Inherently Distinctive Potentialities and Uses of Nanocellulose Based on its Nanoarchitecture

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Native cellulose is mainly found in phytomass, such as trees and other plants. It has a regular hierarchical nanoarchitecture, in which the extended macromolecular chains are aligned and closely packed in parallel to form the crystalline nanofibrils of cell walls. In the context of material utilization, nanocellulose is a collective term for nano-ordered assemblies of cellulose chains. In recent times, it has been produced in large quantities from woody bioresources. In addition, nanocellulose has some fascinating physicochemical properties, such as high strength, light weight, transparency, birefringence, and low thermal expansion. These properties have enabled broad functional design of nanocellulose-based materials; but most of them are facing serious competition from various products that already exist. However, nanocellulose is not just a green alternative to existing materials. Rather, it is expected to make a profound difference in terms of pioneering novel functions. The present review focuses on the unexpected features of nanocellulose materials, triggered by details of the inherent nanoarchitecture of native cellulose.

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INTRODUCTION

Cellulose is a linear homopolysaccharide composed of anhydro-D-glucopyranose units linked together *via β*-1,4-glycosidic bonds. It self-assembles during biosynthesis to form a crystalline nanofiber with dozens of cellulose chains closely packed in parallel (Nishiyama 2009; Daicho *et al.* 2018). Cellulose is the most abundant renewable biopolymer on earth, and it has been used for many years in daily life, for example, as timber products, pulp and paper, clothing fibers, and food and cosmetic additives. From a structural perspective, the conventional uses of cellulose can be classified into two categories: (1) the use of original lignocellulose components at the macro and micrometer levels, such as in building timber, wood chip boards, paper materials, and cotton clothes; and (2) the use of cellulose-derived polymers that have been chemically altered at the molecular level, such as regenerated cellulose and various cellulose derivatives commercially available as fibers, films, resins, and coatings (Hubbe *et al.* 2013; Paunonen 2013; Wang *et al.* 2016). In other words, in the former case the inherent nanostructure of native cellulose constructed during biosynthesis is exploited, and in the latter case the original nanoarchitecture of the cellulose is subjected to irreversible changes. In the last two decades, a third way of using nano-ordered cellulose assemblies has been pioneered.

The strategy uses various techniques to separate/isolate cellulose microfibrils from wood cell walls, while attempting to hold their inherent nanostructures, both at the morphological and crystallographic levels (Isogai *et al.* 2011; Igarashi *et al.* 2018; Heise *et al.* 2021). Recently, the collective term "nanocellulose" has become widely recognized and is generally used with regard to nano-ordered assemblies of cellulose chains in the context of material utilization.

In a broad sense, nanocellulose may refer to a variety of cellulosic materials with at least one dimension of less than 100 nanometers, including regenerated cellulose and its derivatives; however, the present review will focus on the native cellulose I crystalline structures of nanocellulose, in which the extended cellulose chains are closely packed in parallel orientation. Nanocellulose with native crystalline structures has high-aspect-ratio fiber/whisker forms that are 2 to 50 nm in width as a fine nanomaterial; bacterial, algal, and tunicate cellulose nanofibers are also included in this regard. The complete separation of nanocellulose from wood pulp fibers (the raw material used to produce paper) has greatly increased its potential usefulness in terms of practical applications (Igarashi *et al.* 2018). Since the first isolation of cellulose nanofibrils from wood pulp at the single-component level in 2006 (Saito *et al.* 2006), research on nanocellulose—which can be regarded as cellulose I nanomaterials that include cellulose nanofibrils/nanofibers (CNFs), cellulose nanocrystals (CNCs), and nanofibrillated cellulose (NFC) in some cases—has exploded (Moon *et al.* 2011; Hastuti *et al.* 2018). Various nano-downsizing processes have been developed: (1) physical processing using grinders, microfluidizers, high-speed blenders, and high-pressure water-jet systems (Abe *et al.* 2007; Uetani and Yano 2011; Nechyporchuk *et al.* 2016; Moser *et al.* 2019; Zeng *et al.* 2020); (2) chemical and physicochemical processing by sulfuric acid hydrolysis (Beck-Candanedo *et al.* 2005), 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO)-mediated oxidation (Isogai *et al.* 2011; Capron and Cathala 2013), and phosphorylation (Camarero Espinosa *et al.* 2013); and (3) enzymatic processing using cellulase, xylanase, and enzyme cocktails (Pääkkö *et al.* 2007; Penttilä *et al.* 2013; Michelin *et al.* 2020). At present, various kinds of nanocellulose prepared from a diverse array of bioresources through various processes are readily available for research and development.

Several nanocellulose-based composite materials have been developed by exploiting the many fascinating mechanical properties of nanocellulose—such as high strength, high Young's modulus, birefringence, and low coefficient of thermal expansion—which originate from the extended chain crystals of nanocellulose (Moon *et al.* 2011; Feng *et al.* 2019; Pitiphatharaworachot *et al.* 2019). Lightweight and transparent nanocellulose films, which are sometimes called "nanopaper", have also been developed for green electronics (Li and Lee 2017), optoelectronics (Nogi and Yano 2008), tough nanomaterials engineering (Henriksson *et al.* 2008), and packaging applications (Stark 2016; Hubbe *et al.* 2017). Ultrafine filters, transparent films, shear-thinning inks for ballpoint pens, highly elastic soles for running shoes, super-deodorant diapers, cosmetics, and many other products are being marketed (Chin *et al.* 2017; Sharma *et al.* 2019). The Ministry of the Environment of Japan is in charge of the Nanocellulose Vehicle (NCV) project, and the first NCV concept car was unveiled at the 2019 Tokyo Motor Show (Ministry of the Environment 2019). However, most nanocellulose-based products are facing relentless competition from existing inorganic and plastics-based materials. Therefore, there is a strong incentive to exploit the inherent nanoarchitecture of nanocellulose, which cannot be artificially reconstructed.

Recently, many of the limitations of nanocellulose have been overcome during the development of a diverse array of functional nanomaterials. The key to unlocking the potential of nanocellulose lies in understanding its nanoarchitecture-triggered properties. The present review focuses on the unexpected properties of nanocellulose—which arise from its inherent nanoarchitecture—and on unique approaches to the functional design of nanocellulose-inspired nanomaterials. Especially, we introduce three topics: (1) thermally conductive and optical regulation; (2) interfacial organocatalysis; and (3) challenges in biomedical applications. Many studies on nanocellulose-based composites have had a tendency to deal with the functions of the counterparts, rather than the unique features of nanocellulose itself. This review highlights the nanoarchitecture-triggered properties of nanocellulose for nanomaterials design. The emerging properties of nanocellulose, as revealed by continuing research, are expected to far surpass those of current green alternatives to existing products, even though nanocellulose remains valuable in terms of ecological sustainability.

DIVERSE MATERIALS DESIGN

Multifunctional Films

As with ordinary paper made from wood pulp fibers, nanocellulose self-adheres to each other through hydrogen bonding between nanofibers to form film-like materials, commonly known as "nanopaper." This self-adhesive feature is one of the essential natures of nanocellulose and is seldom found in other nanofibers composed of plastics, glass, metals, or carbon. The assembly design to stack crystalline nanocellulose having a modulus of 140 to 150 GPa (Iwamoto *et al.* 2009), a strength of 2 to 6 GPa (Saito *et al.* 2013), a very low coefficient of thermal expansion (Hori and Wada 2005), a relatively high optical birefringence of up to 0.09 (Uetani *et al.* 2019), and high electrical resistance of over 100 TΩ (Celano *et al.* 2016) has some fascinating properties that enable the creation of various functional films. The process by which a nanocellulose film is formed directly affects its physical properties and material performances.

Nanocellulose films have typically been prepared by one of two major processes: (1) cast-drying, in which an aqueous nanocellulose suspension is poured into a mold and dried; and (2) filtration, in which the suspension is forcibly vacuum-filtered to form a wet mat, then dried to make a film. In the case of TEMPO-oxidized cellulose nanofibers (TOCNFs), nematic-structured TOCNF films that have been prepared by evaporation-induced condensation during cast-drying have better mechanical properties, optical transparency, gas-barrier properties, heat transfer properties, and electrical resistivity than filtered films (Zhao *et al.* 2018). However, cast-drying requires a very long drying time, and the casting method results in drying-induced local condensation. Therefore, the evaporation process affects the self-assembly modes of nanocellulose and determines the final film structure (Uetani *et al.* 2018). To avoid lengthy drying and uncontrolled self-assembly, a new high-speed drying technique has recently been developed. It is a multistep drying process whereby an air flow system rapidly reduces the humidity arising from the evaporation of water from the outer surface of the cast suspension (Li *et al.* 2020a). This technique can eliminate the conventional trade-off between drying time and film haze, enabling the rapid fabrication of transparent nanopapers with very low haze.

Owing to the high hydrophilicity of cellulose, nanocellulose films exhibit high moisture absorption in response to environmental humidity (Guo *et al.* 2017, 2018). Such

moisture absorption of nanocellulose films—which sometimes reaches 30 to 40% of their own weight—is often regarded as one of their serious disadvantages, and is very detrimental to their physical properties (Benítez *et al.* 2013; Walther *et al.* 2020). Many attempts have been made to increase the humidity stability of nanocellulose materials by surface hydrophobization and preparation of composite structures (Ansari *et al.* 2014). Contrary to such general concerns, a biodegradable humidity sensor has recently been proposed, which exploits the unique environmentally responsive moisture absorption property of nanocellulose (Kasuga *et al.* 2019). Such unique strategy for materials design that positively uses the inherent hydrophilic properties of cellulose is required to expand the potential of nanocellulose beyond the replacement of conventional materials.

The hydrophobic modification of nanocellulose also enables the development of a variety of functional films, such as composites with hydrophobic polymers (Fujisawa *et al.* 2013; Chin *et al.* 2017; Igarashi *et al.* 2018), low-birefringence films (Soeta *et al.* 2015), oxygen barrier films (Sirviö *et al.* 2014), and thermally stable films resistant to yellowing (Yagyu *et al.* 2015). The interfacial layers between nanocellulose fillers and cellulose triacetate matrices have been successfully regulated by tuning the molecular weight of poly(ethylene glycol) grafts at the interface, making it possible to achieve both low thermal expansion and mechanical reinforcement of composite films (Soeta *et al.* 2017). Recently, in a departure from the traditional two-dimensional decoration of nanocellulose surfaces, the morphological design of three-dimensional topographies—such as striped and helical structures on CNCs—has been developed (Malho *et al.* 2016). In addition to conventional soft polymer grafting and the support of nanoparticles (Koga *et al.* 2010), a new modification concept using hard anisotropic nanospikes (Bahng *et al.* 2015) is expected to enable the structural and functional design of nanocellulose to overcome the huge barrier between hydrophilic and hydrophobic natures. Such approaches for process engineering and chemical surface modification are exactly attracting attention in practical applications of nanocellulose; but paying more attention to its nanoarchitecture-triggered features would have a lot of potential to further expand the possibilities of nanocellulose materials.

Nanoscale Assemblies

Rod-like nanocellulose particles, such as CNCs, self-assemble to form cholesteric liquid crystals with nano-ordered orientation in dispersion (Marchessault *et al.* 1959; Revol *et al.* 1992). This structural chirality is thought to be caused by the inherent twisting of nanocellulose (Araki and Kuga 2001), and the entropy-driven formation of chiral nematic liquid crystals is predicted for twisting polyhedral rods (Dussi and Dijkstra 2016). Such fiber accumulation modes often appear in biological tissues as Bouligand structures and are well known as the origin of the blue iridescence that characterizes *Pollia condensata* fruits (Vignolini *et al.* 2012).

Kondo *et al.* (2002) attempted to artificially assemble nanocellulose using a bioengineering method that allowed nanocellulose-secreting bacteria to propel themselves on a molecular template. Recently, the assembly of nanocellulose has been extended to include multidimensional structures, starting with one-dimensionally aligned macrofibers (1D) (Iwamoto *et al.* 2011; Walther *et al.* 2011; Håkansson *et al.* 2014), followed by unidirectionally aligned films (2D) (Sehaqui *et al.* 2012; Diaz *et al.* 2013), the formation of cellular architectures by 3D printing molding (3D) (Siqueira *et al.* 2017), and even biomimetic 4D printing (4D) (Gladman *et al.* 2016). Although most of the aligned nanocellulose materials described above have been developed for their favorable mechanical properties and controlled anisotropy, there are many competing materials with

equivalent performances. Even nanocellulose materials with fully oriented structures do not exceed single nanocellulose in theoretical strength. Therefore, the multi-functional design of nanocellulose holds the key to avoiding futile competition with other products.

The amphiphilic features of nanocellulose—which has spatially separated hydrophilic and hydrophobic crystalline faces—facilitate the formation of micro- and nanoparticles *via* Pickering emulsion systems (Fujisawa *et al.* 2017a). Such "Janus" structures have prompted the development of high-performance nanocomposites (Fujisawa *et al.* 2017b), functional aerogels (Li *et al.* 2020b), and thermal storage materials (Chakrabarty and Teramoto 2020). Ultrastable Pickering emulsions can be designed by tuning the sources, shapes, and surface charges of nanocellulose (Saelices and Capron 2018). Goi *et al.* (2019) reported that, in an oil-in-water emulsion system, TEMPO-oxidized CNFs played dual roles as emulsifiers at the interface and dispersion stabilizers in the aqueous phase. Kanomata *et al.* (2019) used a biomimetic approach inspired by plant cell wall lignification to achieve the enzymatic radical coupling of monolignol on nanocellulose in a Pickering emulsion system. Pickering emulsions comprising micro- and nanoparticles are potentially very useful for drug delivery systems, and in foods, cosmetics, and paints. Their unique structures provide an alternative to conventional templates for the formation of structural nanocellulose.

Thermal Control by Nanocellulose

Plant-derived pulp and cotton fibers composed of nanocellulose are generally recognized as insulation materials, and they are often used in clothing, paper cups, and building insulation. Thermal insulation for building applications must have a thermal conductivity below 50 $mW \cdot m^{-1} \cdot K^{-1}$ (Jelle 2011). The effective thermal conductivity κ_{eff} of an insulating material is expressed as the sum of the thermal conductivity values in multiple modes: the solid-state thermal conductivity κ_{solid}, the gas-state thermal conductivity κ_{gas}, the radiation conductivity κ_{rad}, and the convection conductivity κ_{conv}. Among these four thermal conduction modes, the adiabatic function is significantly manifested by dividing air into small compartments and controlling κ_{gas} (Sakai *et al.* 2016; Apostolopoulou-Kalkavoura *et al.* 2020). The value of κ_{gas} is determined by the relationship between the mean free path of gas molecules colliding with each other and the pore size of the filled space. At room temperature, air has a thermal conductivity of 26.2 $mW \cdot m^{-1} \cdot K^{-1}$, with a mean free path of approximately 70 nm. When air is confined in small pores (approximately 50 nm or less), its apparent thermal conductivity is reduced as a result of the decrease in the mean free path of the gas molecules and the increase in the frequency of collisions with the compartment walls rather than intermolecular collisions (Knudsen diffusion).

Thermal insulation by air partitioning can be replicated with nanocellulose. Kobayashi *et al.* (2014) reported a supercritically dried nanocellulose aerogel with mesopores of 2 to 50 nm and a large specific surface area of 500 to 600 $m^2\,g^{-1}$ that had an extremely low thermal conductivity of 18 $mW \cdot m^{-1} \cdot K^{-1}$ at 300 K. Nanocelluloses can be used in many ways to control microporous structures (Lavoine and Bergstrom 2017). Various submicron architectures with low thermal conductivities comprising nanocellulose and graphene oxide have been proposed as thermally insulating and fire-retardant composite foams (Wicklein *et al.* 2015), and as thermally insulating "nanowood" that uses the structure of the cell walls of wood (Li *et al.* 2018). However, the inherent thermal conductivity of nanocellulose itself, κ_{solid}, has received less attention in the development of

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insulation, and has been considered to be as low as that of other polymer materials. Many materials other than nanocellulose—such as silicon dioxide, nanocarbons, and synthetic polymers—have been used as thermal insulation.

Contrary to conventional perspectives, pristine nanocellulose has recently been found to have unexpectedly high thermal conductivity. Uetani *et al.* (2015) reported that a densely packed film of ascidian-derived nanocellulose had an in-plane thermal conductivity of 2.5 W·m^{-1}·K^{-1}, which was 3 to 10 times higher than the thermal conductivities of plastic films or glass. The extended chain crystals of natural nanocellulose are presumed to reduce the propagation loss of thermal vibrations, unlike the folded crystals of general synthetic polymers. Molecular dynamics simulations have predicted that the inherently strong hydrogen bonds between nanocellulose surfaces significantly suppress the interfacial thermal resistance from 9.4 to 12.6 m^2 K·GW^{-1} (Diaz *et al.* 2014). The thermal conductivity of the nanocellulose used can be directly evaluated because only mesopores of less than 50 nm exist in the densely packed films of ascidian-derived nanocellulose, and the internal air is adiabatic owing to Knudsen diffusion, as described above. The in-plane thermal conductivity of the nanocellulose films ranged from approximately 1 to 2.5 W·m^{-1}·K^{-1}, and was linearly proportional to the average crystal thickness of the constituent nanocellulose (Uetani *et al.* 2015). The crystal thickness of nanocellulose is specific to the species from which it is derived and ranges from approximately 2 to 3 nm for wood, 4 to 5 nm for cotton, 5 to 7 nm for bacterial cellulose, and 8 to 12 nm for ascidians. There is evidence to suggest that the mean free path of a phonon is limited by the width of the fibrous crystallites (Uetani *et al.* 2015; Dong *et al.* 2020). The unique structural characteristics of nanocellulose are reflected in the "high thermal conductivity" of its films, and highlight the unexpected physics of cellulose, which has only been considered as a thermal insulator.

Nevertheless, direct and accurate measurement of the thermal conductivity of a single nanocellulose fiber remains challenging. Investigations of the physical properties of single nanofibers of nanocellulose by transmission/scanning electron microscopy—which has been used to investigate carbon nanotubes and ceramic nanofibers—have failed because cellulose is readily decomposed by electron beams. Therefore, several indirect methods have been proposed. Uetani *et al.* (2017) stretched bacterial cellulose hydrogels to align the nanocellulose in designated unidirectional orientations and successfully measured the increase in thermal conductivity in the aligned directions in proportion to the degree of orientation. Extrapolating this trend, the anisotropic thermal conductivities of fully oriented nanocellulose are estimated to be approximately 3.4 and 0.37 W·m^{-1}·K^{-1} in the aligned and transverse directions, respectively. Obori *et al.* (2019) predicted a thermal conductivity of 1.47 W·m^{-1}·K^{-1} for a single nanocellulose extracted from wood by parametric model analysis of nanocellulose aerogels. Molecular dynamics simulation estimated that a single cellulose I$_\beta$ crystal has thermal conductivities of approximately 5.7 and 0.72 W·m^{-1}·K^{-1} in the chain and transverse directions, respectively (Diaz *et al.* 2014). Dong *et al.* (2020) also predicted a thermal conductivity of approximately 6 W·m^{-1}·K^{-1} for an infinitely long single cellulose chain *via* molecular dynamics simulations and found that the thermal conductivity values of unit cellulose chains in different crystalline polymorphs (*i.e.*, I$_\alpha$, I$_\beta$, II, and III$_I$) were similar, even though the thermal conductivity depends on the cross-sectional area in crystal models.

Although higher than expected, nanocellulose does not necessarily have a thermal conductivity that is significantly greater than the thermal conductivities of existing

materials such as carbon or ceramics, and its other properties must be explored to avoid competition with thermally conductive materials (Uetani and Hatori 2017). Despite the trade-off between transparency and thermal conductivity in general composites, an optically transparent film with a thermal conductivity as high as 2.5 W·m^{-1}·K^{-1} and a linear transmittance of 73% can be produced from a mixture of ascidian-derived nanocellulose and acrylic resin (Fig. 1a; Uetani *et al.* 2016). Anisotropic heat transfer films have also been successfully designed by aligning the nanocellulose and controlling the direction of heat flow (Fig. 1b; Uetani *et al.* 2017). A slight strain of approximately 0.3% applied to the nanocellulose film enables reversible switching of the in-plane thermal diffusivity by up to 15%, which does not happen at all with metals or plastics (Fig. 1c; Uetani *et al.* 2020a). In this regard, the thermal diffusivity change is large and responsive in the elastic deformation mode, but it is smaller in the plastic deformation mode. Therefore, thermal diffusivity modulation must be driven by the elastic dynamics at the interface of the nanocellulose. This unique thermal property of nanocellulose is expected to prompt the development of further unique functional materials.
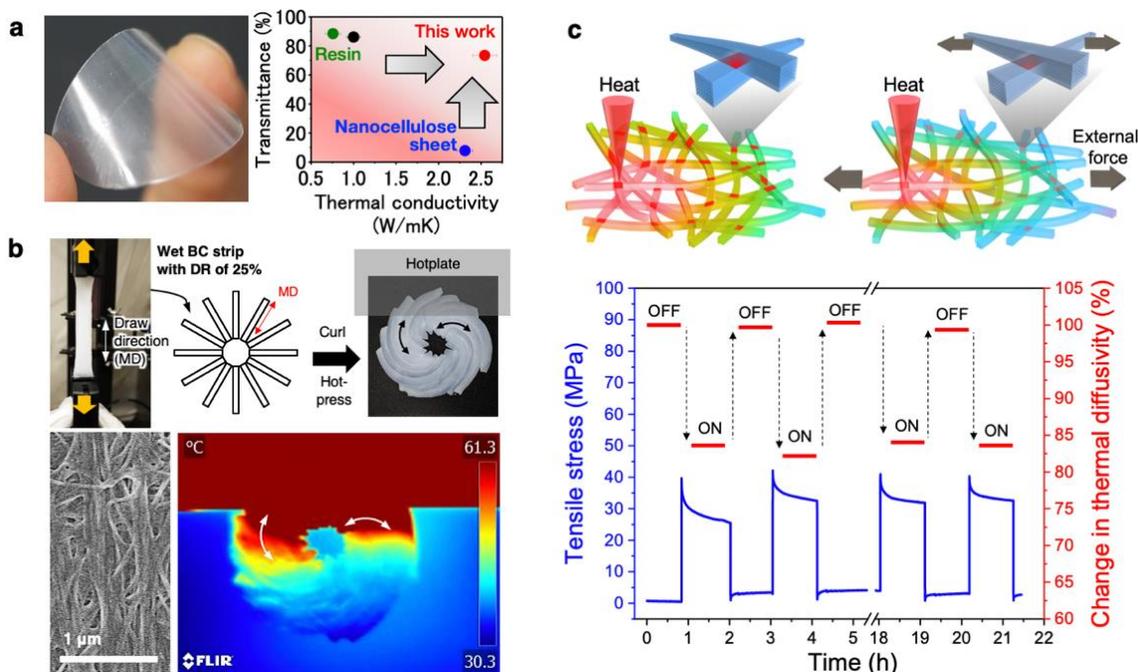

Fig. 1. Development of thermal control materials based on nanocellulose films. (a) A transparent thermally conductive film. Reproduced from (Uetani *et al.* 2016) with permission from The Royal Society of Chemistry. (b) Paper with anisotropic thermal conductivity produced by aligning nanocellulose. Reprinted with permission from (Uetani *et al.* 2017). Copyright 2016 American Chemical Society. (c) Thermal diffusivity modulation film triggered by mechanical force. Reproduced under the terms of the CC-BY 3.0 license (Uetani *et al.* 2020a), published by The Royal Society of Chemistry

Light Manipulation by Nanocellulose

Since the pioneering research into transparent films composed of bacterial cellulose and acrylic resins by Yano *et al.* (2005), transparency has become one of the most significant properties of nanocellulose. The transparency of a film can be enhanced by improving its surface smoothness and reducing its light-scattering behavior, which is

caused by internal voids and interfaces with different components. Therefore, the surfaces of nanocellulose films are mechanically polished to increase their transparency (Nogi *et al.* 2009), and the refractive indices of nanocellulose and resins are adjusted to bring them closer (Nogi *et al.* 2005). Such tailored transparent nanopapers have been used as substrates in optoelectronics because they are highly flexible and have low coefficients of thermal expansion, which are properties that are not found simultaneously in conventional transparent glass and plastics (Koga *et al.* 2014). In recent studies, there have been widespread efforts to afford further optical functions beyond simple transparency; multifunctional optical design is being promoted.

The diffusion of irradiated light is denoted by haze. It is of great significance for transparency, and it can be altered according to the process by which nanocellulose films are manufactured. Isobe *et al.* (2018) and Kasuga *et al.* (2018) reported that the haze of a nanocellulose film prepared by cast drying a wood-derived holocellulose pulp increased as the initial concentration of the nanocellulose suspension increased. Cast drying in a high-humidity environment markedly lowers the haze, and drying slowly in a humid environment produces low-haze films. However, slow-drying is obviously time-consuming. Therefore, high-speed manufacturing techniques with unconventional multi-stage drying systems have recently been developed to ensure films have low haze (Li *et al.* 2020a). The controllability of optical functions through interaction with water is expected as one of the nanoarchitecture-triggered features unique to nanocellulose with high hydrophilicity. Further advances in nanocellulose technology to freely control haze will enable the development of next-generation lighting filters with controllable light diffusion in a simple and speedy manufacturing process.

Another inherent optical property of nanocellulose, in addition to transparency, is optical anisotropy (Uetani *et al.* 2019). In this regard, novel light manipulation materials have been developed by conceptual design through various alignments of nanocellulose. The cholesteric order can be retained when drying rod-like nanocellulose dispersions, resulting in the successful formation of nanocellulose films characterized by circular polarization and selective reflection. Thus, optical manipulation by nanocellulose can be achieved by the self-assembly of cholesteric liquid crystals combined with artificial processing (Dumanli *et al.* 2014; Frka-Petesic *et al.* 2017; Natarajan *et al.* 2017; Yao *et al.* 2017). By using cholesteric liquid crystals of nanocellulose as a template of mesoporous silica matrices, the wavelength of reflected light can be tuned over a wide range (Fig. 2a; Shopsowitz *et al.* 2010, 2012).

Unlike conventional liquid crystal products in severe competition, free arrangement of nanocellulose has opened the door to design new optical materials, not depending on self-assembling of liquid crystals. By extending 3D printing technology, nanocellulose can be aligned and accumulated in multiple directions within the plane of a single film, and domain control of the optical and heat transfer axes has been achieved (Fig. 2b; Uetani *et al.* 2020b). Bottom-up assembly *via* self-adhesion of nanocellulose allows for the design of multifunctional films with a variety of higher-order architectures beyond the structural constraints on self-assembly of liquid crystals. Multiaxial nanocellulose arrays in a single piece of material is a forerunner for highly functional polarizers and optical compensators, which have been quite difficult to form with conventional transparent glass or polymers. Further advances in the design of nanocellulose arrays may result in useful optical behavior that has not yet been accomplished in conventional transparent films.
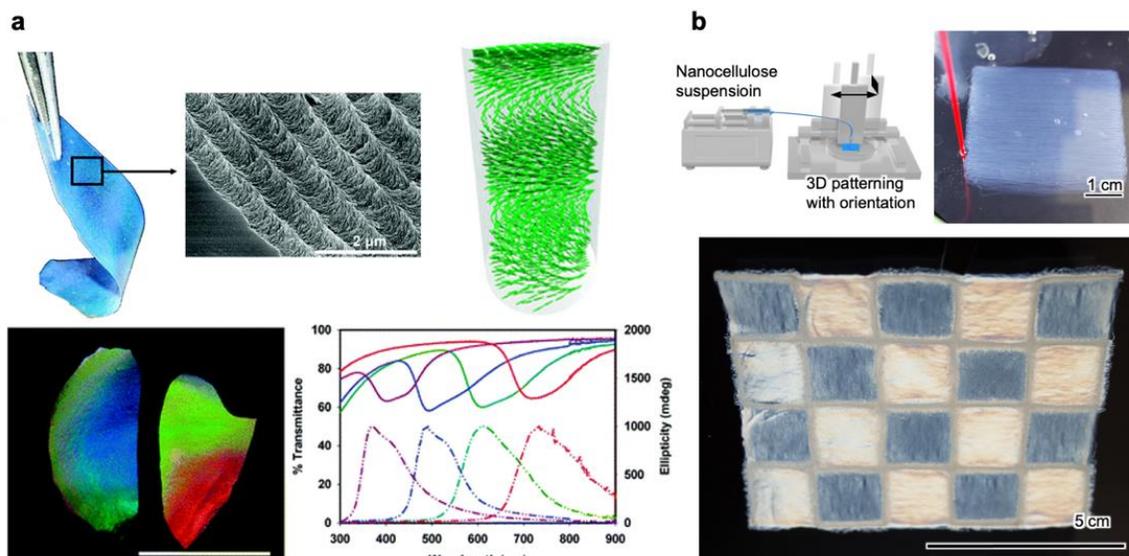
Fig. 2. Development of light-manipulation films made from nanocellulose. (a) A cholesteric liquid crystal film and mesoporous organosilica film. Reprinted from (Shopsowitz *et al.* 2012). Copyright 2012 American Chemical Society. (b) Multi-axis oriented nanocellulose film developed by liquid phase 3D patterning. Reproduced under the terms of the CC-BY 4.0 license (Uetani *et al.* 2020b), copyright 2020, MDPI

INTERFACIAL CATALYSIS

Immobilized Catalysts

Highly efficient catalysis is the key to achieving the production of green energy and materials. Essentially, the manufacture of heterogeneous catalysts from biodegradable and abundant sources—namely cellulose—will further contribute to the sustainability of various processes. Heterogeneous catalysis is generally preferred over homogeneous catalysis. This is because the former is more stable and easier to handle, and the often-solid catalysts can be recovered from the reaction media more easily, which facilitates recycling and cost-effective production. The development of a highly efficient heterogeneous catalyst relies on several interrelated parameters: (1) the specific surface area of the material; (2) the even distribution and size of the catalytic sites; and (3) the stability of the catalyst (mechanical, chemical, thermal, and so on) under the intended reaction conditions.

Nanocellulose has attracted increasing attention in the field as a carrier for metal nanoparticles (NPs). CNFs and CNCs as NP carriers were discussed in a review by Kaushik and Moores (2016). Subsequently, numerous studies have stemmed from this type of catalyst design. A summary of each cited supported catalyst is provided in Table 1. The metal precursor can be anchored *via* ionic or covalent bonding using external reducing agents (NaBH$_4$, poly(ethyleneimine), and so on) (Koga *et al.* 2017; Prathap *et al.* 2017; Zhang *et al.* 2020a), reduction by the hydroxy groups or functional groups of the native cellulose that are introduced by the extraction method (Sultan *et al.* 2019), or by other added functional groups such as aldehyde groups (Azetsu *et al.* 2013; Herreros-López *et al.* 2016).

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Table 1. Metal/oxide Nanoparticle (NP)–nanocellulose Composites with the Corresponding Catalytic Reactions

Metal/oxide NPs* (size in nm)	Precursor (reducing agent)	Nanocellulose used	Reaction	Ref.
AuNPs (4.0 nm) PdNPs (8.2 nm) AuPdNPs (4.3 to 7.7 nm)	$HAuCl_4 \cdot 3H_2O$ $[Pd(NH_3)_4] \cdot Cl_2$ ($NaBH_4$)	TOCNFs	Reduction of 4-nitrophenol to 4-aminophenol	Azetsu et al. (2011)
AuNPs (<100 nm)	$HAuCl_4$ ($NaBH_4$)	TEMPO-oxidized pulp	Reduction of 4-nitrophenol to 4-aminophenol	Azetsu et al. (2013)
CuNPs (6 to 7 nm)	$CuSO_4 \cdot 5H_2O$ ($N_2H_4 \cdot H_2O$)	CNFs	Azide–alkyne Huisgen [3+2] cycloaddition	Chetia et al. (2017)
CuNPs (12 nm)	$CuSO_4 \cdot 5H_2O$ ($N_2H_4 \cdot H_2O$)	CNFs	Selective oxidation of sulfides into sulfoxides and primary alcohols into aldehydes	Dutta et al. (2019a)
β-Galactosidases on FeNPs	$FeCl_3 \cdot 6H_2O$ (NH_4OH)	CNCs	Batch and continuous flow hydrolysis of lactose	Gennari et al. (2019)
AuNPs (3.5 to 9.5 nm)	$HAuCl_4$ ($NaBH_4$)	PAMAM dendrimer grafted CNCs	Reduction of 4-nitrophenol to 4-aminophenol	Herreros-López et al. (2016)
PdNPs PtNPs	H_2PtCl_6, $PdCl_2$ (PEI)	PEI-crosslinked TOCNFs	Reduction of 4-nitrophenol to 4-aminophenol	Hong et al. (2020)
PdNPs (2.7 nm)	$PdCl_2$ (H_2)	CNCs	Hydrogenation of prochiral ketones	Kaushik et al. (2015)
AuNPs (<5 nm)	$HAuCl_4$ ($NaBH_4$)	TOCNFs	Reduction of 4-nitrophenol to 4-aminophenol	Koga et al. (2010)
CuNPs	$Cu(NO_3)_2$ (sodium L-ascorbate)	TOCNFs	Azide–alkyne Huisgen [3+2] cycloaddition	Koga et al. (2012)
TiO_2NPs (<10 nm)	$TiCl_4$ (benzyl alcohol)	BTCA/SHP/TOCNFs monolith	Continuous flow photocatalyzed degradation of organic pollutants	Lucchini et al. (2018)
PdNPs (6 nm)	$PdCl_2$ ($NaBH_4$)	Carboxylic CNFs	Selective reduction of 3-nitrostyrene to 3-aminostyrene or 3-nitroethylbenzene	Meng et al. (2020)
AuNPs (2 to 10 nm)	$HAuCl_4$ (CTAB, ascorbic acid)	PDDA-coated CNCs	Reduction of 4-nitrophenol to 4-aminophenol	Nasseri et al. (2020)
Ni_2B (10 to 40 nm)	$NiCl_2 \cdot 6H_2O$ ($NaBH_4$)	TOCNFs	In-situ reduction of nitroarenes to amines	Prathap et al. (2017)
ZIF-8** (50 to 200 nm)	$Zn(NO_3)_2 \cdot 6H_2O$ (TEA)	TOCNFs	3D printed scaffolds, drug release	Sultan et al. (2019)
PdNPs (15.86 to 19.33 nm)	$[Pd(NH_3)_4] \cdot Cl_2$ (TOCNFs)	TOCNFs	Suzuki–Miyaura cross coupling of aryl halides and phenyl boronic acid	Zhang et al. (2018a)

Table 1. Continued

Metal/oxide NPs* (size in nm)	Precursor (reducing agent)	Nanocellulose used	Reaction	Ref.
AgNPs (<100 nm)	$AgNO_3$ (PEI, then $NaBH_4$)	TOCNFs	Pollutant removal (MB and CR)	Zhang *et al.* (2020a)
AuNPs (2.9 nm)	$HAuCl_4$ ($NaBH_4$)	Poly(4-vinylpyridine)-coated CNCs	Reduction of 4-nitrophenol to 4-aminophenol	Zhang *et al.* (2018b)
* NPs: nanoparticles, ** ZIF-8: zeolitic imidazolate framework-8				

Nanocellulose enables the homogeneous repartition of the NPs on its surface, such that the catalytic sites are well exposed to the reactants (Fig. 3a and 3b; Koga *et al.* 2010). Therefore, in contrast to conventional polymer-supported NPs, in which the catalytic sites may be hidden, or to NPs alone, in which the catalytic sites may be aggregated, superior activity has been reported for Au and PdNPs@CNF in aqueous hydrogenation reactions (Azetsu *et al.* 2011), and for CuNPs@CNF in Huisgen [3+2] cycloadditions (Koga *et al.* 2012; Chetia *et al.* 2017).
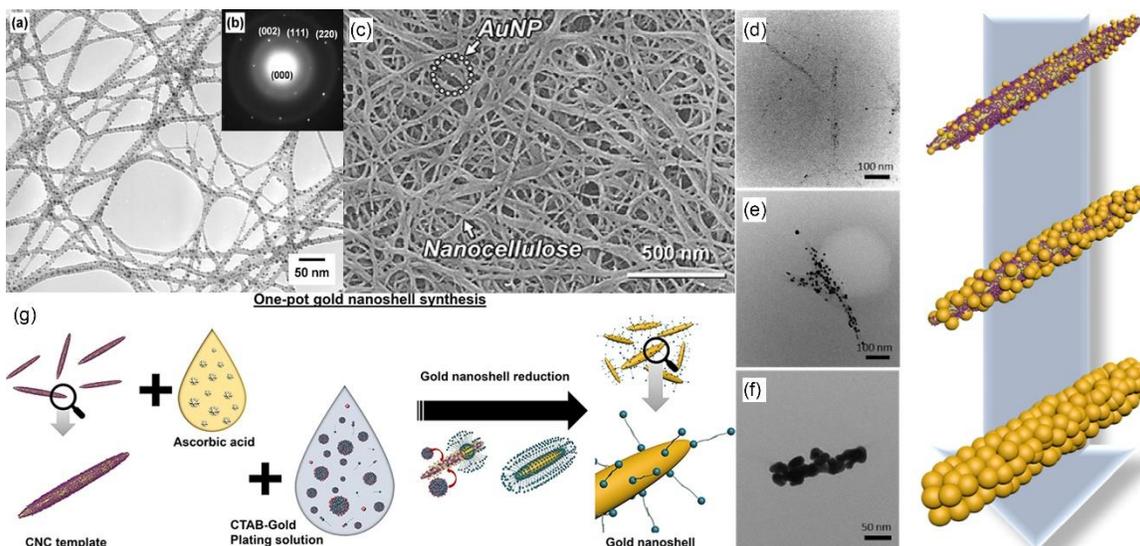

Fig. 3. Uniform dispersion of metal nanoparticles (NPs) anchored on nanocellulose, and the porosity of heterogeneous scaffolding materials. (a) Transmission electron microscopy (TEM) image and (b) selected area electron diffraction (SAED) pattern of Au NPs evenly deposited on TEMPO-oxidized cellulose nanofiber (TOCNF) surfaces. Reprinted from (Koga *et al.* 2010) with the permission of The Royal Society of Chemistry. (c) Paper reactor containing only nanoscale pores decorated with AuNPs. Adapted from (Koga *et al.* 2017) with the permission of John Wiley & Sons, Inc. under the terms of CC-BY. (d) AuNPs grown on poly(diallyldimethylammonium chloride) (PADMAC)-coated cellulose nanocrystals (CNCs), and their evolutions after (e) first, and (f) second rounds of shell growth. (g) Preparation of the gold-plated catalysts. Adapted with permission from (Nasseri *et al.* 2020). Copyright 2020 American Chemical Society.

Another advantage of nanocellulose-supported NPs is that they enable control of the size of the catalytic sites. In a study by Nasseri *et al.* (2020), the surface coverage of gold on CNCs was finely tuned by changing the amount of plating solution (Fig. 3d to 3g). The coverage of the NPs was directly correlated with the turnover frequency (TOF) in the reduction of 4-nitrophenol to 4-aminophenol. Thus, the AuNPs@CNC nanostructures with

smaller NPs were more efficient (TOF of 263–274 h^{-1}) because they had larger specific surface areas and well-exposed catalytic sites compared with the fully gold-plated CNCs (TOF of 85 h^{-1}). The phenomenon was more apparent when poly(4-vinylpyridine)-grafted CNCs with gold NPs with an average size of 3 nm (TOF of 5533 h^{-1}) were used (Zhang *et al.* 2018b). A consequence of uniform NP size and repartition is atom economy because less metal precursor and/or a lower catalyst load is required for the reaction to proceed. For example, only 0.1 mol% of PdNPs@CNF was sufficient to promote the rapid Suzuki–Miyaura cross-coupling of aryl halides and phenyl boronic acid (1 to 2 h, up to 100% yield) (Zhang *et al.* 2018a), and 0.756 mol% of CuNPs@CNF was sufficient to selectively oxidize various sulfides into sulfoxides, and primary alcohols into aldehydes (Dutta *et al.* 2019a).

Nanocellulose can also help stabilize catalytic sites such as nickel boride NPs by preventing the reversion of the metal to its deactivated nickel oxide form when used in hydrogenation reactions (Prathap *et al.* 2017). Moreover, *Aspergillus oryzae* and *Kluyveromyces lactis β*-galactosidases immobilized on magnetic iron NPs@CNFs were more thermally stable than the soluble forms of the enzymes when they were used to hydrolyze the lactose in milk or cheese whey (Gennari *et al.* 2019). It seems that well-defined mesostructured CNFs with metallic oxide frames can protect proteins and enzymes from denaturation.

Moreover, the final NP-decorated material retains the high porosity and relatively high specific surface area (98% porosity, up to 80 m^2/g) of nanocellulose (Lucchini *et al.* 2018). As with NPs@CNFs, TOCNFs provide a porous structure with enhanced mechanical strength when crosslinked with branched polyethyleneimine (bPEI). The primary and secondary amines on the surfaces of the nanosponges can successfully catalyze Henry and Knoevenagel reactions without loss of activity after five reuse cycles (98.6% conversion) (Riva *et al.* 2020). CNFs can confer mechanical rigidity. This is useful for various industrial applications such as the in-flow catalytic reduction of nitro compounds (Koga *et al.* 2017), or precious metal scavenging combined with the direct reuse of the adsorbed NPs (Hong *et al.* 2020).

Of equal importance is the nano-confinement of the reactants in the pores. This arises from the inherent regular agglutination of nanocellulose upon drying, and facilitates rapid, efficient, and chemoselective transformations (Fig. 3c; Koga *et al.* 2017). For example, the effective concentration of nitrophenolate ions in the nanopores of CNF-Pd/NaBH$_4$ enables the almost complete and selective catalytic conversion of 3-nitrostyrene to 3-aminostyrene or 3-nitroethylbenzene (Meng *et al.* 2020). These effects can also be attributed to the enhanced adsorption of the reactants on the surfaces of the CNFs. In fact, aromatic molecules are adsorbed on nanocellulose, possibly *via* CH–π interactions and aromatic–hydrogen bonding on the exposed hydrophobic (100)/(200) surfaces of the type I crystals of the nanocellulose (Mazeau and Wyszomirski 2012).

Most of the previously cited materials can be easily recovered and reused several times. However, despite the advantages of heterogeneous catalysts, nanocellulose itself does not play an essential role in catalysis by metal–organic composites and supported enzymes, and there is direct competition from numerous organic polymer carriers for the role of the support. Therefore, a new approach is greatly desired.

Green Organocatalysis

The introduction of surface charges on CNFs during the extraction of the fibers often leaves functional groups such as sulfate half-esters, carboxylates, aldehydes, and

phosphates. Owing to their mildness in terms of pKa and Lewis basic/acidic strength, these groups are often overlooked as potential catalytic sites. However, Nikoofar *et al.* (2018) reported that CNCs prepared by acid hydrolysis and bearing sulfate esters successfully catalyzed a relatively fast pseudo four-component condensation of barbituric acid, carbohydrates, and heteroaromatic amines in ethanol reflux.

Table 2. Nanocellulose-based Organocatalysts with the Corresponding Catalytic Reactions

Catalytic site/cocatalyst	Nanocellulose used	Reaction	Ref.
SO$_3$H/COOH/NH$_2$	Amine-coupled CNCs	Selective aldol condensation of 4-nitrobenzaldehyde and acetone	Ellebracht and Jones (2018)
SO$_3$H/COOH/NH$_2$	Amine-coupled CNCs	Selective aldol condensation of 4-nitrobenzaldehyde or furfural and acetone	Ellebracht and Jones (2019)
SO$_3$H/COOH/NH$_2$	Amine-coupled TOCNFs, crosslinked by TPA	Batch and continuous flow selective aldol condensation of 4-nitrobenzaldehyde and acetone	Ellebracht and Jones (2020)
Proline derivatives, not CNFs	CNFs, TOCNFs	Aldol reaction of 4-nitrobenzaldehyde and acetone	Kanomata *et al.* (2018)
SO$_3$H	Sulfuric acid functionalized CNCs	Pseudo four-component condensation of barbituric acid, carbohydrates, and heteroaromatic amines	Nikoofar *et al.* (2018)
Proline, not CNFs	TOCNFs	Enantioselective Michael addition of nitrostyrenes and ketones	Ranaivoarimanana *et al.* (2019)
Proline, not CNFs	TOCNFs	Enantioselective aldol reaction of arylaldehydes and cyclopentanone	Ranaivoarimanana *et al.* (2020)
Primary and secondary amines of *b*PEI	PEI-crosslinked TOCNFs	Henry reaction of nitroalkanes and aromatic aldehydes, Knoevenagel reaction of diethylmalonate and aromatic aldehydes	Riva *et al.* (2020)
Native hydroxy groups	CNCs	Hydrolysis of esters, monophosphates, amides, and coat proteins of model viruses	Serizawa *et al.* (2013a)
Native hydroxy groups	CNCs	Enantioselective hydrolysis of amino acids	Serizawa *et al.* (2013b)
COOH	TOCNFs	Acid hydrolysis of acetal	Tamura *et al.* (2018)

In the same context, Tamura *et al.* (2018) found that TOCNFs with surface carboxylic acids were superior heterogeneous catalysts compared with homogeneous weak acids such as acetic acid and strong acids such as hydrochloric acid in the hydrolysis of acetals and ketals. This superiority was attributed to the ability of TOCNFs to form stable network structures in solvents, thereby providing effective contact between the substrate and the surface carboxylic acid groups. It is supposed that the aromatic substrates are preferentially concentrated on the crystalline facet of the catalyst. In a study by Serizawa *et al.* (2013a), an extremely low number of hydroxy groups in native cellulose with an abnormally low pKa value—that is, the sole functional groups at the crystalline surfaces of

the CNFs—efficiently catalyzed the hydrolysis of esters, monophosphates, and even amide bonds. Most importantly, the catalytic activity in the study mentioned above was clearly dependent on the size of the crystallites, and larger CNFs had higher activities. Table 2 summarizes the reported nanocellulose-based metal-free catalysts.

Cooperative catalysis—in which the functional groups on the surfaces of the CNFs and/or the external catalytic centers are far more active than when used alone—are also appealing. Ellebracht and Jones (2018) reported acid–base cooperation on the surface of the nanocellulose in an aldol condensation between acetone and *p*-nitrobenzaldehyde catalyzed by CNCs isolated by partial acid hydrolysis, TEMPO-mediated oxidation, and subsequent decoration with alkylamines. The complex association between free primary amines in proximity to one or more carboxylic acids and sulfate esters resulted in catalytic efficiency that was comparable to that of well-studied and established silicone-supported amines.

The association between proline derivatives, small organic molecules, and catalytically inactive nanocellulose also resulted in highly efficient direct aldol reactions between acetone and several aldehydes compared with the efficiency of the organocatalysts alone (Kanomata *et al.* 2018). In that study, TOCNFs with smaller widths (3 to 5 nm) had a more pronounced effect (86% yield) than thicker mechanically fibrillated CNFs (>10 nm) that were devoid of carboxylate groups (78% yield).

Catalyst aggregation is a serious concern in heterogeneous catalysis. Nanocellulose is highly dispersed in an aqueous medium, although most reactions require organic solvents to dissolve the substrates. In the latter media, the aggregation of nanocellulose is detrimental to aldol reactions (Ellebracht and Jones 2018; Kanomata *et al.* 2018). The presence of water in the system induces limited mass transport and miscibility of the substrates in the vicinity of the fibers, owing to several layers of water molecules that preferentially surround the CNFs and form a hydration shell (Ellebracht and Jones 2018; Ranaivoarimanana *et al.* 2019). Nevertheless, it should be noted that the surface order provided by the crystalline nanocellulose, and the enhanced cooperativity—which are the key factors in superior catalytic activity in such aldol reactions—can overcome the solvent-related issues. In fact, various methods such as solvent exchange by dialysis or centrifugation are known to produce stable organogels that are suitable for use in the reactions mentioned above (Ellebracht and Jones 2019, 2020; Ranaivoarimanana *et al.* 2019, 2020). Finally, nanofibers of other structural polysaccharides, such as chitosan, are expected to demonstrate unique catalytic behaviors, such as highly selective Knoevenagel condensations under green solvents (Hirayama *et al.* 2020).

Interfacial Chiral Catalysis on Nanocellulose

Reports dealing with chiral induction by nanocellulose-supported catalysts or by nanocellulose itself remain scarce, yet it is one of the most fascinating applications of this class of material. Serizawa *et al.* (2013b) reported a successful chiral induction by nanocellulose, in which amino acids were hydrolyzed preferentially, depending on their L or D form. Using CNFs with the same diameters and lengths, both I$_\beta$ and I$_\alpha$-rich CNFs selectively hydrolyzed hydrophilic L-form substrates, but only I$_\beta$-rich CNFs were active on hydrophobic and aliphatic D-form amino acids (Fig. 4a and 4b).
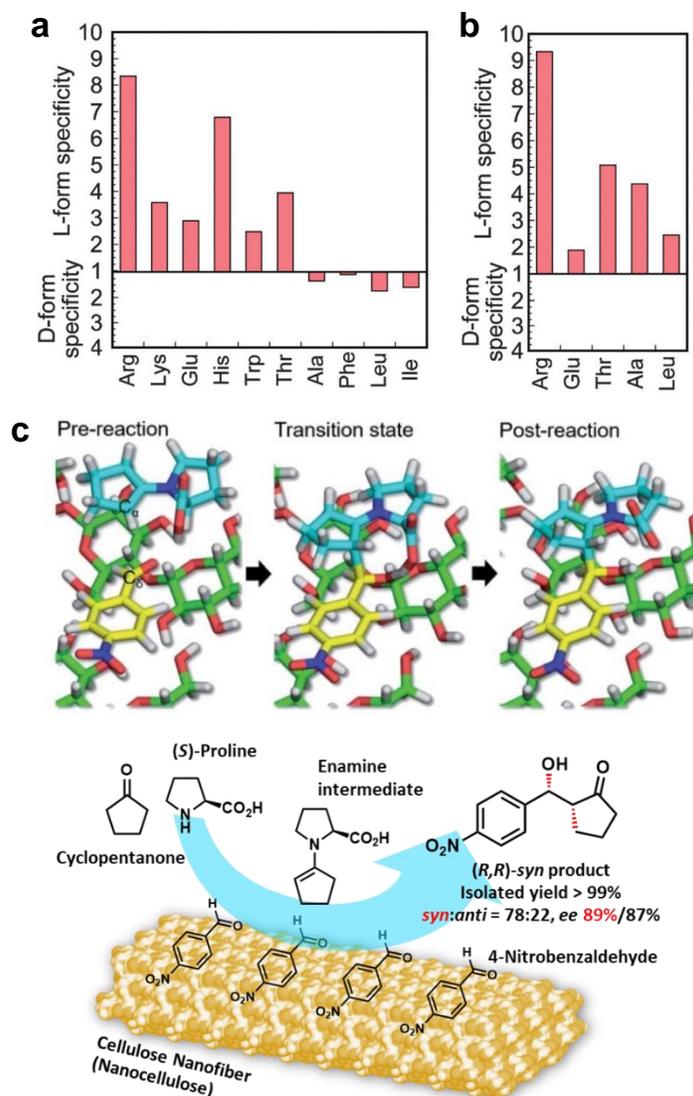
Fig. 4. Enantioselective reactions on the surface of nanocellulose. Dependence of the ratio of amine products on the chirality of the amino acid substrate during hydrolysis by (a) I$_\beta$-rich (tunicates) and (b) I$_\alpha$-rich (green algae) cellulose nanofibrils/nanofibers (CNFs). Reproduced from (Serizawa *et al.* 2013b) with permission from The Royal Society of Chemistry. (c) Model of the orientation of the transition states of the aldol reaction during C$_\alpha$–C$_\delta$ bond formation on the surfaces of the CNFs according to QM/MM-SMD simulation, and a scheme representing interfacial chiral catalysis. Adapted from (Ranaivoarimanana *et al.* 2020) with permission from The Royal Society of Chemistry under the CC-BY 4.0 license terms.

The interaction energies between the CNFs and the substrates in the enantioselective transformations were so small that the UV adsorption experiments were not conclusive. The chirality-specific orientation and the approach of the substrates to the regularly aligned H-bonding chiral centers on the CNFs were the relevant factors. This phenomenon was emphasized in enantioselective ketone hydrogenation reactions catalyzed by CNC-supported Pd NPs (Kaushik *et al.* 2015) and TOCNFs/proline catalyzed Michael reactions (Ranaivoarimanana *et al.* 2019). Further evidence for the involvement of nanocellulose in the preferential orientation of transition states was provided by quantum mechanics/molecular mechanics/steered molecular dynamics (QM/MM-SMD) in the

proline-catalyzed aldol reaction at the surfaces of TOCNFs (Fig. 4c; Ranaivoarimanana *et al.* 2020). The catalysis of the reaction between aromatic aldehydes and cyclopentanone by (*S*)-proline on the hydrophobic (100)/(200) crystalline surface of the nanocellulose delivered products with a high enantiomeric ratio (up to 89% *ee*, *syn* form). Therefore, it is undeniable that the selectivity in various transformations is closely related to the intrinsic crystalline structures of CNFs. Advances in such interfacial catalysis depend on taking advantage of the well-defined crystalline structure and inherent chirality of the nanocellulose surface.

BIOMEDICAL APPLICATIONS

Cell Culture Scaffolds

Cellulose and its derivatives have been used for medical applications—such as in renal dialysis, wound dressings, and anti-bacterial composites—for many years (Sindhu *et al.* 2014). The molecular self-assembly of structural oligosaccharides is one of the targets in the investigation of the effects of carbohydrate clusters on cellular responses, such as in hepatocellular carcinoma cells (Yoshiike and Kitaoka 2011; Kitaoka *et al.* 2013), myoblast cells and their alignment (Poosala *et al.* 2016; Poosala and Kitaoka 2016), human embryonic kidney 293 cells (HEK293) expressing toll-like receptor 2 (TLR2) (Hatakeyama *et al.* 2019a), and lectin-binding (Ogawa *et al.* 2012; Hatakeyama *et al.* 2019b) activities. In turn, nanocellulose, which is a natural nano-assembly of cellulose chains, has recently attracted increasing attention in terms of its suitability for biomedical and medicinal applications (Jorfi and Foster 2015). A fundamental understanding of the nanoscale details of cellular environments is essential for the structural and functional design of biomaterials that can mimic the natural cellular milieu (Hickey and Pelling 2019). Physical properties, such as elasticity, hydrophobicity, roughness, and charge density, cause different cell adhesion and proliferation properties (Kiroshka *et al.* 2014; Alshehri *et al.* 2016; Pedraz *et al.* 2016). Engler *et al*. (2006) reported that the stiffness of the substrate directed the differentiation of stem cells; that is, hardness and softness regulated the fate of the stem cells, although none of the components was a biological material.

The crystalline structures and degrees of crystallization of cellulose have a profound effect on its mechanical and physical properties (Nishino *et al.* 1995; Gibson 2012). Different modes of hydrogen bonding result in different Young's moduli—*e.g.*, cellulose I has a Young's modulus of 138 GPa and cellulose II has a Young's modulus of 88 GPa (Nishino *et al.* 1995). Plant-based cellulose also has a vast range of mechanical properties and porosities (Gibson 2012). Studies focusing on the stiffness of decellularized plant tissues—that is, 3D cellulose substrates—have also been conducted (Modulevsky *et al.* 2014, 2016; Fontana *et al.* 2017; Gershlak *et al.* 2017; Hickey *et al.* 2018).

Cellulose has tunable mechanical and structural properties, and it can be readily functionalized owing to the exposed hydroxyl groups on the surfaces of its microfibrils. Typical modifications include oxidation of the hydroxy groups to carboxylic acid groups using TEMPO (Isogai *et al.* 2011), cationization by grafting glycidyl trimethylammonium moieties onto the surface to introduce positive charges (Courtenay *et al.* 2017), sulfuric acid hydrolysis to produce sulfate half-esters (Capron and Cathala 2013), and diverse derivatization to produce a wide range of cellulose esters and ethers (Braun and Dorgan 2009). Cellular affinity for a biomaterial is regulated by a diverse array of cell–matrix interactions. In most cells except for blood ones, adhesion to the materials is essential for

survival, and occurs at the interface *via* specific recognition among adhesion receptors such as integrins on cell surfaces and extracellular matrix (ECM) proteins (*e.g.*, fibronectin, vitronectin, and laminin). Many of the ECM proteins associated with cell adhesion have a typical cell-binding domain containing an Arg-Gly-Asp (RGD) peptide, or a similar sequence (Yang *et al.* 2002). A conventional method used to enhance and regulate the degree to which cells become attached to a synthetic scaffold is to coat the scaffold with cell-adhesive proteins, such as fibronectin and laminin (Patterson *et al.* 2010; Wade and Burdick 2012). Likewise, cellulose has been modified with ECM proteins and RGD peptides (Lin *et al.* 2011; Bartouilh de Taillac *et al.* 2004). RGD-containing peptides were grafted onto the surface of regenerated cellulose and thereby enhanced the adhesion of osteoprogenitor cells (Bartouilh de Taillac *et al.* 2004). Gehlen *et al.* (2020) reported that TEMPO-oxidized CNFs inherently promoted cell adhesion and found that no additional biofunctionalization with cell-adhesive peptides or proteins was necessary. The reason for this is that under physiological conditions, negatively charged carboxylate groups interact with positively charged proteins, such as collagen, which fulfill important roles in cell adhesion. Courtenay *et al.* (2018) prepared cationized cellulose films using glycidyl trimethylammonium chloride (GTMAC). Bacterial cellulose films getting positive charges by chemical modification with GTMAC facilitate the attachment of MG-63 osteoblast cells. This was due to electrostatic interactions between the negatively charged cell membranes composed of phosphate–lipid bilayers and the positively charged cellulose with quaternary ammonium groups, as shown in Fig. 5.
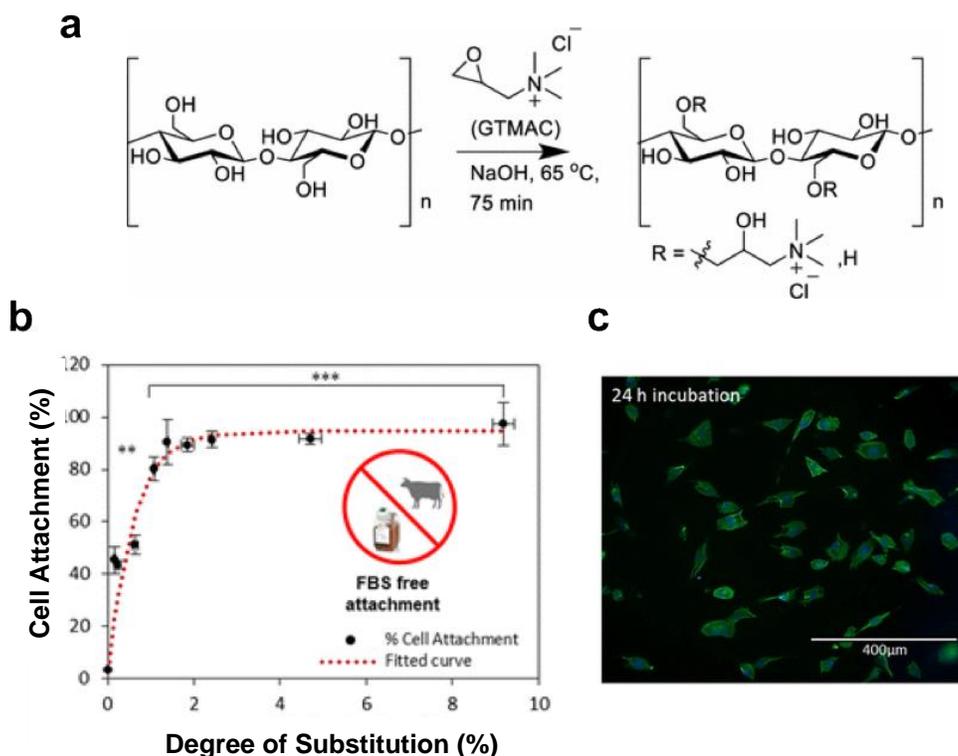

Fig. 5. Modified cellulose for a cell culture scaffold. (a) Surface cationization of cellulose films by glycidyl trimethylammonium chloride (GTMAC). (b) Effect of varying the degree of substitution on MG-63 cell attachment to GTMAC-modified cellulose films, without any ligands adsorbed on the surface. (c) Microscope image of MG-63 cells spreading on cationic cellulose films after incubation for 24 h. Reproduced from (Courtenay *et al.* 2018) with permission from Springer Nature.

Particularly important here is that cell adhesion to this substrate was achieved even in the absence of fetal bovine serum (FBS), which has been considered as the matrix ligands required for cell attachment in the culture medium. Reducing the reliance on growth factors or proteins for cell culture is a key issue with regard to industrial applications because they are very costly and are sometimes contaminated with co-existing biocomponents. Such biocomponents exhibit batch variability because they are derived from animals or humans. Therefore, the structural and functional innovation of cell culture scaffolds is required to provide bioadaptive and controllable microenvironments for the regulation of cell growth and fate.

3D Printing Technology

Three-dimensional (3D) printing is an emerging methodology that allows the fabrication of soft biocompatible hydrogels into 3D tissue-like or organ-like structures in advanced tissue engineering (Zhao *et al.* 2015), drug screening (Thomas and Willerth 2017), and regenerative medicine (Shirwaiker *et al.* 2020). Direct printing using "bio-ink" comprising high-viscoelasticity multifunctional cells/biomaterial composites facilitates the production of printed constructs with mechanical strength. The printability of a hydrogel is profoundly affected by several parameters, such as the ink discharge pressure, the needle diameter, the printing speed, the flow rate, and the printing temperature. Cellulose-based nanomaterials—such as CNFs, CNCs, and bacterial nanocellulose (BNC)—have attracted attention as components of bio-inks because they have superior bio-compatibility, structural similarity to the ECM, and favorable rheological properties (Siqueira *et al.* 2017; Dutta *et al.* 2019b, 2021). At low concentrations of 1 to 2 wt%, CNFs are intertwined with each other to form a network structure, resulting in the formation of a rigid hydrogel that meets the requirements of a 3D printable ink, such as shear thinning, strong thickening behavior, and sufficiently high yield stress (Kuzmenko *et al.* 2018). One of the successful methods is the 3D-printing of TEMPO-oxidized CNF hydrogels based on double network crosslinking. This was achieved first by *in situ* $CaCl_2$ crosslinking, and subsequently by chemical crosslinking with 1,4-butanediol diglycidyl ether (Xu *et al.* 2018a). The post-print using 1 wt% CNF ink successfully provided scaffolds with designable mechanical strength of the 3D-printed hydrogels in the range 3 to 8 kPa. Cell-compatibility tests revealed that the stiffness-tuned scaffolds supported human dermal fibroblast cell proliferation, according to the increased scaffold rigidity. Ink formulations containing auxiliary materials—such as naturally derived polymers including alginates, hyaluronan, and gelatin—have been used to improve the printability and the shape fidelity of nanocellulose-based inks (Liu *et al.* 2018; Xu *et al.* 2018b). Markstedt *et al.* (2015) succeeded in the 3D-printing of a human ear and sheep meniscus-shaped structures using bio-inks containing CNF/alginate blends and human chondrocytes, as shown in Fig. 6. The bioprinted materials with unique 3D architectures were prepared by crosslinking with $CaCl_2$, while the crosslinking properties were controlled by varying the ratios of alginate to CNFs without any viscoelastic changes. The authors also reported that cell viability in the printed constructs increased after 7 days rather than that on the first day. Lignin, a complex phenolic polymer found in various plants, is also expected to be used in biomaterial applications. For example, the antioxidant and antimicrobial activities of lignin and its derivatives can prevent wound inflammation. In particular, its moisture retention capability can promote the wound-healing performance of wound dressing hydrogels (Reesi *et al.* 2018). Based on this strategy, Zhang *et al.* (2020b) developed bio-inks that comprised colloidal lignin particles (CLP), alginate, and CNF. The CLP-containing

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biomaterial inks had excellent properties for 3D printing, up to 25% of CLPs to dry CNFs in a relative concentration, without any alteration of the shear-thinning behavior, an essential property of biomaterial inks for 3D printing. Furthermore, the addition of CLPs improved printing resolution. The CLPs afforded beneficial antioxidant properties on the biomaterial inks and improved the shape fidelity of the printed scaffolds. This was possibly attributed to the fact that the CLPs provided the additional crosslinking sites for divalent ions present in cell culture media (Zhang *et al.* 2020b). Reports of bio-inks comprising CNFs have been increasing in recent years, and bio-inks containing CNFs and CNCs are already being marketed by CELLINK (Boston, USA).
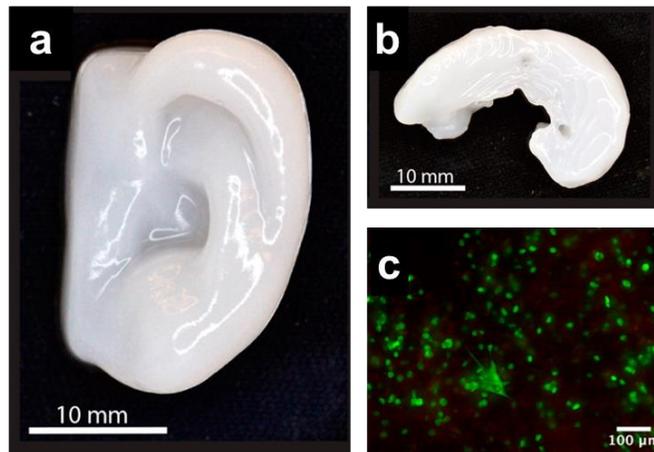

Fig. 6. 3D-printed constructs of (a) a human ear and (b) a sheep meniscus formed using nanofibrillated cellulose/alginate (80:20 wt/wt) bio-ink (water content: 97.5% wt/vol). (c) Viability of human chondrocytes in the printed scaffold after culture for 7 days. The image shows dead (red) and live (green) cells. Reprinted with permission from (Markstedt *et al.* 2015) Copyright (2015) American Chemical Society.

Biomedical Applications of Nanocellulose

The physical and mechanical properties, and bio-compatibility of CNFs make them potentially useful for pharmaceutical and biomedical applications. Wood-based CNF hydrogels have shown potential for the formation of 3D scaffolds for cell cultures, and they support the pluripotency of stem cells, the differentiation of liver progenitors, and the formation of organoid spheroids (Bhattacharya *et al.* 2012; Lou *et al.* 2014, 2015; Malinen *et al.* 2014). CNFs have a variety of advantages—including strength, non-cytotoxicity, and the ability to maintain moisture—and are therefore promising materials for clinical wound-healing applications (Zhang *et al.* 2013; Chinga-Carrasco and Syverud 2014; Powell *et al.* 2016). CNFs derived from wood or other plants are expected to serve as useful alternatives to biomaterials of animal or human origin. Such materials are in demand because the regulatory agencies of Europe, the USA, and Japan are seeking xeno-free biomaterials for use in patient care (Hakkarainen *et al.* 2016). Hakkarainen *et al.* (2016) performed clinical studies on CNF dressings for the treatment of skin graft donor sites among burn patients. In May 2019, UPM (Helsinki, Finland) launched a new wound care product (FibDex®) on the European market; it comprises wood-based nanofibrillar cellulose. The CNF dressing adhered well to the wound bed and detached from the wound surface itself after skin recovery. Wu *et al.* (2014) generated silver nanoparticles that self-assembled on the surface of cellulose nanofibers to prevent bacterial infection. These antibacterial materials enable

the proliferation of cells and have low cytotoxicity. The combination of cellulose nanocrystals (CNCs) and hydrogels is one of the effective approaches to tune physical characteristics and drug-release properties (Bajpai *et al.* 2015). Precise control over drug release was achieved by adding CNCs. CNC-stabilized Pickering emulsion systems with quinalizarin enabled diosgenin-mediated target delivery for human lung/breast cancer cells (Ilkar Erdagi *et al.* 2020). Furthermore, CNFs have attracted increasing attention in drug delivery systems: doxorubicin loading on TOCNFs for breast cancer therapy (Khine *et al.* 2020), and water-insoluble methotrexate release from CNF-reinforced polysaccharides films under colonic pH conditions (Meneguin *et al.* 2017).

Another biomedical application of nanocellulose materials is attracting attention in bone tissue engineering. Natural bone is mainly composed of collagen and hydroxyapatite (Li *et al.* 2012). Mimicking this *in vivo* composition is an essential step for advanced bone tissue engineering. CNF–hydroxyapatite composites can be used to emulate the properties of natural bone—that is, porosity, biocompatibility, a compressive strength of 0.1 to 12 MPa, and a compressive modulus of 6 to 330 MPa (Li *et al.* 2012; Eftekhari *et al.* 2014; Garai and Sinha 2014; Park *et al.* 2015; Huang *et al.* 2017). Biomimicking of the natural microenvironment around cells requires the proper dispersion of hydroxyapatite (Park *et al.* 2015). In the absence of other composites, hydroxyapatite aggregates and immediately precipitates. Therefore, high colloidal stability of components is of significance when used in 3D scaffolding materials. TEMPO-oxidized CNFs with negative charges can be used to attain the desired dispersion (Park *et al.* 2015). Hydroxyapatite was efficiently adsorbed to the TEMPO-oxidized CNFs, resulting in the formation of a hydrogel *via* crosslinking. Li *et al.* (2012) reported that slightly phosphorylated electrospun CNFs interact with calcium ions to increase the rates to form nuclei of calcium and phosphorus crystals, which can allow hydroxyapatite crystals with uniform size and morphology to grow on the CNFs. Mineralized macroporous scaffolding materials also provide a promising environment that resembles native bone tissues, from both topographical and chemical perspectives (Sundberg *et al.* 2015). Mesenchymal stem cells proliferate and differentiate into osteoblasts on the CNF-derived scaffolds, which are potential candidates for use in bone tissue engineering (Park *et al.* 2015; Sundberg *et al.* 2015; Huang *et al.* 2017).

Cellulose scaffolds are gathering attention in nerve tissue engineering. Nerve tissue engineering targets a unique type of cells including neurons and myocytes, which require electrical stimulation in action. Biomaterials with electrical activity, flexibility, and 3D nanostructures are required for this purpose. To satisfy these criteria, electroconductive cellulose materials have been developed by carbonization or coating with poly(3,4-ethylenedioxy-thiophene) (PEDOT) and multi-walled carbon nanotubes (Chen *et al.* 2015; Kuzmenko *et al.* 2016). These composites possess tunable pore sizes and mechanical properties as well as electrical conductivities. Besides, they are biocompatible and can promote neural differentiation (Chen *et al.* 2015; Kuzmenko *et al.* 2016).

In vivo biodegradation is a critical factor in the practical use of nanocellulose as a scaffolding material for tissue engineering. Cellulose including nanocellulose is in general considered biodegradable because of its rapid degradation by fungi and microorganisms. However, cellulose is not reabsorbed *in vivo*, since neither animals nor humans produce cellulases (Lam *et al.* 2012). A long-term monitoring study by Märtson *et al.* (1999) revealed that cellulose-based implants are truly biodurable, as cellulosic sponge scaffolds remained almost unchanged in rat subcutaneous tissue after 60 days. Such slow degradation brings about a potential limitation of cellulose scaffolds when used as an implant in the body. However, from different viewpoints, it is not a disadvantage when used in *in vitro*

cultures related to regenerative medicine and various *ex vivo* applications. The biomedical potential of nanocellulose has barely been explored, and it is expected to provide new bioadaptive materials owing to its unique physicochemical and interfacial properties, which cannot be artificially reconstructed.

CONCLUDING REMARKS AND FUTURE PROSPECTS

This review covers the recent advances in the functional design of nanocellulose materials and highlights the nanoarchitecture-triggered features of nanocellulose itself, especially for thermally conductive and optical regulation, interfacial organocatalysis, and challenges in biomedical applications. Paper material is a well-known thermal insulator, but crystalline nanocellulose is thermally conductive and can control the direction of heat flow. High-aspect-ratio nanocellulose can be aligned to manipulate the direction and diffusion of light. Well-defined nanoarchitecture and inherent chirality of nanocellulose surfaces may regulate asymmetric organocatalysis at the interface. Very thin, rigid nanocellulose is expected to provide bioadaptive and controllable microenvironments for the regulation of cell growth and fate in tissue engineering. Further understanding of the nanoarchitectures depending on a diverse array of nanocellulose sources will provide new ideas for materials design. The functional, eccentric design of nanocellulose to exploit its potential are nascent, and there is a long way to go before non-fungible nanocellulose-based nanomaterials will be available on the market. Nevertheless, the current pioneering work on the extraordinary properties of nanocellulose signals a new trend in the nanoproduct industries and a shift towards Sustainable Development Goals (SDGs). Nanocellulose will soon transition from being an alternative option to being irreplaceable, in the same way that the role of paper has changed over the last two thousand years.

ACKNOWLEDGMENTS

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