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Historical perspective

Nanoengineering and green chemistry-oriented strategies toward nanocelluloses for protein sensing

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ABSTRACT

As one of the most important functional organic macromolecules of life, proteins not only participate in the cell metabolism and gene regulation, they also earnestly protect the body's immunity system, leading to a powerful biological shield and homeostasis. Advances in nanomaterials are boosting the significant progress in various applications, including the sensing and examination of proteins in trace amount. Nanocellulose-oriented protein sensing is at the forefront of this revolution. The inherent feature of high biocompatibility, low cytotoxicity, high specific area, good durability and marketability endow nanocellulose with great superiority in protein sensing. Here, we highlight the recent progress of protein sensing using nanocellulose as the biosensor in trace amount. Besides, various kinds of construction strategies for nanocelluloses-based biosensors are discussed in detail, to enhance the agility and accuracy of clinical/medical diagnostics. Finally, several challenges in the approbatory identification of new approaches for the marketization of biomedical sensing that need further expedition in the future are highlighted.

1. Introduction

Proteins, consisting of colorful amino acids, occupy a decisive position in all life activities. The sequence of the constituent amino acids determines the primary structure of the polypeptides, contributing to different biochemical activity of the resultant proteins [1–5]. In theory, partitioning different polypeptides into transmembrane nanopores plays critical roles in biology. The precise sensing and determination of protein species provide quantitative biological information, including their physicochemical properties and molecular mechanisms in vital movements [6–11]. The commonly used detection technologies for proteins involve coupled plasma atomic emission spectrometry (ICP-AES), ultraviolet absorption spectrometry, flourescence spectrometry, magnetic resonance imaging, atomic absorption/emission spectrometry (AAES), etc., which always need large scale and cumbersome equipments [12–15]. Most importantly, these detection technologies are inevitably time and labor consuming [16,17]. Recently, biosensors have emerged as an advanced inspection technology that exhibit the superiorities of low cost, high efficiency, high sensitivity, strong targeting, good reproducibility and ease of operation in a myriad of applications [18–22]. Biosensors fundamentally innovate the detection technologies to obtain pivotal parameters of human and other biological activities, including disease diagnostics, environment monitoring, food safety, food quality control and industry security, etc. [23–26] The action mechanism of the biosensors is based on the direct contact of a transducer element with the biological identification element, in which the specific nanomaterials are fabricated and used as the probe molecule.

Nanocelluloses, including cellulose nanofibers (CNFs), cellulose nanocrystals (CNCs) and bacterial nanocelluloses (BNC), are derived from the raw celluloses (such as wood, biomass, bacteria, fungi and zyeasts, etc) via mechanical or chemical approaches [27–29]. CNCs are often generated by chemical approaches, in which order steps are involved, namely mechanical crushing, alkali wash, delignification, and the final acid hydrolysis [30–33]. The resultant CNCs have the diameter of about 5–50 nm and each nanocellulose is about 100–300 nm in length. CNFs are generally fabricated by mechanical approaches, including high pressure ball milling and the asymptotic homogenization [34–39]. The resultant CNFs have the diameter of about 5–50 nm and each nanocellulose is about 500–1500 nm in length. Fundamentally, BNC is a type of cellulose nanofibriles, which tends to be changed into CNCs in the driven force of acid hydrolyzation [40–42]. Nanocellulose-derived nanomaterials not only have the advantages of high

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biocompatibility, low cytotoxicity, high specific area, good durability and marketability, but also have excellent photonics, colloidal performance and surface chemistry behavior [43–47]. These superiorities endows nanocelluloses with a flexible network for biosensing field. Nanocelluloses have long been used as the ideal host substrates, and at the same time, repeatedly been applied as stable biological templates and scaffolds for diverse biosensing market, including clinical/medical diagnostics, electronics, environment monitoring, food agriculture and healthcare [48–50]. More importantly, nanocellulose-derived hybrids get the upper hand in detecting a great deal of medical analytes, for example, structurally variable proteins, DNA, pathogens, toxic gases, drug carrier, other hazardous compounds and biomarkers, etc. Next-generation protein sensing over nanocelluloses requires higher sensitivity and higher efficiency, while maintaining high biocompatibility and good durability [51,52].

There is an urgent need for new approaches to achieve the high-efficient sensing and examination of proteins in trace amount. This review aims at presenting new opportunities and approaches by using chemistry and nanotechnology strategies to improve the agility and accuracy of nanocellulose-oriented protein sensing.

2. Diverse kinds of nanocellulose-derived biosensors

Nanocelluloses, which are derived from the raw celluloses, have exhibited an ideal platform for the construction of diverse kinds of nanocomposites [15,17]. Because of the existence of abundant hydroxyl groups (-OH) on the surface of the nanocelluloses, the molecule structure of nanocelluloses is easy to be modified, leading to its excellent chemical and physical properties, such as high specific surface area, high mechanical strength, good biocompatibility, biodegradability and low toxicity [39,43,45]. The nanocellulose market value will reach $660 million by 2025 [51,53]. With the rapid advances of modern science and nanotechnology, nanocelluloses have demonstrated amazing annual output and desirable development in biomedical industry. The reactivity and solubility are different for different cellulose substrates, which play critical role in the final nanocelluloses-based products.

2.1. Overall structuration and subunit composition of cellulose substrates

Nanocelluloses are derived from a vast range of cellulose substrates, which are ubiquitously renewable macromolecules containing amphiphilic groups. It was estimated that the annual output of celluloses could reach as high as 7.5×10^{10} tons, contributing to a steady flow of sustainable polysaccharide substrates to tailor diverse forms of nanocellulose-based body materials with particular physicochemical properties [53]. Nanocelluloses can be extracted from a rich flow of plant fibers and bacteria. The academic and industrial circles have long been focused on the extraction of inexhaustible nanocellulose-derived fine chemicals. It certainly needed to consider the efficient management of the biowastes generated in the extraction of the targeting nanocelluloses molecules [54].

The following natural and living sources can be used as the raw materials for the fabrication of nanocelluloses (Fig. 1): 1) agriculture residues, such as fallen leaves, sugarcane bagasse, straw, sugarcane branches, corn stover, weeds, coconut husks, vines, corncobs, wheat and rice husks, palm oil residues and other wastes; 2) forest residues, such as dead trees, shrubs and epiphytes; 3) energy crops, such as cassava, potato, jerusalem artichos, sugar beet, sugarcane, sorghum, corn, *amorpha fruticosa*, jujube, dry willow, paulownia; 4) food waste, such as wheat husk, rice husk, peanut shell, tea seed shell, fruit shell and peel, and fruit dregs, etc.; 5) city and industry waste, such as scrap paper, paper skin, and used construction timber, etc. [55] (See Table 1.)

In the light of the composition, the above mentioned natural sources belong to the lignocellulosic biomass, which consist of three different homopolysaccharides, namely the cellulose (30–50 wt%), hemicellulose (15–45 wt%), as well as lignin (15–35 wt%) [56]. Different biomass contains different homopolysaccharides, for example, cotton has the highest cellulose component (> 90%), leading to different physicochemical properties [57,58]. Fig. 2a shows the repeat unit of cellulose, which is a type of glucose unit with the chemical name of β-1,4-anhydro-D-glucopyranose [59]. The flexible glucose residues can rotate in the linear networks of cellulose. Each β-1,4-anhydro-D-glucopyranose contains two different hexatomic rings (anhydroglucose, $(C_6H_{10}O_5)_n$). The blue arrow in Fig. 2a shows the orientation of the hexatomic rings. Different raw biomass sources and different fabrication processes endow the cellulose with molecule weight, in which the number of the

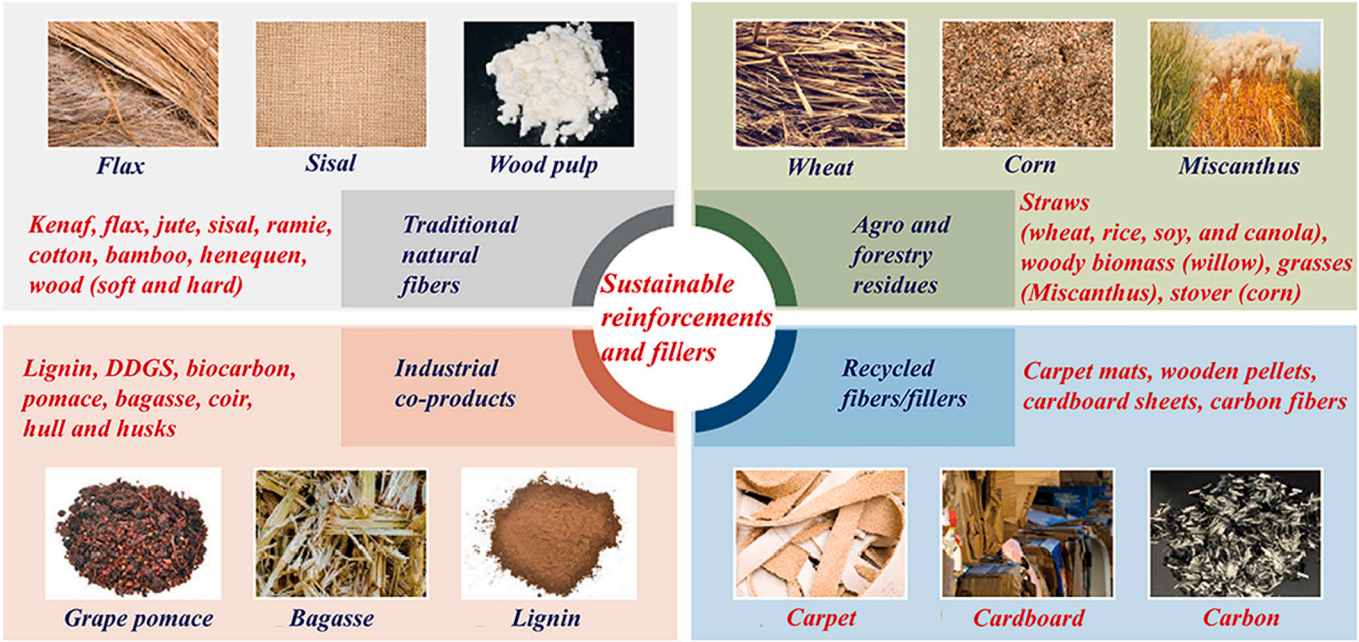

Fig. 1. Diverse forms of substrates for the fabrication of nanocellulose-based protein biosensors. Reproduced with permission from ref. [55].

Table 1
Relationship between different kinds of cellulose based nanocelluloses involving raw materials and fabrication method, type of generated product, dimensions of formed biosensors.

Nanocellulose type	Source	Functionalization technique	Nanocellulose dimensitions		Ref.
			Length (nm)	Width (nm)	
CNF	Softwood sulphite pulp	Mechanical disintegration	1300–2000	1.6–2.1	34
CNF	Wood cellulose	Acid-induced gelation	—	4–5	67
CNF	Wood powder from poplar trees	Acetic acid hydrolysis and high-intensity ultrasonication	A few micrometers	5–20	71
CNF	Wood powder of Japanese cedar	High-speed blending	—	~ 15	76
CNF	Oxidized holocellulose pulps	Twin-screw extrusion	Within the micrometer scale	< 5 nm	35
CNF	Hemicellulose and lignin	Layer-by-layer method	100–5000	103–106	36
CNF	Norway Spruce	Enzymatic pre-treatment and acid hydrolysis	A few micrometers	3–5	66
CNF	Pineapple leaf fibers	Steam coupled acid hydrolysis	200–300	32.5	73
CNF	Norwegian spruce and scots pine	TEMPO oxidation	Several micrometers	3–4	65
CNF	Orange peel residue	Hydrothermal microwave-assisted selective scissoring	500–2000	3–15	37
CNF	Wet ascidian tunicate	Evaporation-induced self-assembly	2310	~ 300	38
BNC	Bacterial cellulose pellicles	Mechanical homogenization	—	30–60	92
BNC	*Gluconacetobacter xylinus*	Citric acid hydrolysis	100–2000	2–14	102
BNC	Acetobacter xylinum	Citric acid hydrolysis	20–100	2–4	104
BNC	Fiber sludge	Shake-flask cultivation	—	—	40
BNC	Bacterial *Acetobacter aceti* strain	In situ biosynthesis	Several micrometers	50–100	41
CNC	Cotton linters	Hydrochloric acid hydrolysis	25–320	6–70	125
CNC	Nata de coco	Hydrochloric acid hydrolysis	855	17	126
CNC	Ramie fibers	Sulfuric acid hydrolysis	150–250	6–8	127
CNC	Eucalyptus wood pulp and chitosan	Sulfuric acid hydrolysis	145	6	128
CNC	Microcrystalline cellulose	TEMPO/NaBr/NaClO oxidation	200–400	5–10	129
CNC	Native cotton fibers	Sulfuric acid hydrolysis	100–300	10–30	130
CNC	Whatman cotton ashless filter aid	Sulfuric acid hydrolysis	60–240	2–10	139
CNC	Q-90 softwood pulp sheets	Chlorite oxidation and hydrochloric acid hydrolysis	200	10	30
CNC	Whatman 541 ashless filter paper	Surface-initiated atom-transfer radical polymerization	202	28	31
CNC	Pulp fiber	Monochloroacetic acid hydrolysis	328	21	32

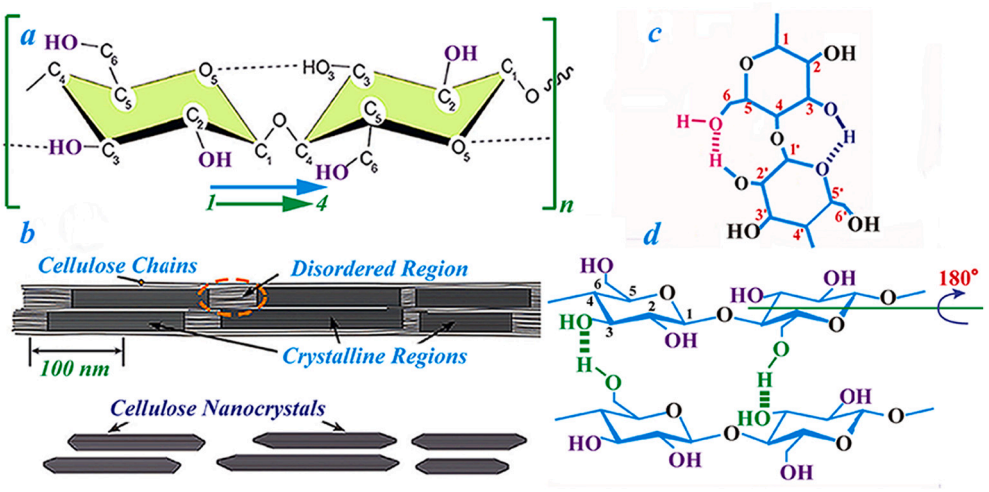

Fig. 2. (a) Molecule structure of β-1,4-anhydro-D-glucopyranose, (b) the crosslinking networks of cellulose fibrils. Reproduced with permission from ref. [59] (c, d) Pendant -OH groups distributed in the molecule chains of cellulose. Reproduced with permission from ref. [60].

repeating units can range from 10,000 to 15,000. The crosslinking networks of cellulose fibrils contain two parts, one is the highly ordered crystalline and the other is the disordered amorphous structure (Fig. 2b). It is noted that that the disordered amorphous structure is easy to be disintegrated under the chemolysis, mechanical disruption or the enzymatic processes. Obviously, there are numerous pendant -OH groups distributed in the molecule chains of cellulose (Fig. 2c, d) [60]. The -OH groups stabilized hydrogen bonds and the β-1,4-linkage stabilized van der Waals forces built a chair conformation for the crosslinking networks of cellulose. Particularly, the inter- and intramolecular -OH groups in the repeat unit endow the cellulose with tunable physicochemical properties as a result that -OH groups have high chemical reactivity in the reactions of esterification, condensation, oxidation, reduction and substitution.

2.2. Scalable engineering the architecture of nanocelluloses

2.2.1. CNFs

There are enhanced interactions between nanofibrillated celluloses and surrounding species, such as hydrophilic or hydrophobic molecules, organic or inorganic small molecules, nanoparticles, and even the biological materials [61–68], endowing the biosensors with high biomedical performance for disposal high amounts of contamitants. Generally, nanofibrillated cellulose is synthesized using pulps as the raw material via the high-pressure homogenization. Other methods such as high-speed mixing [69], cryo crushing [70], high-intensity ultrasonication [71], and steam explosion [72,73] have also been investigated. Nevertheless, these processing strategies are so complex that they cannot be applied in industrial mass production. The versatile characteristics of

different substrates, including broad resource of raw celluloses, low cost and relatively mature processing technology have endowed the nanofibrillated celluloses with diverse derivatives. Higher plants and diverse algae, fungi, bacteria, and animal, tunicate can be used as the substrates to fabricate nanofibrillated cellulose, especially cellulose nanofibers [74–81]. As sodium chloride is used to remove lignin and potassium hydroxide is used to remove a large amount of hemicellulose in the chemical purification methods for removing the matrix from wood, the nanofiber lines of intracellular cellulose can be clearly shown [81].

Mimicking biomineralization for the synthesis of new structural materials has aroused considerable interests from academics and industry. A variety of biomolecules, including proteins, DNA and peptides have been applied as templates for the fabrication of diverse functional materials by using technically more feasible components and operations [82–85]. Cellulose based aligned assemblies consisting of exfoliated graphene and nanofibrillated cellulose was generated during the growth of graphene monolayers (Fig. 3a). The fabricated biomimetic composites exhibited good tensile mechanical properties (Young's modulus: 16.9 GPa, ultimate strength: 351 Mpa) [86]. Linder et al. constructed novel biomimetic nanocomposites derived from the native nanofibrillated cellulose, the exfoliated graphite and proteins (Fig. 3b). Specifically, protein molecules contained hydrophobic block were linked to a cellulose-binding block and graphene through genetic engineering. The biomimetic nanocomposites displayed outstanding mechanical properties. The modulus and strength of the generated biomimetic composites are as high as 20.2 GPa and 278 MPa, respectively as a result of the bifunctional protein molecules [87]. Evaporation-induced self-assembly is also an effective way for the preparation of biomimetic nanocomposites. For example, nacre-mimetic clay/poly(vinyl alcohol) composites with the thickness of several centimeters were assembled by the lamination of monolayer films (Fig. 3c). There were approximately 10^6–10^7 aligned clay nanoplatelets in the bulk plates, which were exfoliated by the poly(vinyl alcohol) macromolecule chains. Despite the exposure to humidity, the resulting bulk plates still had high stiffness (25 GPa) and high strength (220 MPa) [88].

Ordered porous nanostructures of cellulose fibers play vital roles in the sensitive detection of diverse proteins. Chemical modifications are highly efficient for the improvement of the regularity of ordered porous nanostructure [89,90]. As illustrated in Fig. 4, Walther and coworkers reported novel topographically complex hydrogels based on a facile reverse templating approach, in which nanoscale building blocks of nanocellulose fibers were self-assembled into mathematically defined pore geometries. It provided a versatile way of generating structured cellulose based hydrogels with gel-like dispersions of cellulose and chitin nanofibrils in water.

With regards to the construction of nanofibrillated cellulose based composites, the pursuit for high biosensing performance is governed by the used compatibilizer, as well as the selected reaction ways (Fig. 5). The compatibilizer, also called an emulsifying agent, is a type of polymers or micromolecules used to increase the compatibility of different phases and the bonding strength of the interface. The introduction of the multifunctional compatibilizer (diblock copolymer) into the nanofibrillated cellulose based composites can decrease the interfacial tension, increase the dispersity, the mechanical properties and the stability of the hybrids, contributing to an ideal biosensor with good reusability and stability. Despite that the grafting process of polymer can be flexibly controlled, chemical modifications through silane treatment and maleation of the polymer and the cellulose fiber are mature approaches in biomedical application so as to greatly enhance their intrinsic reactivity.

2.2.2. BNCs

Bacterial nanocelluloses are fascinating building blocks for advanced bio-based devices and biocompatible injectable devices. In addition to being the dominant sector of cell walls, bacterial nanocelluloses are often secreted by synthetic cellulose fibers of several bacterial species under specific culturing conditions. Typically, bacterial nanocellulose can safeguard the survival of the basic bacteria. Bacterial nanocellulose can be used as a barrier to UV light because of the conjugated structure existed in its crosslinking network. The conjugated structure can effectively absorb UV light to protect the bacterial nanocellulose from UV radiation. Besides, they can protect themselves from fungi, yeasts and other organisms [71]. Bacterial nanocellulose is obtained by the cultivation of suitable bacteria in carbon and nitrogen containing nutrient solution for several days. The choice of suitable carbon resources play vital role in the yield of the generated bacterial nanocelluloses. The commonly used carbon resources include glucose, fructose, galactose, sucrose and mannitol, etc. The organic and inorganic nitrogen resources are involved for the cultivation of bacterial nanocelluloses. The commonly used organic nitrogen resources include corn pulp, peptone, yeast extract and beef paste, etc. The commonly used inorganic nitrogen resources include ammonium sulfate and ammonia, etc. *Acetobacter G. xylinus* species is the most frequently used bacteria for the production of

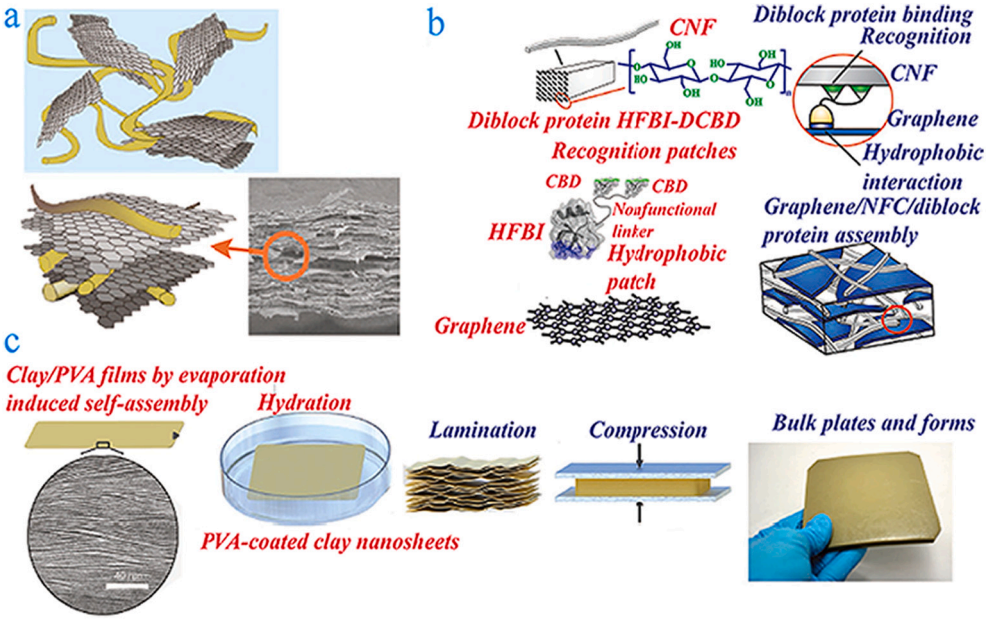

Fig. 3. Biomimetic synthesis of cellulose-based biosensors. a) Exfoliated graphene embedded in nanofibrillated celluloses. Reproduced with permission from ref. [86]. b) Biomimetic nanocomposites derived from the native nanofibrillated cellulose, the exfoliated graphite and proteins. Reproduced with permission from ref. [87]. c) Evaporation-induced biomimetic nanocomposite consisting of clay nanoplatelets and poly(vinyl alcohol) macromolecule chains. Reproduced with permission from ref. [88].

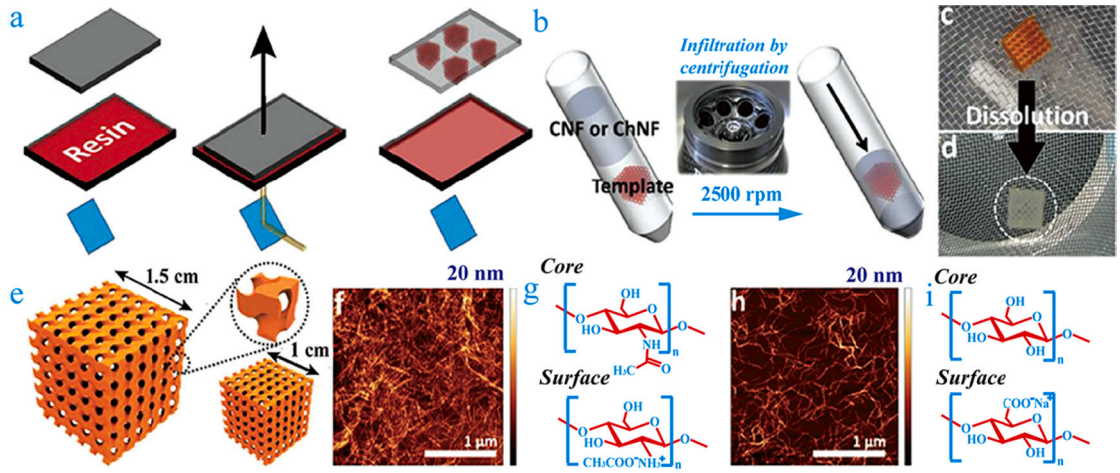

Fig. 4. (a) Fabrication process of cellulose nanofibers template hydrogels based on lithographic printing, (b) separation of cellulose nanofibers from the template by centrifugation and (c, d) removal of the template via dissolution treatment, (e) the generated scaffold skeleton, (f) the corresponding AFM images of the cellulose nanofibers, and (g) its chemical structure. Reproduced with permission from ref. [89].

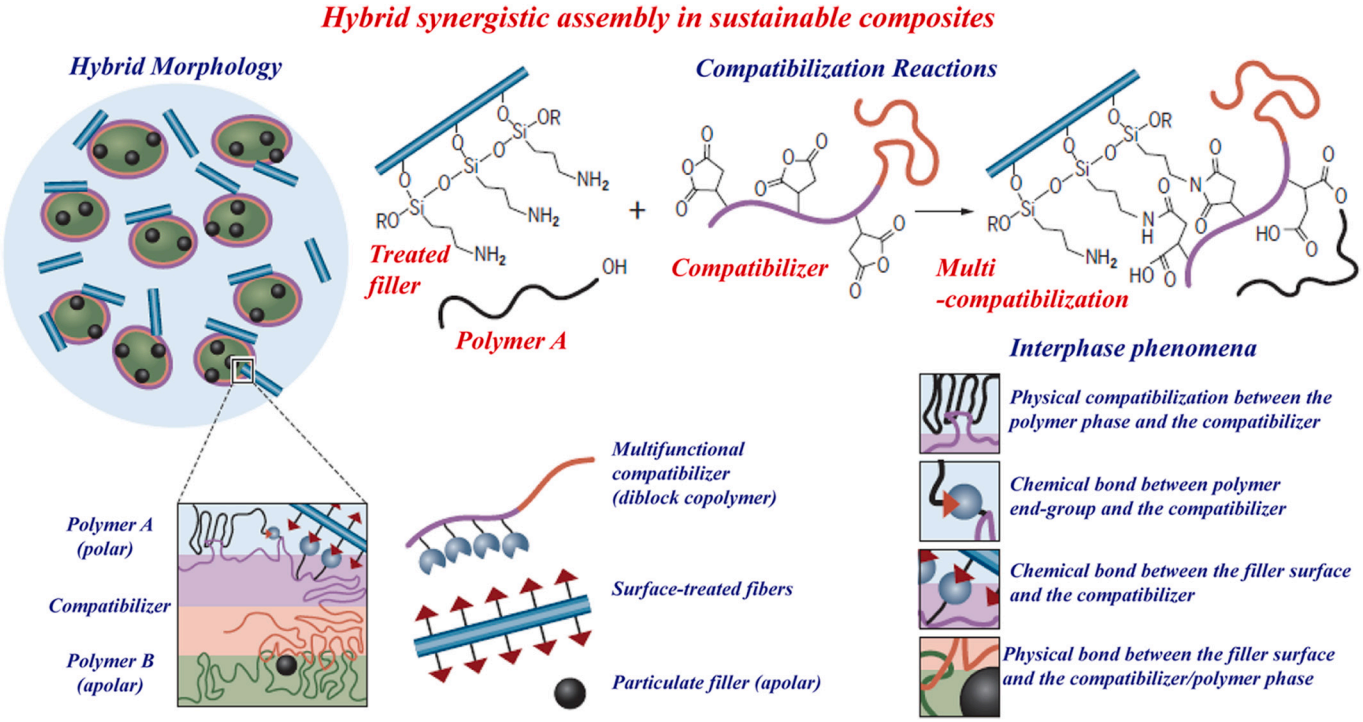

Fig. 5. High cost-performance strategies of hybrid synergistic assembly of nanofibrillated derived nanocelluloses. Reproduced with permission from ref. [50].

bacterial nanocellulose. Biosynthesized bacterial nanocellulose has the advantage of high purity and stable 3D nanofibrous structure, which endows it with great potential for protein detection. The bacterial nanocellulose with high purity can ensure that no foreign impurity would be introduced into the detection system of proteins. The stable 3D nanofibrous structure of the bacterial nanocellulose can ensure the biosensor with good reusability and stability.

The molecule structure of bacterial nanocellulose is similar to that of nanofibrillated cellulose. There are numerous microfibrils in the nanostructure of bacterial nanocellulose. The microfibrils embedded in the backbone of bacterial nanocellulose can gather together into twisted ribbons. The generated ribbons have the size of 20–50 nm and intertwine with each other. Therefore, the formed bacterial nanocellulose can reflect the size of the used raw materials [91–97]. Besides the common performance of cellulose, bacterial nanocellulose possesses several particular features, which includes high specific surface area, high stiffness and tensile strength, low density as well as low thermal coefficient of expansion [98–101]. Its particular nanostructure generally contributes to fast detection reaction in the analysis of diverse proteins.

Introducing polymer networks into the nanostructure of bacterial nanocelluloses can adjust its chemical and physical properties such as crystallinity, hydrophilicity, hydrophobicity, mechanical or thermal property, depending on the performance of the incorporated polymers. The grafting process is often initiated by UV-light or γ-radiation. The strong oxidizers such as persulfates and azobisisobutyronitrile, etc. can also initiate the grafting process. In the approach of grafting of monomers containing functional groups such as carboxyl, acetyl, hydroxypropyl, amine, or amide, the chemical and physical properties of the

composites are flexibly adjusted after grafting a distinct network structure. Recently, Catchmark et al. fabricated a novel bacterial crystalline nanocellulose through acid hydrolysis [102]. Diverse fiber morphologies, geometrical dimensions, crystal structure and mechanical strength can be realized by controlling the amount of polysaccharides in the growth of culture medium (Fig. 6). Bacterial exopolysaccharides can tune the bundling of cellulose microfibrils in the formation process of bacterial cellulose, leading to the generation of particular bacterial crystalline nanocelluloses with excellent physicochemical properties. Therefore, enhanced sensitivity of biosensors onto these bacterial crystalline nanocelluloses can be achieved by the polymer-modification strategy.

The inherent vast amounts of -OH distributed on the molecular chain of bacterial nanocelluloses enhance its various biomedical applications [103]. With *Acetobacter xylinum* as the pure culture, Hu and coworkers firstly reported a type of ultrastrong and ultratough bacterial nanocellulose film [104]. As displayed in Fig. 7, the fabricated densely packed film had hierarchical cellulose nanofibrils alignments. Numerous long-chain cellulose molecules are stacked together, leading to the formation of subfibrils. Soon afterwards, nanofibril bundles are obtained though the alignment of subfibrils. It was found that the bacterial nanocelluloses demonstrated superhigh tensile strength (≈1.0 GPa) and toughness (≈25 MJ m^{-3}). Furthermore, the formed bacterial nanocellulose film is very soft and can be folded into arbitrary shapes, which paves the way to enabling functionalities in mechanical, electrical, fluidic, photonics, and biocompatible applications.

2.2.3. CNCs

In principle, CNCs possess almost all of biophysicochemical features, for example biodegradability, biocompatibility, low density, green and environmental protection, high toughness, reproducibility, optical transparency, high thermal stability, gas impermeability, modifiable surface, as well as improved mechanical properties. CNCs generally present highly crystalline nature and exhibit the morphologies of needles or rods with at least one dimension <100 nm. Diverse raw materials can be used for the fabrication of CNCs [105–108]. The raw materials used in the preparation of the CNCs have significant importance on the geometrical dimensions of the final products. In general, the width of CNCs has certain level (about a few nanometers). Nevertheless, the length of CNCs has long has short, ranging from tenths of nanometers to several micrometers. Modifying the surface of nanocelluloses with grafted polymers can greatly enhance the removal ability for extended contaminants [109–112]. Not only can polymer-cellulose composites stabilize the network of nanocellulose, but they also can adjust its hydrophilic or hydrophobic characteristic [113]. There are mainly three ways to realize the polymer grafting, namely grafting-to, grafting-from, and grafting-through (Fig. 8). With regards to the grafting-to method, linking the end group of the polymers or peptides with linkable functionalities to the –OH groups of the molecule chains of cellulose can generate a great deal of polymer-cellulose composites. With regards to the grafting-from method, an initiator is necessary to firstly functionalize the cellulose. Subsequently, vast numbers of monomers are assembled through polymerization, leading to diverse polymer-cellulose composites with high densities and polydispersity. In the grafting-through approach, the cellulose molecule chains are firstly modified with polymerizable radicals, such as vinyl group, acetenyl group. Then comonomers are added into the modified cellulose and contribute the polymerization of the mixture. Among all these approaches, grafting-from is mostly used in the synthesis of nanocellulose based composites, which involves ring-opening polymerization [114–117], radical polymerization [118–121], and colloidal stability method [122,123]. The formed particular nanostructure generally contributes to fast sensing reaction in the detection and analysis of diverse proteins.

The crystalline regions can be liberated by the hydrolysis of the semicrystalline cellulosic fibers under the catalysis of mineral acids, leading to the generation of CNCs. Specifically, polysaccharide molecules bound at the surface of fibrils are initially removed during the chemical process. Then, the amorphous regions in the semicrystalline cellulosic fibers supply a suitable place for the degradation reaction, resulting in the formation of rods-shaped crystalline cellulose sections. As the hydrolysis proceedes, the glucose molecule chains are gradually depolymerized, resulting in the dilution of the acidic mixtures. Highly pure CNCs are subsequently produced after the removal of the residual acids and impurities through centrifugation and extensive dialysis. Finally, stable and uniformly dispersed CNC suspension is formed by ultrasonification process. It should be noted that the strength and concentration of the used mineral acid play vital role in the nanostructure, and phase stability of the resulting mixture.

Acid hydrolysis of glycosidic bonds is the main process for the separation of CNCs. Acid hydrolysis can efficiently separate the crystalline domains and degrade the amorphous regions, leading to the assembly of diverse CNCs with different geometry, crystallinity index, and aspect ratio [27–30]. Besides, the degree of polymerization for the resultant CNCs is determined by the used cellulose source [31–33]. It was

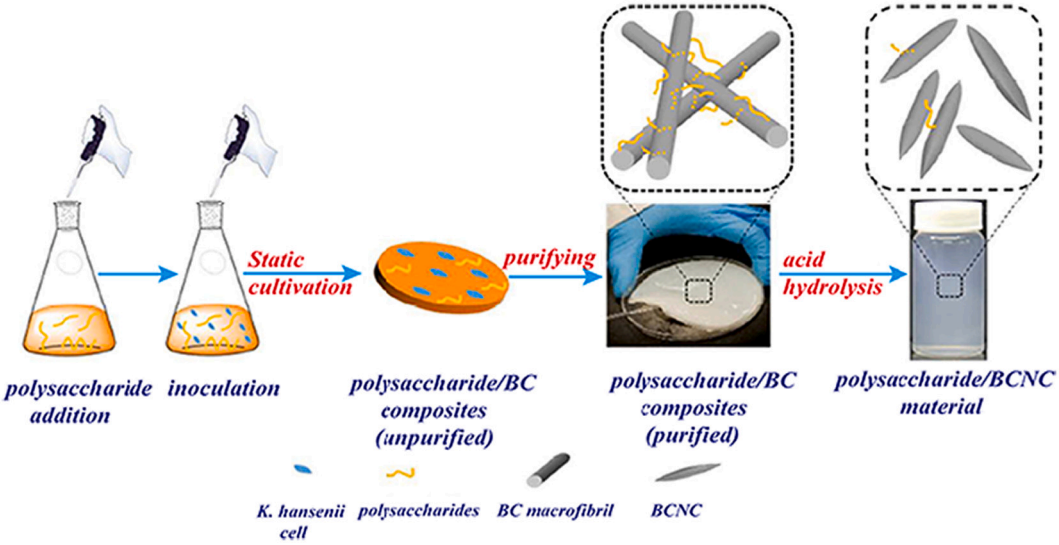

Fig. 6. Production process of polysaccharide/bacterial cellulose composites and polysaccharide/bacterial crystalline nanocellulose. Reproduced with permission from ref. [102].

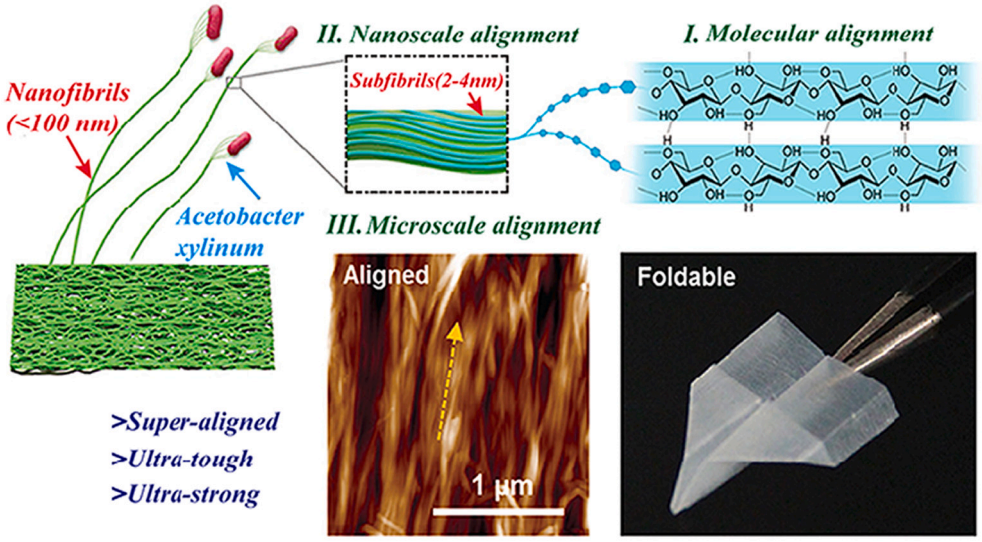

Fig. 7. Fabrication process of highly flexible cellulose film. Reproduced with permission from ref. [104].

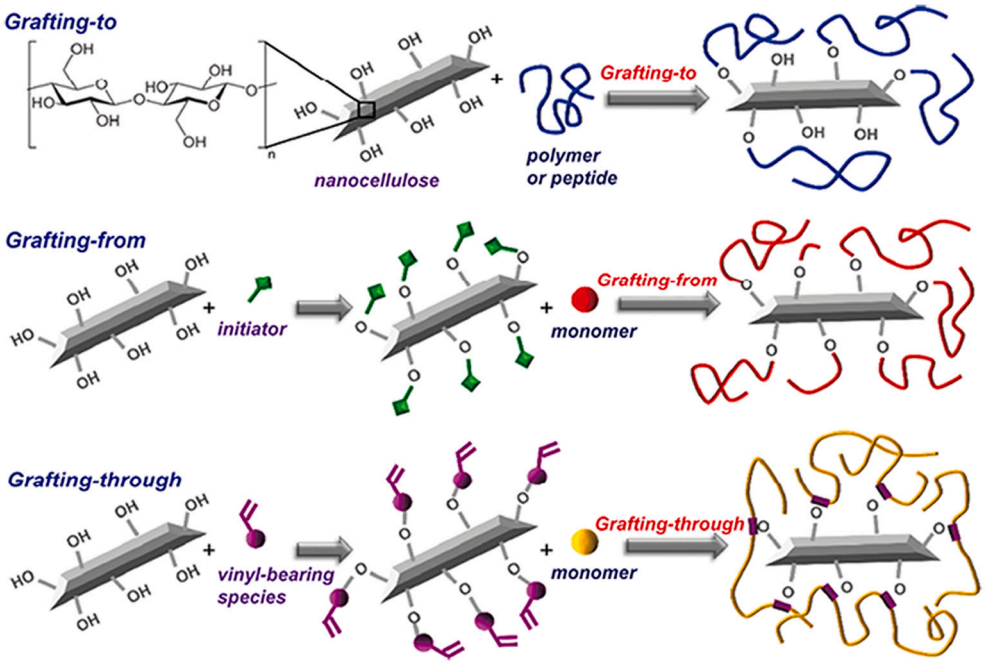

Fig. 8. Schematic illustration of grafting polymer on the surface of cellulose, including grafting-from, grafting-to, and grafting-through approach. Reproduced with permission from ref. [113].

reported that a degree of polymerization value can reach to 250,000 when using cotton as the raw material for the acid hydrolysis reaction [124]. The obtained hydrolysis products have the similar crystalline structure to the used raw materials [125–128]. H_2SO_4 as the most commonly used acid catalyst has the advantage of improving the dispersibility of reagent molecules in solvents, leading to the formation of stable cellulose suspension. In addition, numerous $–OSO_3$ groups can also endow the CNCs with enhanced sensing sensitivety for different proteins based on electrostatic adsorption. The typical example is the highly efficient adsorption of positively charged proteins by CNCs derived microfiltration membranes [129]. As shown in Fig. 9a and Fig. 9b, different modified CN samples (CN-1, CN-2, CN-3, CN-4, CN-5, CN-6, CN-7 and CN-8) with different crystal properties and morphologies can be obtained by controlling the reactant ratios (0.5,1, 1:1, 1.5:1, 2:1) and reaction time (0.5, 1, 1.5, 2 and 3 h), and the alkaline (NaOH) concentration (0.5, 1, 1.5 and 2 M) of the hydrolysis reaction [130].

Moreover, the unique crystalline properties would hardly be disrupted in the modification of CNCs using the above mentioned mature strategies [131,132]. Considering the large number of biodegradation strategies existing at present, the continuous decrease of these materials indicates that these materials are less worrying under long-term environmental exposure, bioaccumulation and nutrition transfer [133,134]. Besides, as the emerging of different facile design of diverse CNCs-based composites, it is more likely to replace carbon nanotubes with CNCs. Rational structural optimization can endow the CNCs with enhanced mechanical strength and selective absorption of pollutants [135–138]. As shown in Fig. 10, Hoare et al. fabricated a type of CNCs and poly (oligoethylene glycol methacrylate) derived hydrogels [139]. It was found that the mechanical strength of the hydrogels based on the physical incorporation of rigid rod-like CNCs into cross-linked molecular

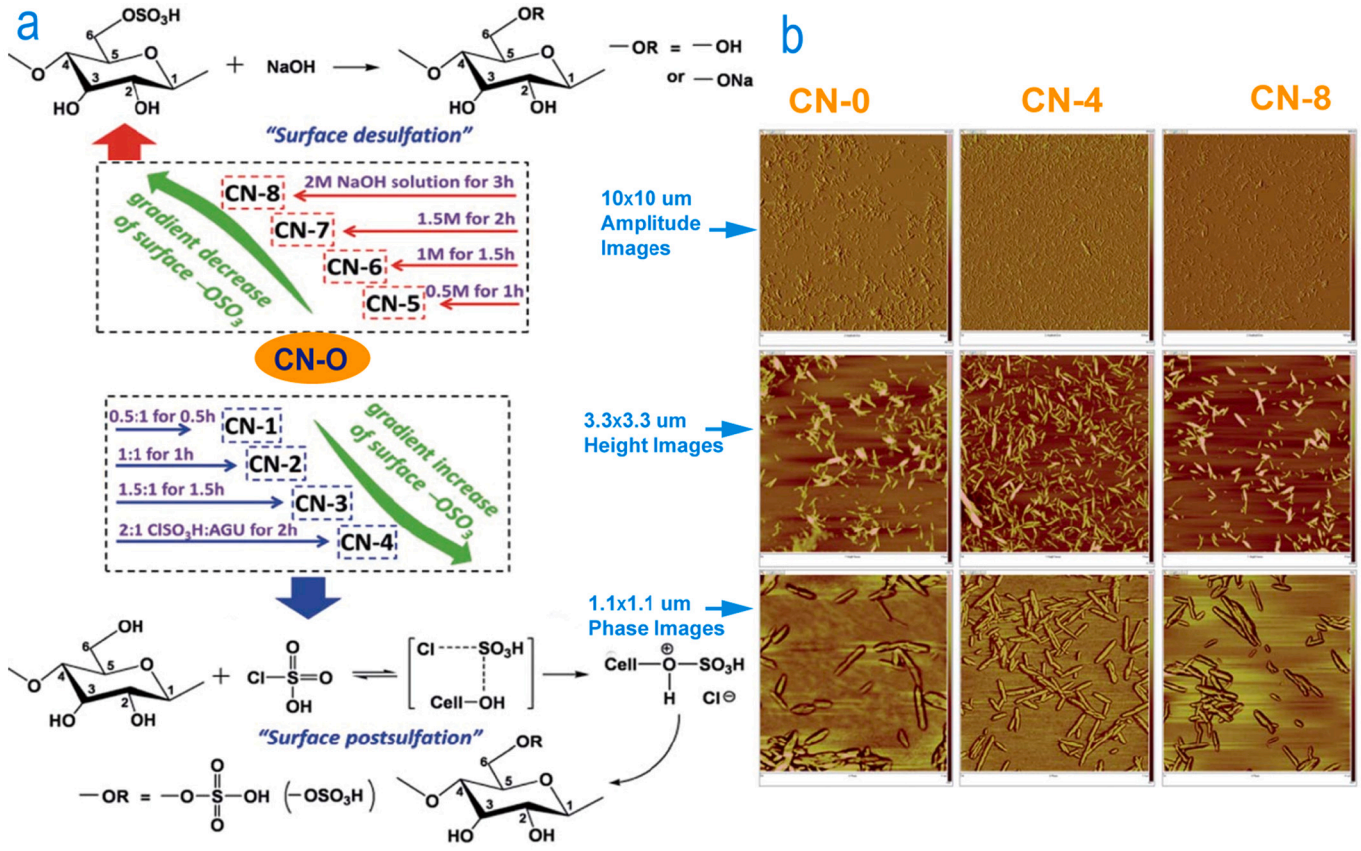

Fig. 9. (a) Chemical modification of CNCs by gradiented sulfonation. (b) AFM images of CN-0, CN-4, and CN-8. Reproduced with permission from ref. [130].

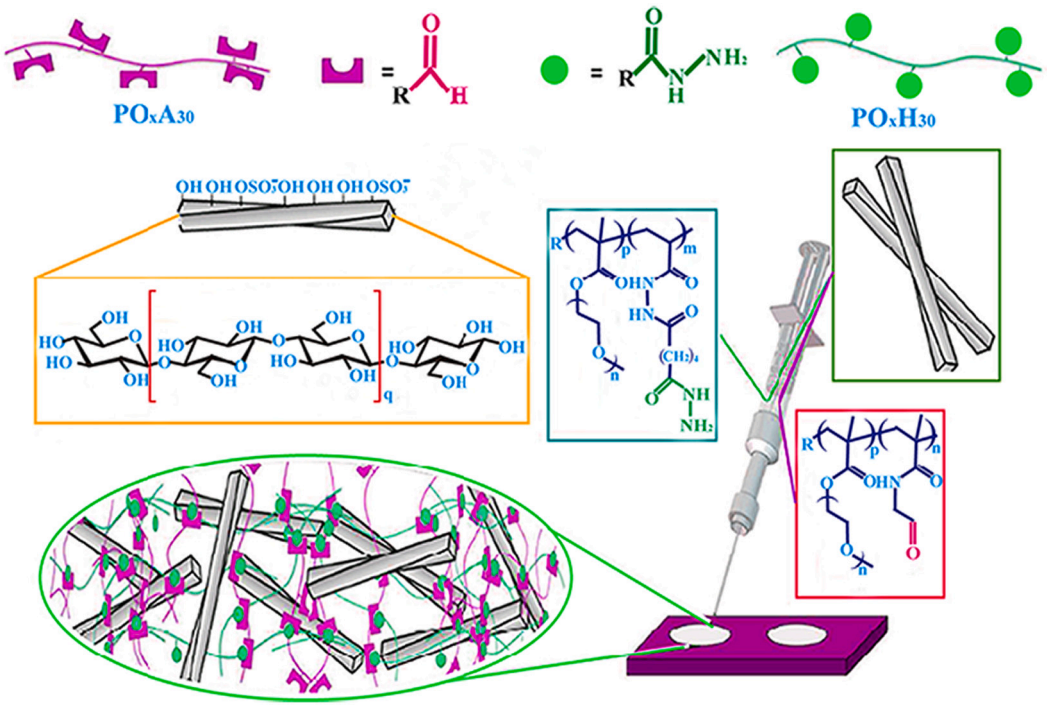

Fig. 10. Preparation process of CNCs and poly(oligoethylene glycol methacrylate) derived hydrogels. Reproduced with permission from ref. 139.

networks of poly(oligoethylene glycol methacrylate).

Esterification [140–143] and oxidation [144–146] routes are often used in the preparation of CNCs. Besides, a completely new approach based on HCl vapor hydrolysis was presented (Fig. 11a) [147]. Kontturi et al. found that cotton-based cellulose fibers could be rapidly hydrolyzed under the HCl vapor atmosphere, which can solve the common

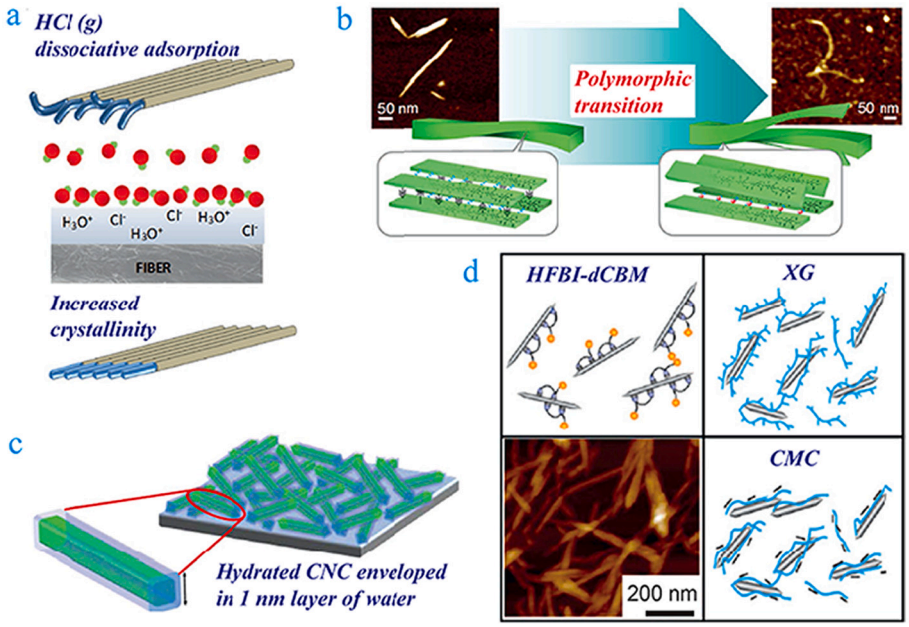

Fig. 11. (a) High-yield synthesis of CNCs through the simultaneous degradation and crystallization process via adsorption of HCl vapor. Reproduced with permission from ref. [147]. (b) Polymorphic transition induced detachment of individual CNCs via van der Waals bonding. Reproduced with permission from ref. [148]. (c) Abundant absorption of water vapor on polysaccharide decorated ultrathin CNC films. Reproduced with permission from ref. [149]. (d) Fabrication of tailored cellulose binding proteins and cellulose binding polysaccharides. Reproduced with permission from ref. [150].

difficulties in the preparation of CNCs, such as the tedious purification steps and the difficulties in acid recycling. In addition, high yield (>97%) of CNCs can be achieved in this approach. Besides, Salminen and co-workers reported that the immobilization of the cellulose nanocrastals on a solid substrate can result in detachment of molecular sheets or stacks of sheets, leading to polymorphic transition on individual CNCs (Fig. 11b) [148].

Similarly, abundant absorption of water vapor can be achieved by polysaccharide decorated ultrathin CNC films (Fig. 11c) [149]. Improving the processing performances of the native cellulose nanocrastals can extend its biomedical application. Nevertheless, its processing performances were impaired as a result of the existed surface charges. Fabrication tailored cellulose binding proteins and cellulose binding polysaccharides can overcome these difficulties (Fig. 11d) [150]. Even small fraction of proteins and polysaccharides (5–10 wt%) can improve the dispersibility of CNCs.

3. Protein sensing over nanocellulose-derived biosensors

The precise sensing of different small molecules, macromolecules, as well as various biomolecules in human life activities plays vital role in maintaining physiological homeostasis and protecting human from a variety of diseases [1–5]. The superiorities of high mechanical performance, tunable nanofibrous networks, high biocompatibility, low cytotoxicity, good durability and marketability have brought nanocelluloses to a mature biosensor field [3–8]. The world sensor market has grown at an astonishing rate. It is anticipated that the market value of the world sensor would reach $30 by 2025 under the driving force of the reinforced global production competition and the rapid progress of health care and environment protection [1,2]. Nanocellulose-derived composites exhibit good photonic, colloidal, piezoelectric and surface charicteristics, making them very outstanding sensors to detect diverse molecules, such as proteins, enzymes, glucose and cholesterol, etc. [29–34]

There are diverse types of nanocellulose-derived sensor platforms for protein detection, including photonic, piezoelectric, thermoelectric, photoelectric, photomagnetic, elastoelastic and thermoelectric, etc. depending on the collected signal form in protein detection [29]. Introducing dielectric materials with photonic crystal structures into the molecular skeletons of nanocelluloses can create a photonic crystal biosensor, which is made up of optical transducer, photonic crystal structure and detector [29,30]. Photonic crystal biosensor can particularly interact with light to provide high efficiency reflection at specific wavelengths. When using nanocellulose-derived photonic crystal as the biosensor for protein sensing, a biochemical covalent interaction between nanocellulose and the photonic crystal occurs, leading to a change in the effective refractive index and then a shift of the resonance wavelength peak, which is proportional to the concentration of the tested protein. Piezoelectric biosensor has the advantages of real–time, label-free transduction, simplicity and low price, which provides an important means for the direct sensing of the proteins through label free affinity interactions between the piezoelectric crystals and the proteins [31,32]. The vibrating behavior of piezoelectric crystals induced by the electric field, and the relationship between the change of the resonant frequency and the mass of molecules adsorbed or desorbed from the surface of the piezoelectric crystal are the basis of the transduction mechanism in piezoelectric biosensors.

The immobilization of protein molecules on the surface of nanocellulose-derived composites is critical for the design of a biosensor [33,34]. Once immobilized, the proteins will become inactivated to facilitate the sensing reaction. The choice of a suitable immobilization technique is determined by three aspects: the protein type, the nanocellulose-based transducer, as well as the physical-chemical environment. Generally, the immobilization methods in protein sensing fall into two patterns, namely physical (non-covalent) and chemical (covalent). With regard to the physical or non-covalent immobilization techniques, no chemical bonds are created during the attachment of proteins to surface of the nanocellulose-based transducer. The commonly used physical or non-covalent immobilization techniques involve physical adsorption and physical entrapment such as sol-gel method, electropolymerization and microencapsulation [151–155]. With regard to the chemical or covalent immobilization techniques, strong chemical bonds (covalent binding or covalent linking) are formed between the surface of the nanocellulose-based transducer and the functional groups of the proteins. The covalent binding mechanism is based on the interaction between the reactive groups on the surface of the nanocellulose-based transducer and the functional groups of the proteins. The covalent cross-linking mechanism is based on the formation of covalent cross-linkages between two different molecules, namely the nanocellulose-based transducer and the proteins [168–173].

To set up a high-performance and useful biosensor system, several relevant certain static and dynamic requirements are required. Sensitivity is an important parameter for the evaluation of biosensor performance [160–165]. It indicates the minimum amount of proteins that can be correctly identified in minimum steps and in low concentrations to verify the presence of proteins in the sample. The limit of detection is also called detection limit, which usually indicates the three times the smallest concentration or mass generated by the matrix blank and can be detected with a specified level of confidence. Stability is also one of the important parameter for protein sensing system when continuous detection is required. Stability indicates the ability to withstand the environmental disturbances inside and outside the biosensing device. The sensitivity and accuracy of nanocellulose-based sensors is to a great extent controlled by the origin of the celluoses, the assembly methods and chemical or physical modification methods employed [151–157].

Human neutrophil elastase (HNE) belongs to a serine protease and appears inevitably in the neutrophils (immune cells) of a broken body, causing pain and suffering to humans and animals. It was found that the peptide conjugated CNCs exhibited highly sensitive sensing activity for HNE [151]. The involved biosensors were assembled by the diazotization of succinyl-Ala-Ala-Val-p-nitroanilide with glycine-cellulose, leading to the formation of CNCs, and then conjugation with different peptides (Fig. 12a, b). There were three functions of CNCs in the as-synthesized biosensors: immobilization of peptides on the surface of the hybrids; increase the specific surface area of the hybrids; increase the sensitivity of the hybrids. The sensing mechanism over the peptide conjugated CNCs was based on the generated colored dye (para-nitroaniline). In detail, pNA was generated in the hydrolyzation of the peptide para-nitroanilide analog, which subsequently reacted with NEDH or DACA, leading to the color response of the CCN sensor. The concentration of HNE was determined by the relationship between the detectable diazotized color complexes (a colored dye) and the para-nitroaniline). As a result of the high specific area of the prepared CNCs (131 m^2 g^{-1}), the sensitivities of the resulting tripeptide/CNC biosensors were 10–20 folds higher than that of the tripeptide/paper counterpart. Because of the high specific surface area, the detection range for HNE over such tripeptide/CNC biosensors can be extended to other elastases, leading to the successful improvement of the sensitivity with trace amount (as low as 50 mU mL^{-1} wound fluid). Besides, Edwards continued to discover novel CNCs-derived sensors for HNE sensing with lower sensing limit (0.1 mU mL^{-1}) [152]. The biosensor was fabricated by immobilizing the glycine-esterified fluorescent peptides on the crosslinking networks of CNCs. In addition to HNE, the prepared elastase sensors had significant function against porcine pancreatic elastase (PPE). In detail, the sensitivity of the tripeptide/CNC complex toward HNE in the mixtures of sodium phosphate buffer solution (0.1 M) and NaCl (0.5 M) was 5 folds higher than that of single tripeptide. Immobilizing different peptides onto the suface of CNCs could bring different sensing activity fot the resultant biosensors. (Fig. 12c) It was deteced that the detection limit of the tripeptide/CNC and tetrapeptide/CNC complexes was 30 and 50 mU mL^{-1} toward HNE test (Fig. 12d), respectively, funther demonstrating the vital roles of the structure of the peptide-cellulose conjugates in the activities of the biomarkers.

Introducing more detection sites into the backbones of CNCs can endow the biosensors with high specific surface areas, leading to rapid responses to different proteins. Schyrr and *co*-workers reported a functional biomedical scaffold using the functionalized porous CNCs and

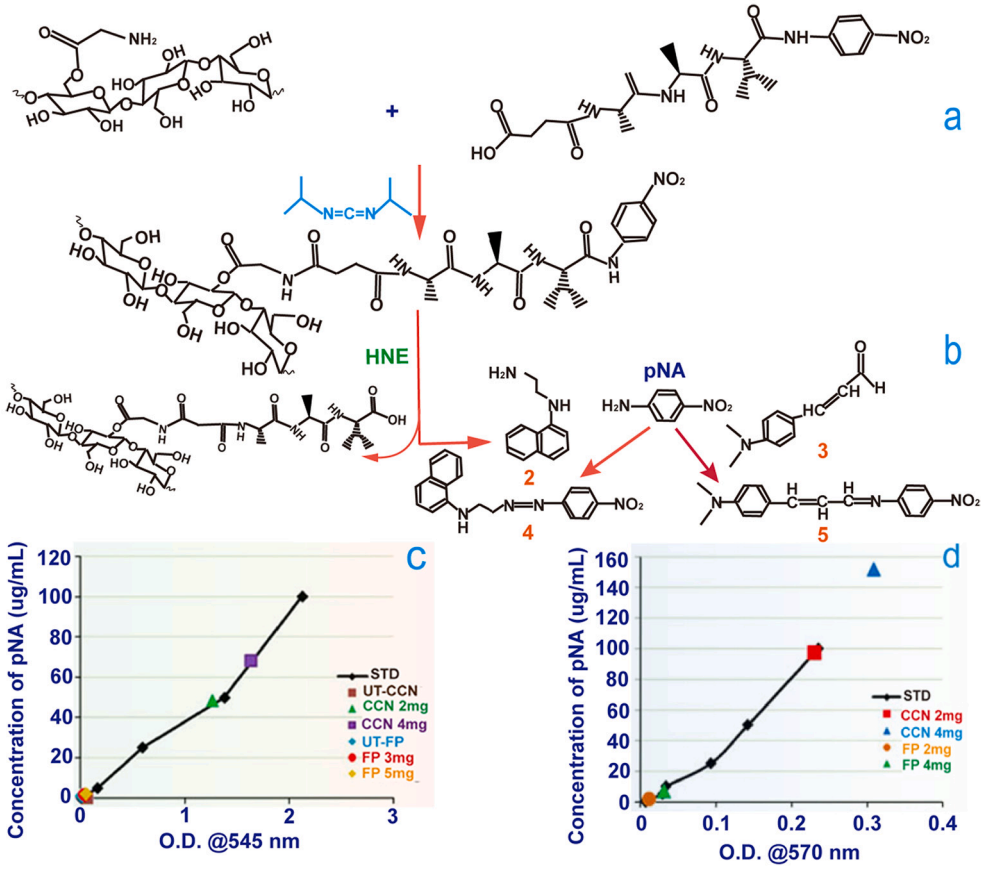

Fig. 12. (a) The preparation of the peptide conjugated CNCs. (b) The sensing mechanism over the peptide conjugated CNCs. The relationship between the concentrations of (c) the detectable diazotized colored dye, (d) the Schiff base-derived colored dye and the para-nitroaniline. Reproduced with permission from ref. [151].

polyvinyl alcohol (PVA) as the raw materials [153]. The sensing mechanism of the fluorogenic peptide is based on a Förster resonance energy transfer (FRET) technique. During the immobilization process, the compound 5-carboxyfluorescein as a fluorophore was linked to a specific peptide sequence through a quencher (DABCYL). The fluorescence in the molecular structure of 5-carboxyfluorescein is suppressed to DABCYL by means of FRET. When the peptide sequence was cleaved by a protease, the DABCYL quencher was released. But 5-carboxyfluorescein molecule was still immobilized on the scaffold, and the fluorescence was turned on. In this case, the existence of the protease molecule could be detected by testing the enhancement of the emission intensity of the sensor system. The scaffold had high efficiency for fluorescence-based protease sensing depending on the Michael addition reaction of the –OH groups on the surface of CNCs and 2-(acryloxy)ethyl (3-isocyanato-4-methylphenyl)carbamate (Fig. 13a,b). After the PVA/CNCs scaffold was linked with luorogenic peptide, the formed nanocomposite film biosensor had rapid response to trypsin under different pH conditions, even when the concentration of the tested trypsin was as low as 250 μg mL^{-1} (Fig. 13c). The peptide was linked by the fluorophore, as well as the compound 4-(4′-dimethylaminophenylazo) benzoic amide (DABCYL). With regard to the enzymatic sensing, the detection limit of the formed scaffold could reach as low as 20 μg mL^{-1} trypsin (Fig. 13d).

Monitoring the reduction of sugars generated from the hydrolyzation of enzymes is considered to be a flexible approach for enzyme sensing, which is highly accurate and reliable. The disadvantage of this approach is that extra instruments, for example, the UV–vis spectrophotometer is required [154]. Cerclier and coworkers fabricated a new biopolymeric material consisting of CNCs and xyloglucan (XG) for enzymatic detection depending on the structure change-induced color change of the biosensor (Fig. 14a) [154]. In the detection experiment, when a streak of incident light rays hit the interface of the air-nanocomposite film, the incident light will be reflected and partly be refracted. The refracted incident light will transmit into the biosensor film. Soon afterwards, the transmitted light enters into a special instrument with the interface of silicon and film, it will be reflected and partly be refracted again. The intensity of the reflected light in the air–film interface is different from that in the film-silicon interface. The intensity difference value between the both reflected light is dertermined by the specific visible color (wavelength) (Fig. 14c,d). As a result, adjusting the film thickness in the film-silicon interface can achieve different feedback of colors. In the specific enzyme detection process, different chemical reaction will occur between the as-synthesized film and the enzyme molecule. In this case,

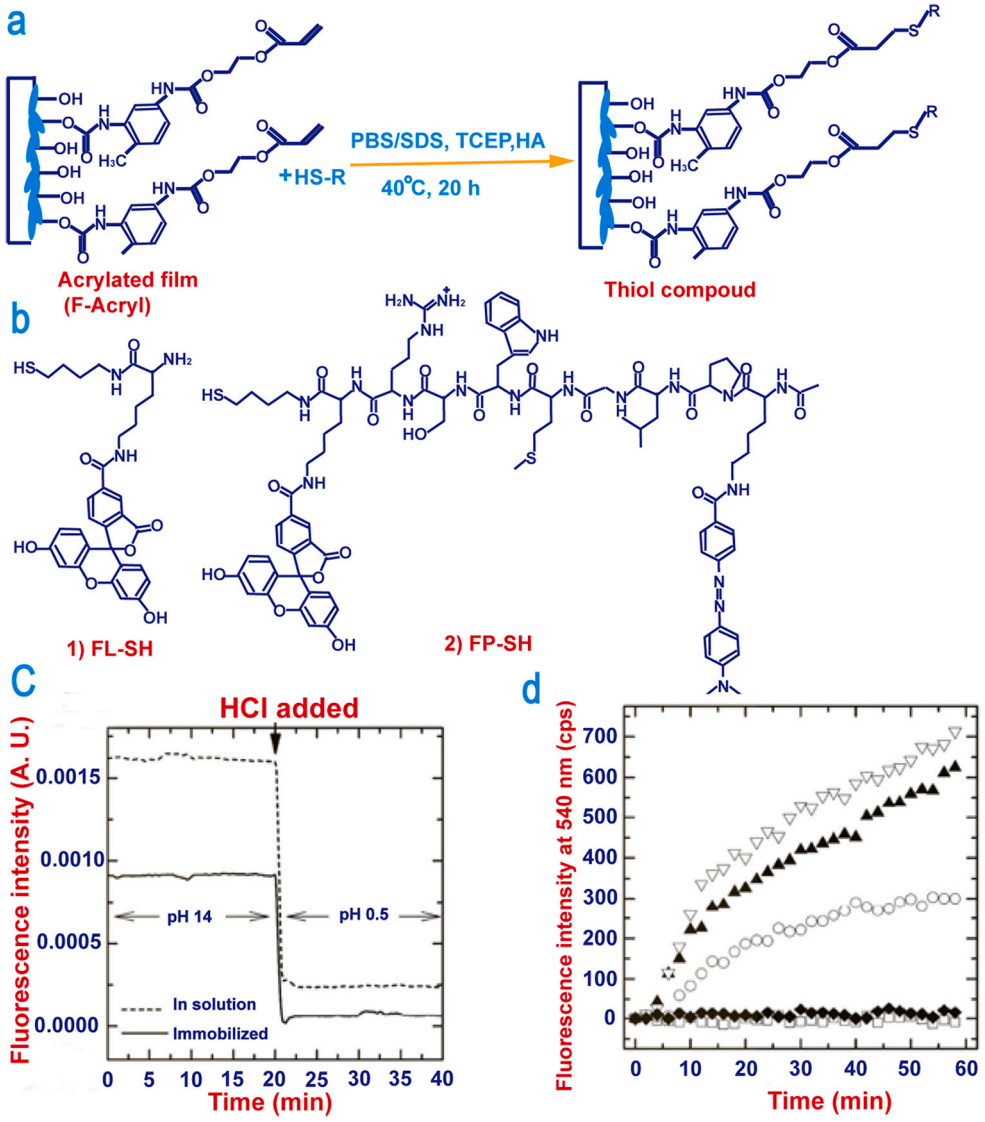

Fig. 13. (a,b) Michael addition reaction of the –OH groups on the surface of CNCs and 2-(acryloxy)ethyl (3-isocyanato-4-methylphenyl)carbamate. (c) Fluorescence spectra of the porous CNCs/PVA nanocomposite films under different pH conditions. (d) Fluorescence spectra of the porous CNCs/PVA nanocomposite films in the presence of trypsin. Reproduced with permission from ref. 153.

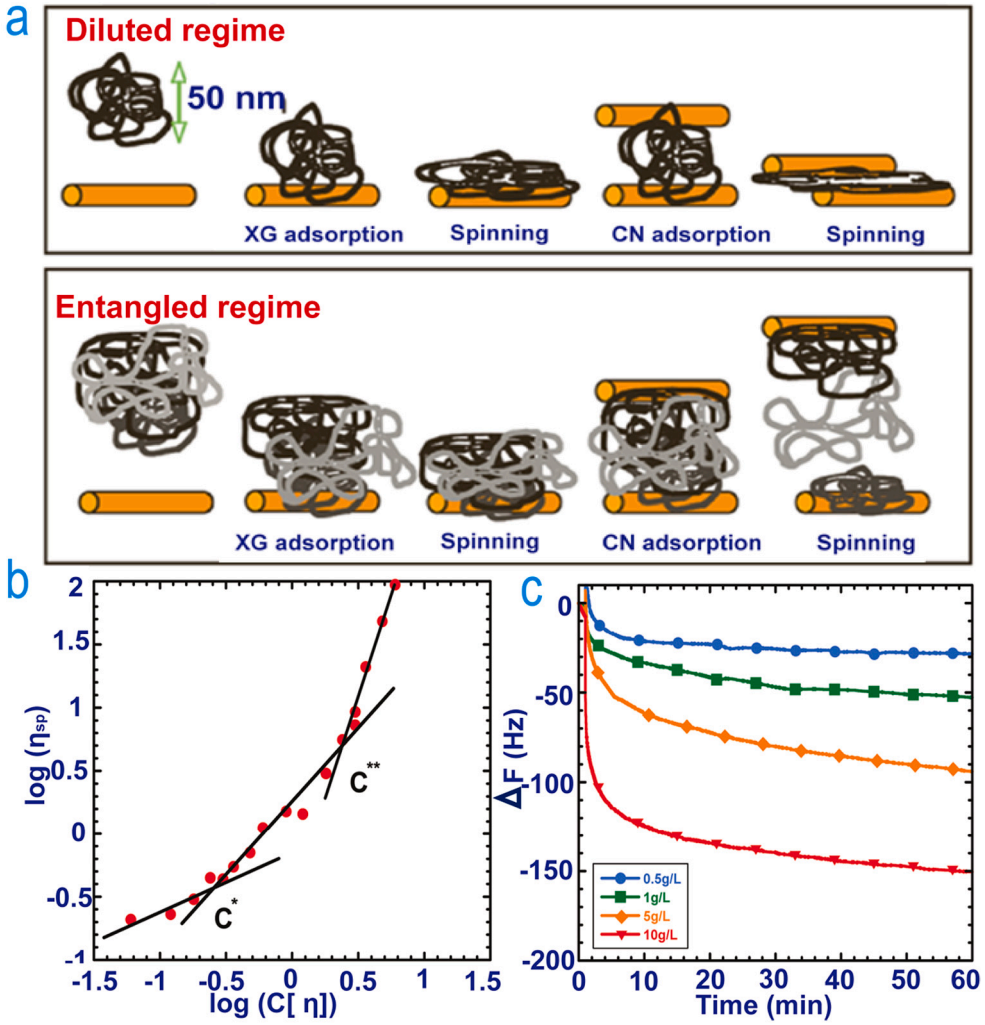

Fig. 14. (a) Schematic illustration the interaction between the crosslinking networks of CNCs and XG. (b) Relationship of the specific viscosity (η) and concentration (C), and (c) the corresponding kinetics. Reproduced with permission from ref. [154].

the biosensor film would be gradually hydrolyzed, leading to the consumption of the film and the reduction of the film thickness. Therefore, rapid responses would be detected as a result of the color change.

The exploitation of rapid, convenient and sensitive sensing technique for hydrolytic enzymes can significantly increase the marketing competition and opportunity of the biosensors. To achieve this goal, Cerclier and coworkers fabricated new colored multilayered thin films using CNCs and XG as the constitutional unit for highly-efficient enzyme detection (Fig. 15a) [155]. The prepared colored CNCs/XG thin films were semi-reflective, and easy to be degrated by the cellulase, leading to the color change of the film. The sensing mechanism over the $(CN/XG)_4$ multilayered thin films is based on the gradual degradation of the thin films by a cellulase mixture because that both cellulose and the XG molecules are sensitive to cellulolytic enzymes. Detailedly, the hydrolysis of the thin films can cause the reduction of the thickness of the layer, in which the activity of the enzyme can be tested by the naked eye according to the color changes in a span of few minutes. As the CNCs/XG thin film was mixed with cellulase, the film color would fade as a result of the degradation of the XG unit in the film by the coexisting cellulolytic enzymes (Fig. 15c). The starting color of the CNCs/XG thin film was determined by its initial thickness (Fig. 15b,d). This fading process could be seen by the naked eyes (Fig. 15c,e). This method not only had the advantages of ease operation, rapid and reliable, but it also could quantitatively analyze the concentration of enzymes by the precise control of film thickness and structure (Fig. 15b), which could be expanded to the sensing of other biomass-hydrolyzing enzymes.

A similar method was used for the xylanase sensing based on new multilayered thin films with CNCs and cationic xylans (CX) as the raw materials by spin coating (Fig. 16a) [156]. The fabricated multilayered thin films (CNCs-CX) were formed by electrostatic-induced layer-by-layer self-assembling technique, in which the layers of the thin films were as high as 10 (Fig. 16b). The thickness of the CX conjugated CNCs thin film was reduced after the film was exposed to the xylanase solution, in which xylans were gradually hydrolyzed (Fig. 16c, d). The enzymatic detection mechanism is based on the colored multilayered thin films (CN-CX). When the thin films are submitted to enzymatic hydrolysis of xylans, the thickness of the film would reduce, leading to a visible color change. The sensitivity of the test was evaluated in comparison with a usual colorimetric measurement, which depends on the detection of reducing sugars set free by enzymatic hydrolysis. The xylanase enzymatic activities was determined by a colorimetric measurement, depending on the detection of the set free of the reducing sugars under the hydrolyzation of the xylanase (Fig. 16e). The proposed method opens up new opportunities for the detection and analysis of xylanase and other proteins. (See Fig. 17.)

Laccase is a type of multicopper oxidase. The previous detection of laccase lied in its catalytic activity. The involved sensing method had many limitations, for example, complex environmental parameters were always needed, such as the required electron acceptors (molecular oxygen). In order to break through the limitation of the previous detection

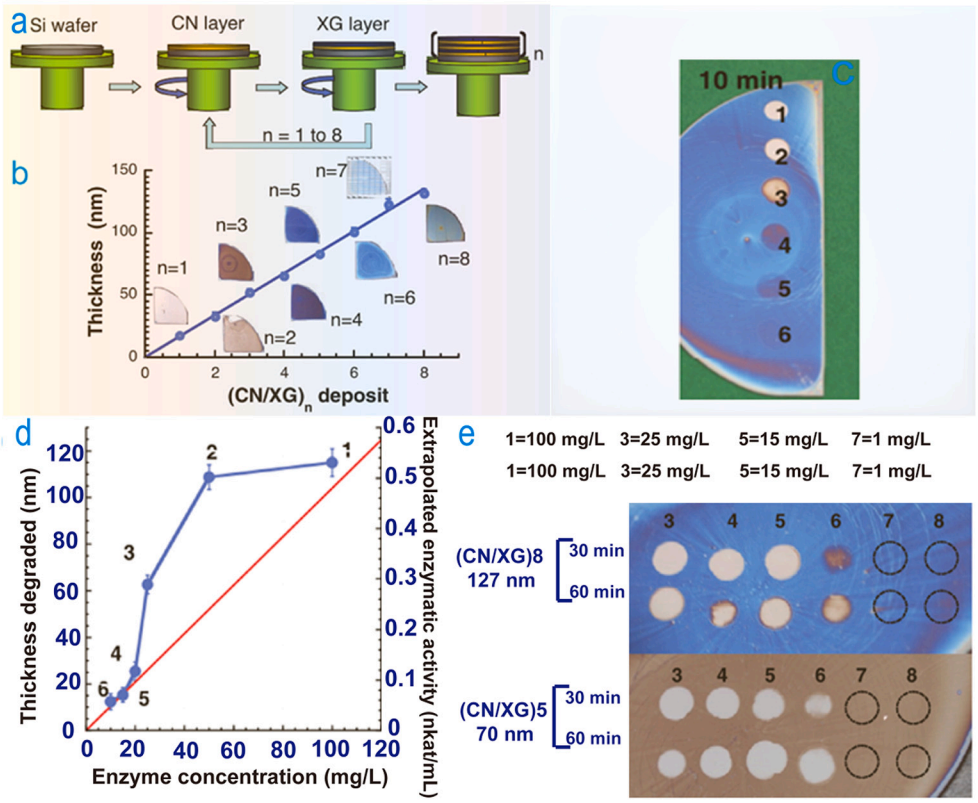

Fig. 15. (a) The preparation process of the colored CNCs/XG thin films. (b) The color changes of the colored CNCs/XG thin films by naked eyes. (c) The degradation images of the colored CNCs/XG thin films caaused by the coexisting cellulolytic enzymes. (d) Relationship of the film thickness of CNCs/XG and the concentration of enzyme. (e) degradation images of the colored CNCs/XG thin films in different enzyme solutions for different treatment time. Reproduced with permission from ref. [155].

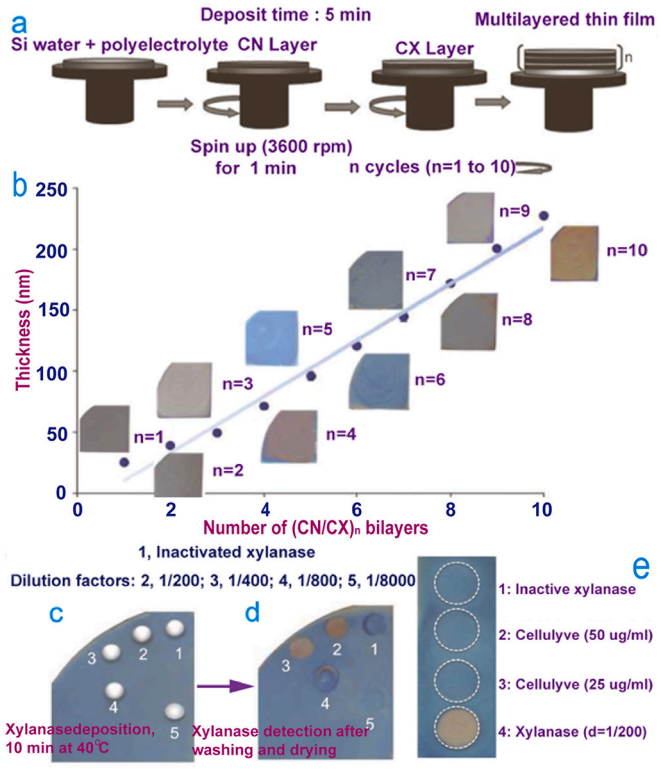

Fig. 16. (a) Schematic illustration of the preparation process of CX conjugated CNCs thin film and (b) the corresponding thickness evolution. (c,d) Xylanase deposition and xylanase detection process on a CNCs/CX film. (e) Degradation of the CNCs/CX film under different xylanase enzymatic solution. Reproduced with permission from ref. [156].

method, Palomero and coworkers immersed sulfur, nitrogen-codoped graphene quantum dots (S,N-GQDs) into the crosslinking networks of nanocellulosis (NC) to obtain novel hydrogels (S,N-GQDs/NC) with strong fluorescence response for the detection of the laccase enzyme [157]. The introduction of NC into the matrix of S,N-GQDs not only strenthened the fluorescence signal of S,N-GQDs as a result of the avoidance of the self-quenching phenomenon, but it could also avoid the fluctuation of the fluorescence signals, leading to the enhancement of the sensitivity toward laccase. The sensing mechanism for the detection of laccase over the as-synthesized S,N-GQDs/NC was based on the fluorescence response of the hydrogels containing GQDs, which was served as a luminophore toward laccase. On one hand, the prepared gel matrix increased the fluorescence signal intensity of GQDs by avoiding their self-quenching. On the other hand, it stabilized its fluorescence signal and increased their sensitivity toward laccase. The noncovalent interactions between the sensor and the biomarker were considered to be giving rise to the significant quenching effect without peak-shifts of GQD fluorescence via energy transfer. It was found that the detection limit of diverse laccases extracted from different shampoos was as low as 0.048 U mL^{-1}. As a result of the combined advantages of NC and GQDs, the assembled S,N-GQDs/NC fluorescent sensor would play increasingly important roles in the detection, storage, as well as the recycling of enzymes.

4. Structure-properties relationship for nanocellulose-based protein biosensors

Nanocellulose-derived biosensors takes the leading position in the field of protein sensing as a result of its particular physical, chemical, and biological characteristics, including high surface area and superficial chemical reactivity, special morphology and geometric dimensions, porosity, low toxicity, biocompatibility, biodegradability and inertness, etc. [1–3,27] The structure of the nanocelluloses plays a decisive role to the sensing properties of the biosensors. Nanocelluloses differ absolutely

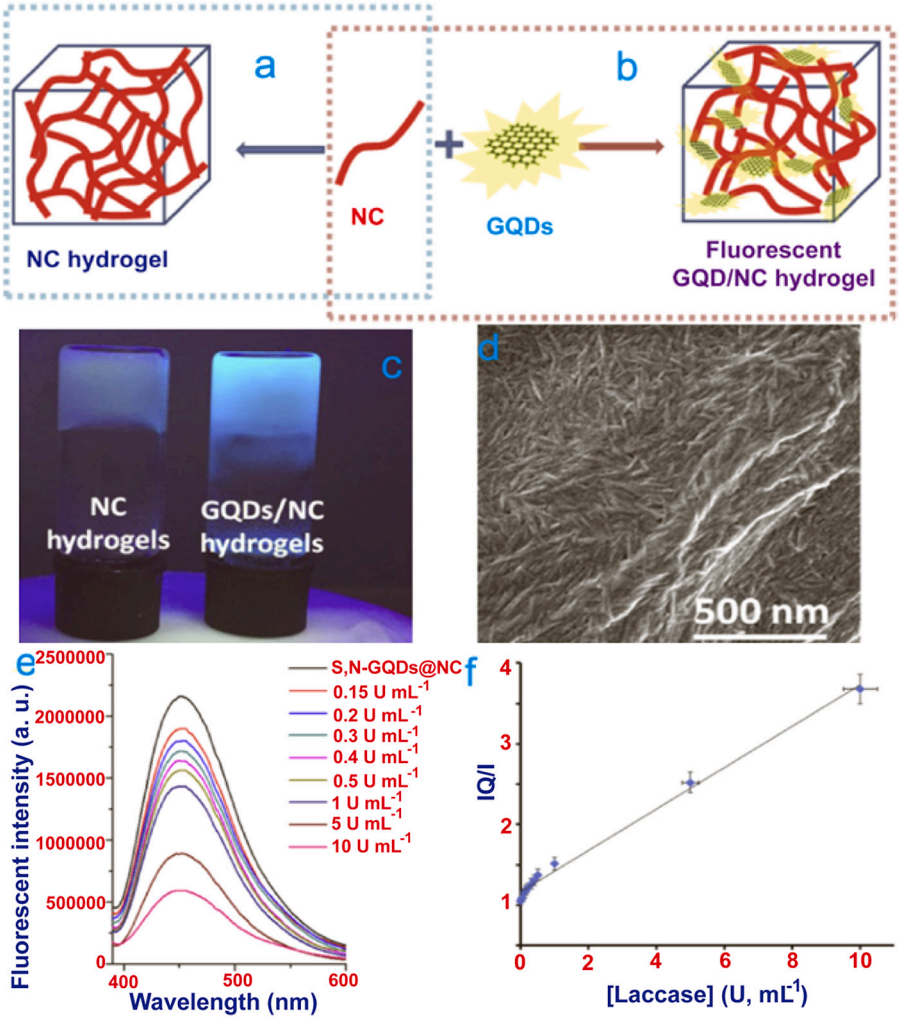

Fig. 17. Schematic illustration of the S,N-GQDs/NC fluorescent sensor. (a) Synthetic pathway for the fabrication of NC hydrogels and (b) the corresponding fluorescent sensor. (c) Photographs of the NC hydrogels under the irradiation of UV light. (d) The SEM image of the S,N-GQDs/NC fluorescent sensor. (e) Fluorescence spectra of the S,N-GQDs/NC fluorescent sensor under different concentrations of the enzyme. (f) The calibration graph of the formed sensing ethodology. Reproduced with permission from ref. [157].

in the aspects of the appearance, size, morphology, surface microstructure and physicochemical properties, which determine its practical usage in protein sensing [28–32]. It is noted that there are abundant highly reactive groups on the surface of nanocelluloses, such as –OH and -SO_3H groups [42–50]. These active groups can feasibly react with numerous macromolecular matrices based on the hydrogen bonding or ionic interactions, which finally form a reinforcing effect into the composites so as to enhance the reusability and stability for the nanocellulose-based biosensors [76–82]. Furthermore, another outstanding feature of nanocelluloses is its high specific surface, which ranges from 100 $m^2\ g^{-1}$ to several hundred $m^2\ g^{-1}$ [27–30]. This advantage greatly promotes the interfacial interaction and the immobilization between the biosensors and its surrounding proteins.

Another outstanding structure feature for the nanocelluloses is its ability to modify its surface through its surface –OH groups. Diverse desired functions can be achieved by the surface functionalization of the nanocelluloses, including improving its compatibility with different matrices, precise controlling of water absorption, and releasing and bringing desired chemical functionality and expanding utilization in protein sensing. The commonly used functionalization means include oxidation and acetylation reactions of aliphatic and aromatic isocyanates, and the silylation reaction with 3-aminopropyltrimethoxysilane (APTES) [85–92]. The silylation reaction of the nanocelluloses with APTES can introduce reactive amino-terminal group into the crosslinking networks of the nanocelluloses, allowing the covalent attachment of the protein molecules based on the altered hydrophobic and hydrophilic surfaces. Besides, new detection devices can be created by the chemical modification, which can directly determine the protein composition and structures to expand the application market of nanocellulose-derived biosensors in protein sensing.

The combination of these structure characteristics makes nanocellulose and its derivatives attractive for protein detection. For the most part, nanocelluloses are served as one of the components that work with other stimuli-responsive materials, such as field-effect transistors (FETs) based single-walled carbon nanotubes (swCNTs), carboxylethyl quaternized cellulose (CEQC), nitrogen and sulfur doped carbon dots (N, S-CDs), cellulose decorated graphene-Au-nanocrystals, and TEMPO-oxidized nanofibrillated cellulose, etc. [158–165] Table 2 lists a range of nanocellulose-derived composites for the detection of diverse proteins, including human serum albumin (HSA), trypsin, human neutrophil elastase (HNE), cysteine, glutathione and bilirubin, etc. Compared with other biosensors for protein detection in the previous studies (listed in Table 2) [166–173], it is apparent that nanocellulose-derived biosensors have much lower detection limit for diverse proteins; therefore, nanocellulose-derived biosensors are very promising for the sensitive detection of proteins in biomedical application.

5. Research gaps and future perspectives

The developemnt of proteins sensing over nanocellulosic materials is showing promising trends for years to come. There is much interest in developing academic research and potential biomedical usage for this

Table 2
Protein sensing by nanocellulose-based derivatives and other biosensors.

Biosensor description	Biosensor type	Biosensor dimension	Proteins	Detection limit	Ref.
Curcumin embedded in BNC nanopaper	Optical	2D	HSA	100 μg mL^{-1}	[158]
CNT-FET	Electrochemical	3D	HSA	100 pM	[159]
Carboxylethyl quaternized cellulose (CEQC)	Optical	3D	Cysteine	20 nM	[160]
N, S-CDs	Optical	Pseudo 0D	Glutathione	5.98 μM	[161]
Cellulose decorated graphene-Au-nanocrystals	Optical	2D	Bilirubin	54.5 μM	[162]
TEMPO-oxidized CNF	Optical	1D	HNE	0.5 μmol mL^{-1}	[163]
Wood CNC	Optical	1D	HNE	0.015 μmol mL^{-1}	[164]
Cotton CNC	Optical	1D	HNE	0.005 μmol mL^{-1}	[165]
Paper-based polyion-sensitive optodes	Electrochemical	3D	Trypsin	1.4 μg mL^{-1}	[166]
Cyclometallated iridium complex	Optical	N/A	HSA	0.8 nM	[167]
Chalcone-based dyes	Optical	N/A	HSA	8.6 nM	[168]
Citric acid-derived carbon dots	Optical	Pseudo 0D	Cysteine	0.036 μM	[169]
An indium tin oxide electrode loaded with g-carbon nitride	Photoelectrochemical	3D	Cysteine	9.2 μM	[170]
Boron-dipyrromethene -modified β-cyclodextrin	Optical	N/A	Glutathione	N/A	[171]
Cu^{2+} modified metal organic frameworks	Optical	3D	Glutathione	12.4 μM	[172]
Gold Nanoclusters Film Supported on Polydopamine	Optical	3D	Bilirubin	0.61 μmol L^{-1}	[173]
Peptide sequence	Electrochemical	3D	HNE	250 pM	[174]
Mn doped ZnS quantum dots	Optical	Pseudo 0D	Trypsin	42 ng mL^{-1}	[175]

fascinating material. Despite significant progress has been achieved, there are still great challenges when considering nanocellulosic materials as biosensors for proteins detection. The biggest challenge is the issue of large-scale production of nanocelluloses-derived biosensors. It is because that the nanocellulose precursors are easy to be aggregated and have weak dispersion as a result of their high active surface, which cause undesirable sensing and repeatability properties of the biosensors. Therefore, using nanotechnology and green chemistry-oriented strategies to obtain the large-scale production of nanocellulosic nanomaterials can greatly promote the commercialization and marketization processes. Besides, the complicated post-preparation process is another barrier to the commercial application of nanocelluloses-derived biosensors because of their hydrophilic features. For this reason, it is difficult to obtain very dry nanocelluloses products and then obtain a homogeneous dispersion with hydrophobic species. Increase the devotion of the precise understanding and a profound store of knowledge in nanocelluloses and morphology evolution, as well as the control of their surface properties are effective ways to resolve this issue. These factors can fundamentally affect the assembly and production, as well as the reproducibility of nanocelluloses-derived sensors.

Based on the above challenges, the following aspects should be taken into consideration with regard to the development style of nanocelluloses-derived sensors in life research area:

1) Exploring green extraction methods and fabrication techniques for the generations of high-quality nanocelluloses precursors so as to lower the use of toxic acid and organic solvents. Future works are required for implementing novel pretreatments that allow obtaining BNC and CNF of plant origin with an ideal quality for its application in the biomedical field. It is expected that feasible implementation of novel pretreatment techniques can be developed to obtain high-pure BNC and CNF using the plant origin as the raw materials to expand its application in the biomedical field.

2) Optimizing the dispersion and orientation of nanocelluloses using advanced nanotechnology and green chemistry-oriented strategies, which is the key to structural and sensing performance of the sensors. It is necessary to fully utilize the structure characteristics of nanocelluloses to greatly promote the interfacial interaction and the immobilization between the biosensors and its surrounding proteins.

3) Developing compact, portable and lightweight nanocelluloses-derived sensors which require less complicated pre-treatment steps. For example, nanopaper-based biosensors such as the lateral flow assay and micro-fluidic paper provide low-cost, portable and disposable platforms to engineer advantageous devices for protein sensing. On one hand, nanopaper possesses all the advantages of the conventional paper. On the other hand, as compared with the conventional paper, nanopaper endows the biosensor with better optical transparency, lower thermal expansion, lower surface roughness and higher chemical, mechanical and thermal stability. Besides, nanopaper still remains stable 3D structure in water. These advantageous features make nanopaper a superior substrate to evolve up-to-date optical/electrical biosensors.

4) Incorporating nanocelluloses with a broad range of host materials or stimulus materials to extend their detection possibilities for multi-proteins. The versatility and multifunctional features of nanocelluloses provides a perfect chance to create advanced biosensors by using similar composites such as metal-decorated nanocelluloses for protein sensing.

All in all, the above issues should be placed on the agenda so as to expand the application of nanocelluloses in protein sensing. It should be addressed that a large sample is required for biosensor devices, which always cause false-positive or false-negative results. Very few biosensors have attained commercial success on a global scale. There is also a need to produce nanocellulose-based biosensors at an affordable cost with high sensitivity and accuracy. More efforts should be devoted to the area of nanocellulose-based biosensors to form commercially viable prototypes in industry in near future.

6. Conclusions

Nanocellulosic materials provide an ideal platform for proteins sensing via nanotechnology and green chemistry-oriented strategies. This review summarizes the particular structure of nanocelluloses, the flexible design and fabrication of functionalized nanocellulosic materials, and the potential of vast numbers of nanocelluloses for highly-efficient, sensitive and repeatable detection of diverse proteins, focusing on the relationship between the structure-the detection performance of nanocelluloses-derived biosensors. Depending on the advanced nanotechnology and green chemistry-oriented strategies, nanocellulosic materials can be incorporated with a wide range of components, such as polymers, metals, metal oxides, and carbon, etc. to monitor and analyze a broad spectrum of proteins. Actually, either as the support matrices or as the stimuli-responsive components, nanocellulosic materials not only retain the original properties of celluloses but are also attractive because of high aspect ratio and large specific surface area in addition to a reactive surface of –OH side group to facilitate self-assembly, controlled dispersion within a wide range of matrix polymers, and control of both the particle–particle and particle-matrix bond strength. Therefore, the great possibility of chemical modifications endows nanocellulose and/or cellulose composites with the potential of advanced sensing technologies for multi-proteins. With the combination of the nanoengineering and green chemistry-oriented strategies toward nanocelluloses, it will promote the identification of trace proteins and revolutionizing the state-of-the-art of the sensing technology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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