affecting the adsorption of proteins are on the surface, including electrostatic interactions, the exact role of water-mediated hydrophobicity and hydration, but the detailed mechanism is still not clear. Further notice would be focused on the competitive adsorption of proteins on the surface of the material, the conformational changes of the protein when it was adsorbed on the surface, the effects of these different coatings on the biocompatibility and the systematic study of the effect of the protein coating in vivo in the future.

Tables

Table 1: The advantages of different coatings for biomaterials.

Polymer	Basic Material	Advantages	ref
poly(phosphoester)	polystyrene nanocarriers	reduce non-specific cellular uptake	14
polypeptide	surface plasmon resonance (SPR) biosensing	great retention of activity for the antibodies	19
PEG	Au	improve hydrophilicity	20
polyoxazoline	niobia (Nb_2O_5) surfaces	high antibacterial properties	23
poly(propylene sulfoxide)	Au	hydrophilic repeating unit; well-solvated; conformationally flexible oligomer	24
polyvinylpyrrolidone (PVP)	polysulfone membranes	high hydrophilicity	25
PEG	nanoparticles (NPs)	biodegradable	26
sulfobetaine	poly(ether urethane) (SPEU) surface	bind water molecules even more strongly via electrostatically induced hydration	27
sulfobetaine	polyurethane (PU)	more stable and easier to prepare	28
Poly (oligo ethylene glycol methacrylate) POEGMA	surface plasmon resonance (SPR) and quartz crystal microbalance (QCM) biosensors	enhanced signal-to-noise ratio	45
poly(oligo ethylene glycol methacrylate) POEGMA	Au	excellent anti-pollution performance	47
poly(carboxybetaine acrylamide) (pCBAA)	plasmon resonance (SPR) sensor	ultralow fouling background,	48
poly(carboxybetaine) (PCB)	cellulose paper	excellent fouling resistance; superhydrophilic properties	61
2-methacryloyloxyethyl phosphorylcholine (MPC)	silicone hydrogels	high oxygen permeability	73
poly(vinyl alcohol) (PVA)	nelfilcon A	increasing the comfort	75
hyaluronic acid (HA)	poly(2-hydroxyethyl methacrylate) (pHEMA)	high hydrophilicity and transparency	77
hyaluronic acid (HA)	hydrogel lens	high water content, optical transparency	78
hyaluronic acid (HA)	silicone hydrogel	improving hydrophilicity and decreasing lysozyme sorption	79
ω-dopamine-pCBAA	silicon resonator	ultra-low fouling functionalized surface coatings	50
Poly (carboxybetaine methacrylate) (pCBMA)	SiO_2 substrates	high sensitivity	51
poly(carboxybetaine) (pCB)	gold SPR sensors	high sensitivity and specificity detection	53
PEG-based hydrogel	polyamide nanofiltration membranes	improved fouling resistance	85
poly(ethylene glycol) diacrylate (PEGDA)	ammonium salt (RNH_3Cl) on polysulfones (PSF) membranes.	High antibacterial activity	86
hyperbranched poly(amido amine) (PAMAM)	polyamide reverse osmosis membrane	high salt rejection and low protein absorption	87
poly(ethylene glycol) methacrylate (PEGMA)	methacryl-POSS	high water absorption and water permeability	88
PEG	ultra-fine cellulose nanofibers	excellent anti-fouling properties	89
N,N'-methylene-bisacrylamide	sodium alginate hydrogel	excellent anti-pollution performance	90
Polyvinylpyrrolidone (PVP)	polyurethane (PU) substrate	improve the surface hemocompatibility of blood-contacting medical devices	92

Figures

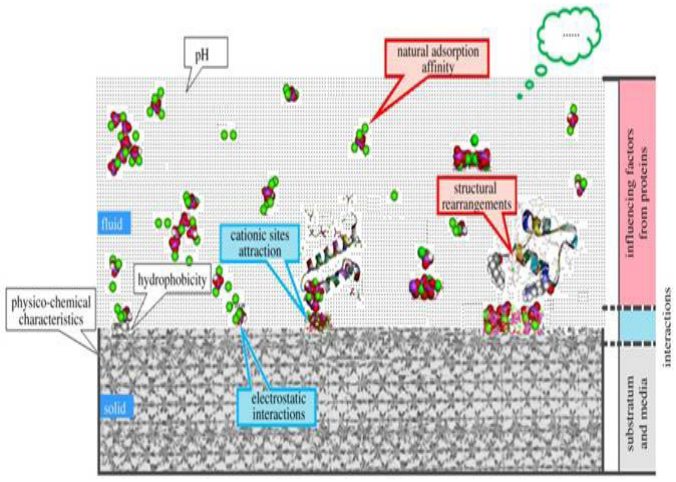

Figure 1: The advantages of different coatings for biomaterials. Figure reproduced from Ref [5]

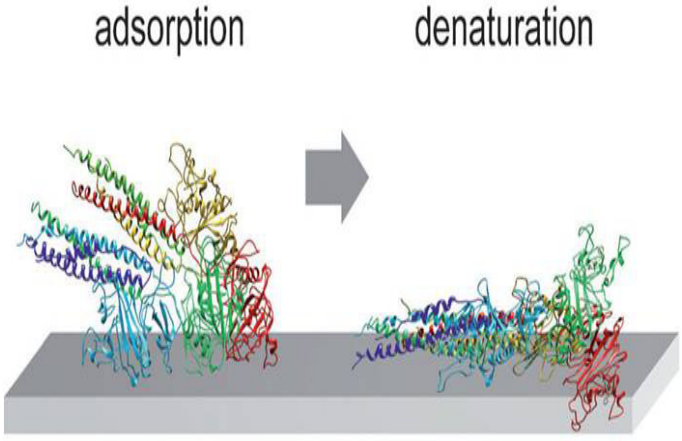

Figure 2: Dynamic adsorption and denaturation of proteins on a bare surface. (Figure reproduced from Ref [8]).

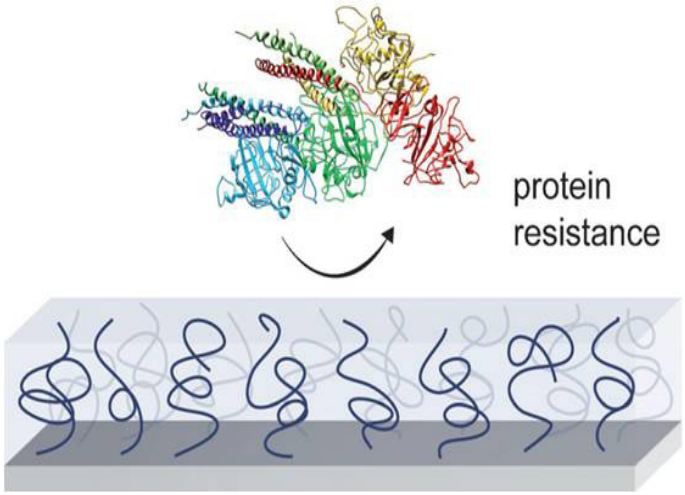

Figure 3: Protein resistance is imparted by polymer-coated surface. (Figure reproduced from Ref [8])

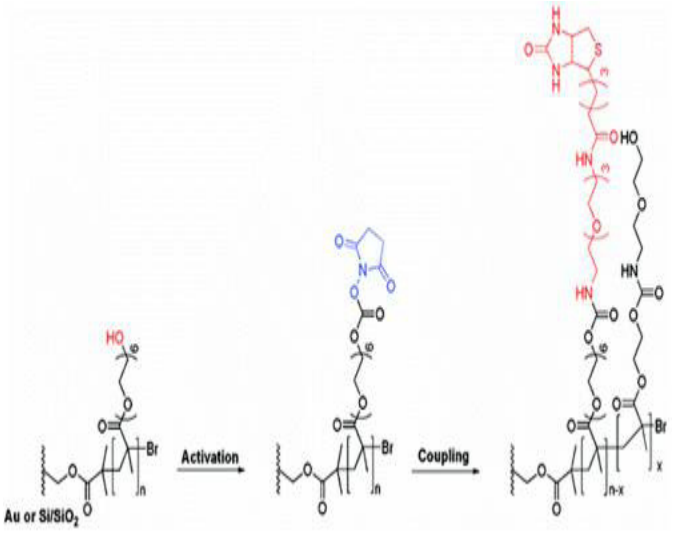

Figure 4: Schematic representation of the biotin conjugation reaction on POEGMA brushes on the sensor surface. (Figure reproduced from Ref [46]).

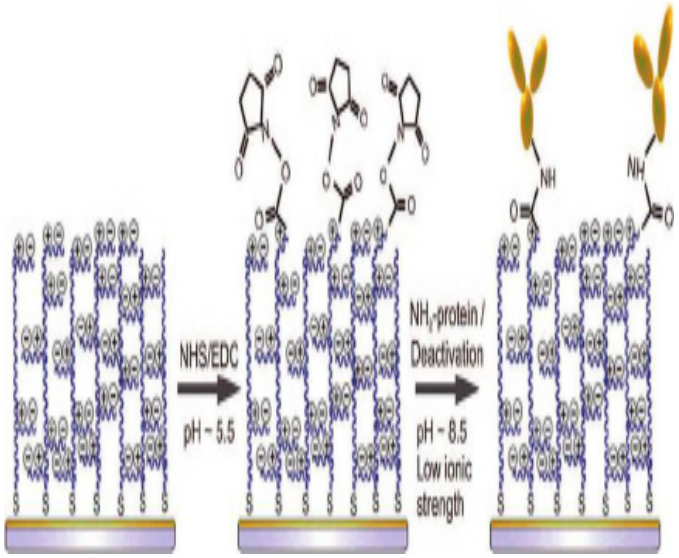

Figure 5: Schematic of the surface activation, protein immobilization, and surface deactivation of a pCBAA coated surface. (Figure reproduced from Ref [48]).

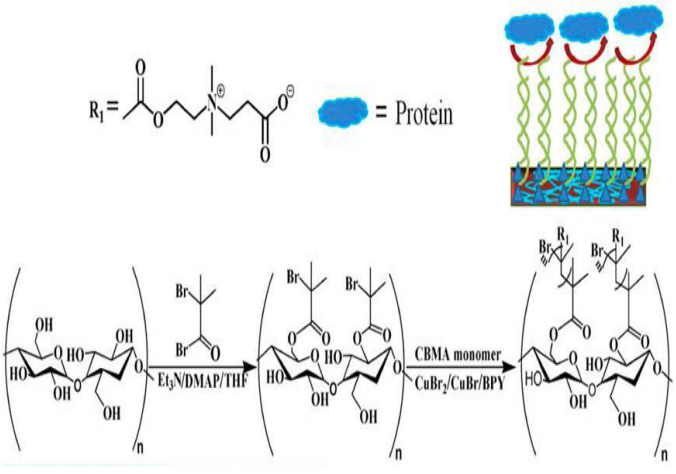

Figure 6: The reaction scheme of grafting protein-resistant poly(carboxybetaine) (PCB) onto cellulose substrates. **(Figure reproduced from Ref [61]).**

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