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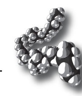

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Interactive Polymer Gels as Biomimetic Sensors for Carbohydrate Interactions and Capture–Release Devices for Pathogens

Stephan Schmidt, Tanja Janine Paul, and Alexander Klaus Strzelczyk*

Adhesive processes mediated by carbohydrate-decorated interfaces play a crucial role in many biological processes such as cell development or pathogen invasion. The involved carbohydrate scaffolds are soft and present multiple subsites forming complex and dynamic bonds to carbohydrate binding proteins. New tools and data are needed to understand how ligand presentation and mechanical properties drive these binding processes. This article highlights recent developments in the area of adhesion assays with a focus on soft biomimetic carbohydrate scaffolds as probes of adhesion forces. Key findings state that carbohydrate functionalized polymer networks largely show additive multivalency (statistical effects) and that the overall interaction forces are strongly affected by the stiffness of the network. These results indicate that phase transitions of carbohydrate bearing polymer gels may enable tunable affinity toward carbohydrate binding proteins. As an example, polymer networks undergoing large changes in mechanical rigidity, density, and spacing of carbohydrate ligands upon temperature stimulus are shown to bind or release carbohydrate binding bacteria such as *Escherichia coli*. The presented adhesion assays and the developed responsive systems can provide new insights into the mechanism through which carbohydrates mediate adhesion processes and establish new avenues toward scaffolds for the capture or release of cells or pathogens.

1. Introduction

Nearly all adhesion processes at the cellular level are dominated by carbohydrate interactions because a dense glycan layer, the glycocalyx, surrounds every eukaryotic cell. Consequently, important functions such as cell motility, development, pathogen invasion, fertilization, or cell communication involve carbohydrate interactions.[1,2] In the carbohydrate domain, multivalent binding has a crucial role in determining the overall affinity and selectivity of the resulting interactions. Due to their overall low affinity, carbohydrate ligands and their corresponding protein receptors usually show multiple binding sites. In addition, carbohydrate interactions typically occur between interfaces of larger entities, for example, between different cells or a cell and a pathogen. Binding between surfaces covered with ligands is likely enhanced as multivalent interactions can form between surface anchored clusters composed of many carbohydrate units. This so-called glycocluster effect serves to increase in avidity and biological activity.[1,3] Additionally, mechanical properties and mobility of ligand molecules at the crowded cell interface may affect their affinity.[4,5] Consequently, investigating the interactions of carbohydrates decorated surfaces has gained increasing attention in the past decade.

A major milestone for the analysis of carbohydrate interactions was the development of glycoarrays, which allowed large-scale screening of glycan binding partners and quantification of their interaction.[6,7] Besides identifying carbohydrate-binding proteins via such arrays, surface-immobilized carbohydrates allow analyzing “material cues” such as spacing, composition, microstructure, flexibility, or stiffness as modulators for carbohydrate interactions and multivalent binding. As of yet, significant progress has been made on understanding the effect of different ligand spacing on carbohydrate interaction. Using various surface printing and lithography tools, several groups established surface anchored carbohydrates at different densities and analyzed their interactions using labeled carbohydrate binding proteins via fluorescence readout[8–11] or surface plasmon resonance (SPR)[12] for label-free detection. From these studies, it was observed that an increased density of the carbohydrate ligands resulted in an increase in the multivalent binding thus increasing the overall fluorescence signal. However, the exact multivalent binding modes, of the studied carbohydrate such as chelate-, subsite-, or statistical binding were difficult to interpret from these experiments. In part, this problem is due to the readout indicating the adsorbed amount of carbohydrate binding partners with high throughput, but does not reveal the nature of the underlying interaction. Moreover, carbohydrate SPR chips and arrays typically lack the physiochemical material

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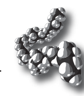


properties found in the natural environment, in particular, low stiffness of the cell environment and the mobility of the ligand presenting scaffold. Therefore, our lab established the so-called soft colloidal probe (SCP) adhesion assay for improved carbohydrate interaction studies (**Figure 1**) because it better reflects the biological situation of carbohydrates coupled to highly hydrated and soft scaffolds. The SCP adhesion assay employs poly(ethyleneglycol) (PEG) microgels with a diameter of about 20–100 µm as adhesion sensors. After functionalization with carbohydrates,[13] the particles adhere to planar glass slides coated with carbohydrate binding proteins. Since the SCPs are soft, their adhesion causes the SCP to mechanically deform in contact with the glass slide. The extent of the mechanical deformation is read out by reflection interference contrast microscopy (RICM) and then related to the adhesion energy. By evaluating the RICM interference pattern, the contact radius a and the SCP radius R can be quantified. A mechanical model developed by Johnson, Kendall, and Roberts (JKR-model)[14] gives the adhesion energy

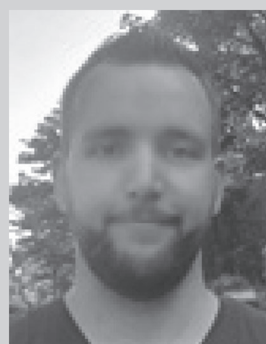
$$W_{\mathrm{adh}} = \frac{2Ea^3}{9\pi R^2(1-\nu^2)}$$

where E is the SCPs elastic modulus of the as determined by atomic force microscopy (AFM) indentation measurements and ν the Poisson ratio. Using the SCP approach, we can systematically study the effect of material parameters such as stiffness and ligand spacing on biomolecular interactions. Additionally, the SCP assay uses mechanical force as a readout whereby the physiological function of carbohydrate interactions is captured more closely when compared to SPR or fluorescence-based assays.

With the SCP technique is available, we analyzed the effect of material parameters on specific ligand–receptor interactions. This article first shows the effect on the scaffolds' elastic modulus properties on carbohydrate interactions, then the influence of ligand density and flexibility is presented. With these results at hand, we then established stimulus responsive scaffolds that can capture and release carbohydrate binding pathogens using large changes in scaffold elastic modulus and density upon temperature change.

Stephan Schmidt was born in 1978 in Potsdam. From 2000 to 2005, he studied chemistry and polymer science in Potsdam and Berlin. He received his Ph.D. in the lab of Andreas Fery at the University of Bayreuth. After working as a postdoc at the Max Planck Institute of Colloids and Interfaces and Fraunhofer IBMT in Potsdam, he started his independent research at the University of Leipzig in 2013. Since 2016, he has been an assistant professor at the University of Düsseldorf where he studies adhesion phenomena and switchable polymer materials.

Tanja Janine Paul was born in Haan, Germany. She received her B.Sc. in chemistry in 2014 from the Institute for Bioinorganic Chemistry and Catalysis at the Heinrich-Heine-University Düsseldorf. For her master's degree (2016), she joined the working group of Prof. Stephan Schmidt in the Department of Organic and Macromolecular Chemistry, where she then became a Ph.D. student. Her research interests include the thermosensitive display of carbohydrate ligands on microgels for switchable binding of proteins and bacteria.



Alexander Klaus Strzelczyk received his bachelor's degree (2014) from the Institute for Bioinorganic Chemistry and Catalysis at the Heinrich-Heine Universität followed by his master's degree (2016) from the Department for Organic and Macromolecular Chemistry in Prof. Schmidt's group. His research interests during his Ph.D. include the synthesis of thermoresponsive, carbohydrate bearing polymers and the study of specific carbohydrate–lectin interactions.

2. Effect of Mechanical Properties on the Affinity of Carbohydrate Scaffolds

The stiffness of materials represents a material property that can strongly affect cell behavior such as adhesion, motility, and development.[4,5,21,22] To explain this phenomenon, it is argued that depending on substrate stiffness, cell adhesion proteins undergo conformational changes followed by signal transduction and cell response.[23,24] On the other hand, theoretical work hints at a much more direct effect of material stiffness on adhesion. These studies consider thermal fluctuations of the adhering scaffolds which is closely related to its stiffness.[4,5,25] The main finding was that increased thermal fluctuations (decreased stiffness) have an adverse effect on adhesion due to conformational entropy. Under some circumstances, however, a decrease in stiffness and an increase in flexibility can lead to enhanced binding due to the increased spatial reach of adhesion molecules maximizing the number of adhesive ligand–receptor interactions.[26]

To identify which of these contradictory findings applies to carbohydrate functionalized hydrogel networks, we analyzed the effect of material stiffness on specific adhesion using a series of mannose (Man) functionalized SCPs with varying elastic modulus. Interactions were studied by quantifying the SCP adhesion on a surface coated with the Man-specific receptor concanavalin A (ConA).[27] For comparison, a similar series of

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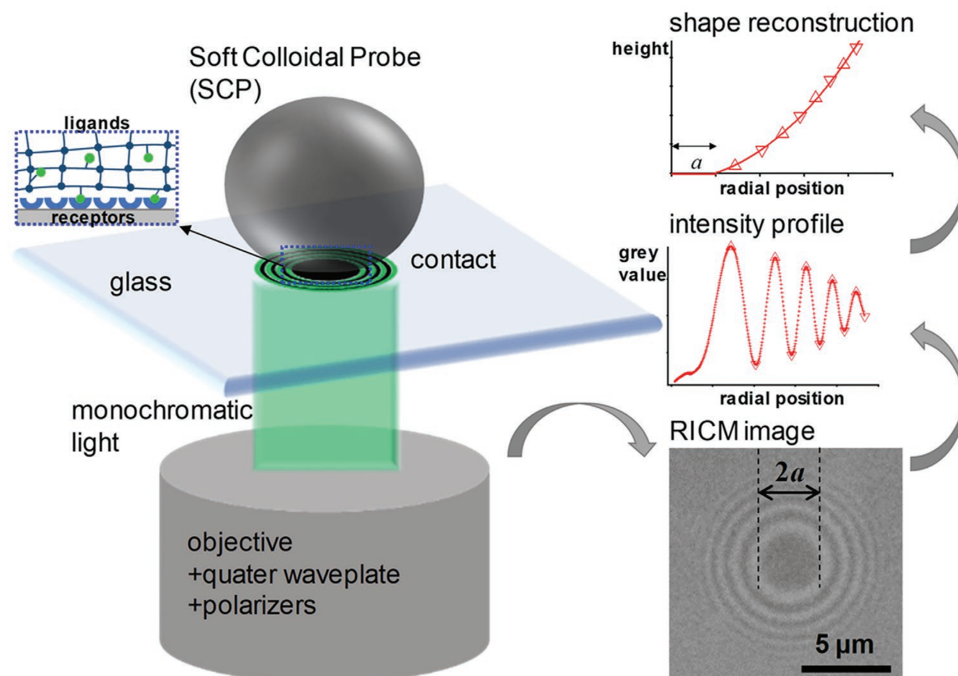

Figure 1. The SCP adhesion assay:[15–17] Ligand functionalized hydrogel-based SCPs adhere to a receptor functionalized glass slide. The adhesion leads to mechanical deformation of the probe, which can be quantified by measuring its contact radius *a* and overall shape by RICM.[18–20] With the previously determined elastic modulus of the probes, the adhesion energies can be then quantified by the JKR (Johnson–Kendall–Roberts) approach.[14]

SCPs was functionalized with biotin to quantify the adhesion to avidin coatings that bind biotin with a fivefold higher free binding energy compared to Man-ConA (7 k_BT for Man-ConA, 35 k_BT for biotin-avidin). When the SCP elastic modulus was increased by an order of magnitude, the carbohydrate mediated adhesion increased fivefold. Conversely, biotin-avidin mediated adhesion showed only a small variation with the elastic modulus, a 20% adhesion decrease when increasing the stiffness of SCPs. This suggests that weak carbohydrate–protein interactions are strongly affected by the scaffold's stiffness, reducing the stiffness of the scaffold can significantly reduce affinity (**Figure 2**). This is likely due to the increased chain entropy of the softer, less crosslinked polymer networks. Increased chain entropy leads to increased entropic repulsion of the scaffold resulting in dissociation of weak ligand–receptor complexes like Man-ConA. For carbohydrate ligands binding in solution, there have been similar findings on the adverse effects of flexible linkers on affinity.[28] The SCP adhesion measurements showed that this entropic repulsion effect could be present also in glycocalyx-like hydrogel networks, which would be relevant for glycocalyx engineering.[29] For strong interactions such as biotin-avidin, the increased thermal fluctuations for a softer network does not increase complex dissociation significantly. Here, changes in stiffness affect binding only in the highly rigid regime, where the special sampling range for binding sites is significantly reduced.[26] Therefore, we could show that entropic repulsion due to flexible polymer chains mainly affect weak interactions. These results suggest that in order to increase the binding strength of polymer scaffolds presenting multiple low affinity ligands, the scaffold's flexibility should be reduced, for example, by introducing more crosslinks.

3. Effect of Ligand Presentation on the Affinity of Carbohydrate Scaffolds

Due to the comparatively low affinity of carbohydrate–protein interactions, a large variety of multivalent carbohydrate scaffolds with sometimes drastically increased avidity have been developed. For example, compared to monovalent carbohydrate ligands, linear polymers presenting carbohydrate subunits along their backbone can increase avidity up to a 1000-fold.[30–32] Several groups established additional types of multivalent scaffolds to improve carbohydrate binding, for example, 2D-surfaces, nano- or microparticles, branched polymers, or dendrimers.[1,33–38] Usually these systems were designed for a specific purpose, for example, to bind certain receptor molecules or organisms. However, it is still difficult to assign a specific molecular mechanism to their binding behavior. Therefore, we used so-called precision glycomacromolecules presenting Man as ligands that allow for the precise variation of the spacing and number of Man-groups in the SCPs (Figure 4). The readout of adhesion energies of the glycomacromolecule-functionalized SCPs against a ConA surface mimics binding processes at the cells glycocalyx due to the involvement of the large glycan-like precision glycomacromolecules. It was expected that the glycocalyx-like SCPs were able to form chelate-like bonds at the close-packed ConA receptor surface due to dense presentation of Man-units in the network. To test this, the binding energies from SCP adhesion measurements were compared to binding free energies of freely dissolved ConA and glycomacromolecules using isothermal titration calorimetry (ITC). The comparison between SCP and ITC measurements showed that the different precision glycomacromolecules

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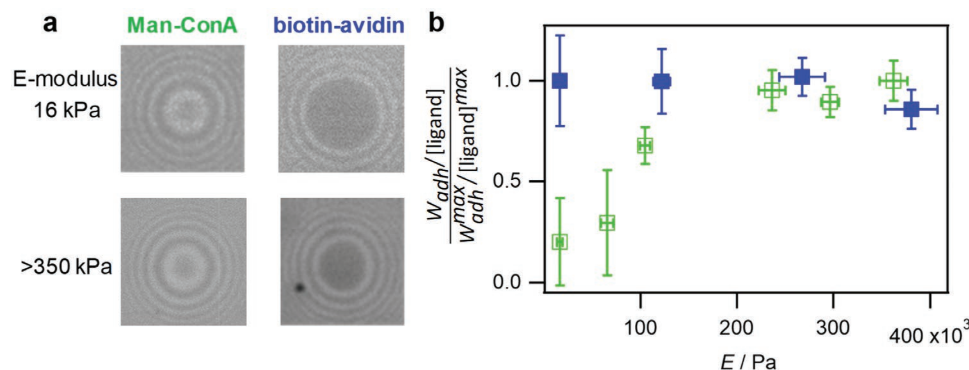

Figure 2. a) RICM images of the softest (top) and stiffest (bottom) biotin-functionalized SCPs (left) and Man-functionalized SCPs (right). b) Adhesion energy W_{adh} normalized by the concentration of ligands in the SCP (ligand) as a function of the elastic modulus. For comparing Man-ConA and biotin-avidin, the data are normalized by the maximum value. The adhesion of biotin ligands (full symbols, blue) stays constant, while adhesion for Man ligands (empty symbols, green) increases with the elastic modulus (E). Reproduced with permission.[27] Copyright 2017, Wiley-VCH.

showed an identical ranking in terms of ConA binding energy. Importantly, however, the absolute interaction energies between SCP-adhesion and binding in solution (ITC) was very similar, ≈20 kJ per mol of ConA. This showed that the glycomacromolecules presented in microgel scaffolds do not show the proposed chelate-like binding against the ConA surface. Nevertheless, such cooperative binding modes are proposed for glycans at the cell's glycocalyx. Therefore, to correctly mimic glycan-like binding in the glycocalyx, their large and branched structure and the crowded but mobile nature of the cell surface needs to be considered.[29] Examples include incorporation of glycopolymers in lipid bilayers,[39–41] vesicles,[42] or even in live cells[43,44] to then probe the interactions to glycan binding proteins or cells. These studies focus on analyzing biological functions of the prepared synthetic glycan mimetics with great success but due to the complexity of the involved materials, analysis of underlying binding processes was not the focus.

From our work,[27,46] we have seen that increasing the density of carbohydrate units in the SCP scaffold leads to an additive increase of the overall interaction, also described as statistical multivalency effect.[3,47] However, additional molecular-scale details of the multivalent binding modes besides the statistical effects could not be seen via SCP adhesion. Other direct binding assays using various scaffolds such as dendrimers[48] or nanoparticles[49] as scaffolds also mainly showed additive effects due to the multivalent presentation of carbohydrates, but not positively cooperative interactions due to chelate-like binding or subsite binding to the receptor. To shed more light on the molecular mechanisms of carbohydrate binding X-ray crystallography,[50–53] or single molecule techniques based on labeled carbohydrates for NMR spectroscopy[54] and single molecule AFM[55–60] were used. For example, Drescher and coworkers showed that flexible PEG-based ligand scaffolds can stretch to accommodate an additional binding site after binding to a first site at a carbohydrate binding protein.[54] Such chelate-like binding potentially leads to an increase in affinity and specificity as well as glycoclustering as a trigger for cellular functions.[61] On the other hand, Ratto et al. showed via single molecule AFM that the dissociation of the four ConA binding sites from a dense layer of mannose resulted in less than additive contribution from each binding site,[62] that is, negatively cooperative multivalency.[28] Our single molecule atomic force microscopy studies (SM-AFM) on sequence defined glycomacromolecules (Figure 4) confirmed that linear structure can simultaneously bind to multiple receptor sites; however, stretching of the ligands in contact with the carbohydrate binding protein to accommodate more binding sites was not observed.[60] In addition, large and highly multivalent glycomacromolecules capable of clustering multiple receptors actually showed a reduced binding propensity, owing to their flexibility and steric repulsion.[32] These examples show that also single molecule binding studies on multivalent carbohydrate ligands often yield ambiguous results due to the structural diversity of the studied ligand systems as well as the varying experimental conditions. Although it is still difficult to assign precise multivalent binding modes for glycopolymers, two main factors driving their interactions have emerged: 1) statistical multivalency leading to additive binding contribution of multiple carbohydrate units; 2) entropic repulsion due to molecular flexibility leading to reduced binding for more flexible system owing to the generally low affinity of carbohydrate interactions.

4. Switchable Carbohydrate Presenting Scaffolds

Switchable polymers have become quite essential in biomedical research. For example, the polymer phase behavior and physical properties like polymer stiffness and coil size can be controlled by stimuli-like temperature, pH, or ionic strength, which is relevant for triggered drug release, or sensing.[63] In case of carbohydrate functionalized hydrogel scaffolds, we have seen that their specific interactions could be controlled by two main factors:1) the scaffold stiffness, where stiffer scaffolds exhibit larger interactions (**Figure 3**); 2) the carbohydrate density, where increased density of ligands in the scaffold results in a proportional increase in receptor binding due to statistical multivalency (**Figure 4**). Both parameters can be used in combination to design carbohydrate bearing scaffolds with switchable binding to protein receptors and pathogens (**Figure 5**).

Our lab has utilized polymers with a lower critical solution temperature (LCST) in the physiological temperature range that is, poly(N-isopropylacrylamide) or poly[oligo(ethyleneglycols)].[64]

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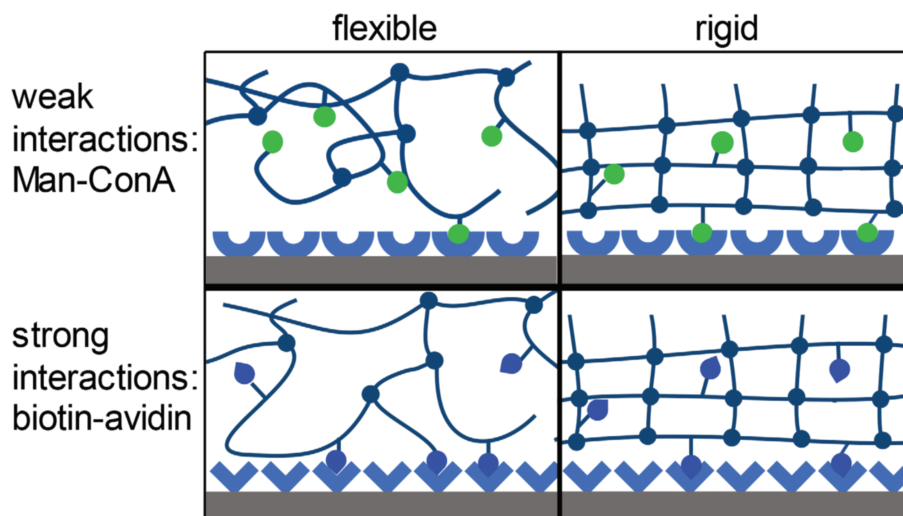

Figure 3. Formation of complexes by weak binders is significantly reduced in case of soft, flexible scaffolds due to entropic repulsion. For strong binders like biotin-avidin higher spatial sampling range in case of soft networks enhances overall adhesion of biotin ligands. For stiff networks, the spatial sampling range and the number of formed complexes is reduced.

Using an anionic peroxide as initiator, the respective monomers, a crosslinker, and a surfactant monodisperse microgels are formed at temperatures above the LCST in a single reaction step.[65] When varying the temperature below or beyond the LCST (≈32 °C), these microgels swell or collapse, that is, their density as well as the elastic modulus varies.[66] In addition, above the LCST, the microgels are hydrophobic and show a smooth surface whereas below the LCST the surface is fuzzy and the polymers are hydrated.[67–69] The temperature-control over hydrophobicity, surface structure, and stiffness was

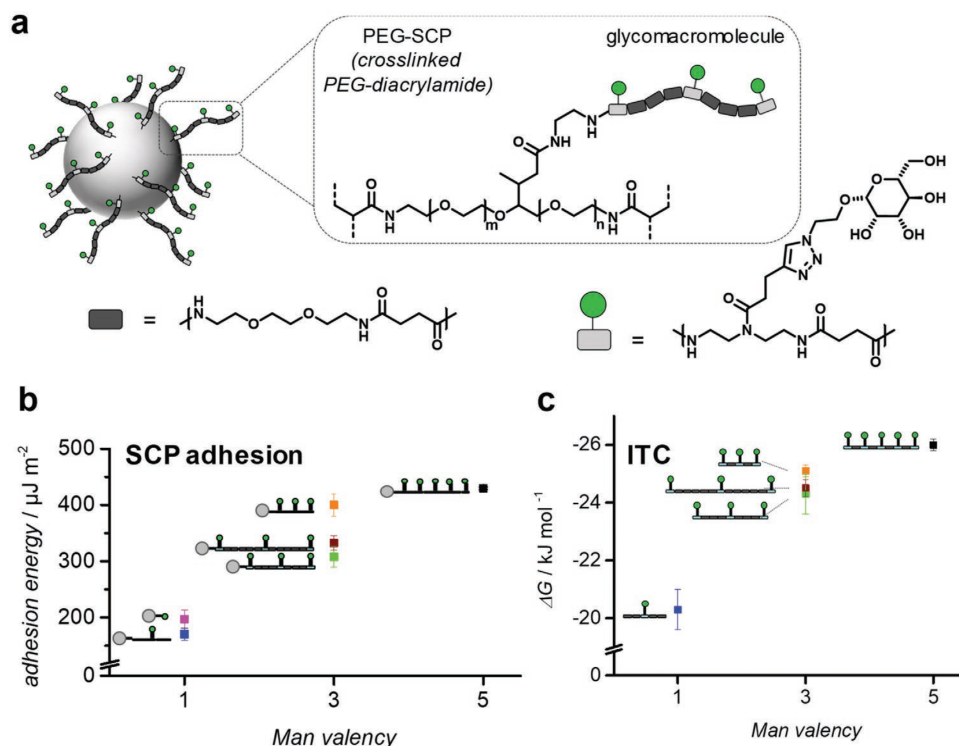

Figure 4. a) Schematic overview of precision- glycomacromolecules functionalized SCPs with different number of Man units and spacing along the glycomacromolecules backbone b) SCP-adhesion energies determined for the series of glycomacromolecules on ConA surfaces. c) Gibbs free energy ΔG of freely dissolved glycomacromolecules and ConA measured by isothermal titration calorimetry (ITC). Reproduced with permission.[45] Copyright 2018, American Chemical Society.

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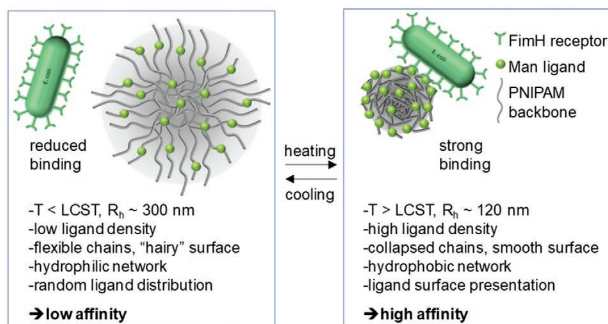

Figure 5. Illustration of Man-functionalized poly(*N*-isopropylacrylamide) microgels and the control of *E. coli* binding upon changing the temperature below (left) and above (right) the LCST. At temperatures above the LCST, the microgels collapse and they become hydrophobic. This likely leads to surface enrichment of Man units and overall increase in Man density, increasing specific binding to carbohydrate binding proteins and bacteria. Reproduced with permission.[64] Copyright 2019, American Chemical Society.

successfully used to construct microgel coatings for switchable cell culture surfaces.[69,70] However, these materials do not specifically bind certain cells or bacteria but are quite promiscuous and would bind to virtually any protein, which makes it difficult to control their adhesive properties. The established Man-presenting LCST microgels were designed to specifically bind to *Escherichia coli* (*E. coli*) or any other Man-binding pathogen above the LCST (**Figure 6**). However, once bound above the LCST, complete release of the bacteria from the microgel still proved to be difficult and was achieved only for short incubation times of less than 30 min. Releasing *E. coli* from microgels below the LCST is probably hindered due to the long bacterial fimbriae that can form entanglements within the microgel network and ultimately lead to permanent binding.[71]

Other work on thermosensitive materials for the switchable presentation of carbohydrates used grafted polymers on nanoparticles[72–74] or 2D surfaces.[75,76] Typically, these systems were able to capture and release carbohydrate binding proteins upon temperature change, but the successful release of bacteria was not yet confirmed,[75] probably due to the strong adhesion and additional entanglements of the fimbriae.[71] In comparison to these grafted LCST polymers, the microgels additionally undergo a large change in the density of ligands to switch between binding and non-binding. This considerably increases the difference in affinity below and above the LCST and may ultimately enable the release of captured bacteria after further optimization.

In sum, polymer scaffolds functionalized with complex glycans have emerged as model systems to mimic binding processes at the cells glycocalyx or to identify and analyze carbohydrate binding proteins. Our adhesion studies with soft hydrogel-based probes have shown that material parameters such as the scaffold rigidity have a strong effect on carbohydrate interactions. The SCPs are ideal for fast, high throughput optical readout[20,77] but can also serve as a biomimetic colloidal probe in AFM to directly study adhesive properties on cells.[78] This will be particularly useful to investigate the molecular mechanisms underlying the cell-instructive properties of specifically interacting carbohydrate functionalized scaffolds.[79,80]

In addition, systems with carbohydrate decorated scaffolds can serve as tools to selectively capture proteins, cell, or bacteria. We have shown that carbohydrate ligands are compatible with LCST polymers to switch their affinity toward pathogens via temperature stimulus. We expect that the low selectivity of carbohydrate interactions remains a significant obstacle for

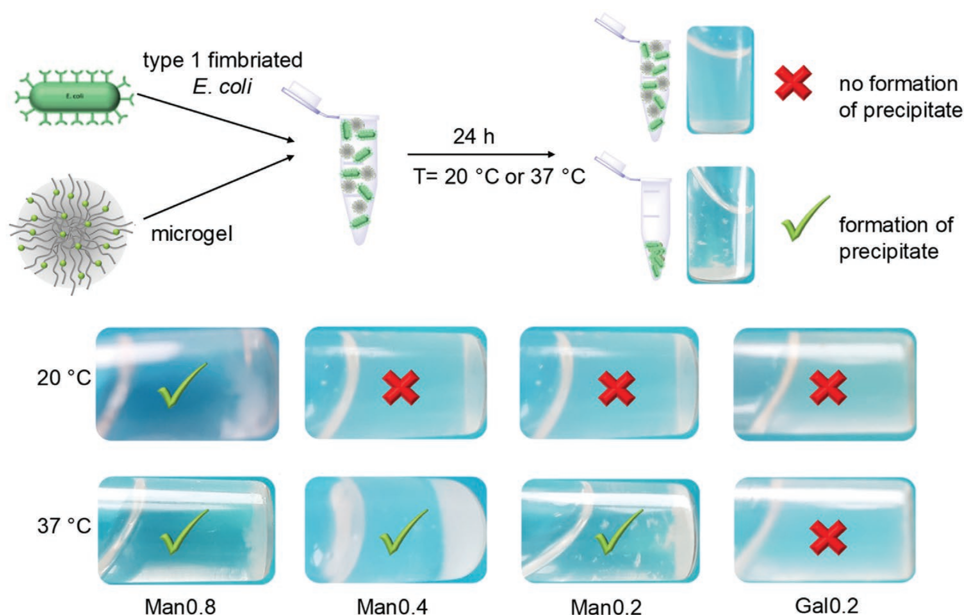

Figure 6. Top: Schematic overview of bacteria/microgel aggregation. Pictures of the experiments at 20 °C and at 37 °C indicate temperature-dependent capture of *E. coli* at intermediate and low concentration of Man in the microgels (0.4 and 0.2 mol%). Galactose functionalized microgels (negative control) do not bind the bacteria. Reproduced with permission.[64] Copyright 2019 American Chemical Society.

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biomedical applications. Therefore, further advances in precision synthesis of polymers and nanomaterials will be needed to improve selectivity and to better analyze and control the biological effects of these materials. Hence, a joint effort in glycopolymer design, scaffolds synthesis, bioconjugation, and physiochemical and biological characterization of the material are required to realize the next generation glycomaterials and their applications.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

glycomacromolecules, LCST polymers, lectin, microgels, RICM, thermosensitivity

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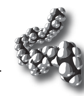

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