Sweet building blocks for self-assembling biomaterials with molecular recognition

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5.1 Introduction

Carbohydrates are the most abundant biomolecules on our planet. They are the main structural components and a source of energy in various biological systems. Their role, however, goes far beyond these simple functions: carbohydrates are involved in a plethora of recognition events triggering specific pathways and defining organism's diversity [1–3]. Together with other two classes of biopolymers, proteins and polynucleotides, they are responsible for coding and transferring bioinformation within the living world. In fact, glycosylation is the most common posttranslational modification of biomolecules such as proteins and lipids. It is used by nature to instruct proteins' folding and to create specific scripts readable in recognition events (Fig. 5.1).

The use of carbohydrates in the design of molecular self-assembling blocks for the synthesis of functional supramolecular materials is just emerging. Several challenges are associated with this late exploitation as compared with proteins and peptides. On one hand, carbohydrates seem to be the perfect building block for self-assembling biomaterials with molecular recognition as they can form simultaneously multiple hydrogen bonds (H-bonds). They are also quite specific because of the available different chiral centers; for example, glucose (Glc), mannose (Man), and galactose (Gal) differ in only one chiral center but have different bioactivity/specificity. On the other hand, these advantages turn into drawbacks when studies in aqueous environment are in quest [4,5]. Such studies have proved impossible to discriminate carbohydrates differing only in a single chiral center in water and difficult to control precisely the formation of H-bonding. Besides troubles with the biospecificity in physiologically relevant environment, the self-assembly of carbohydrates in aqueous media is also challenging. They differ from the lipids that self-organize because of the hydrophobic interactions. They also lack aromatic units allowing complexation with metals (often used to assemble materials from nucleobases) or assembly by π-π stacking. Thus, carbohydrate units must be usually incorporated within building block that are molecularly designed to present a

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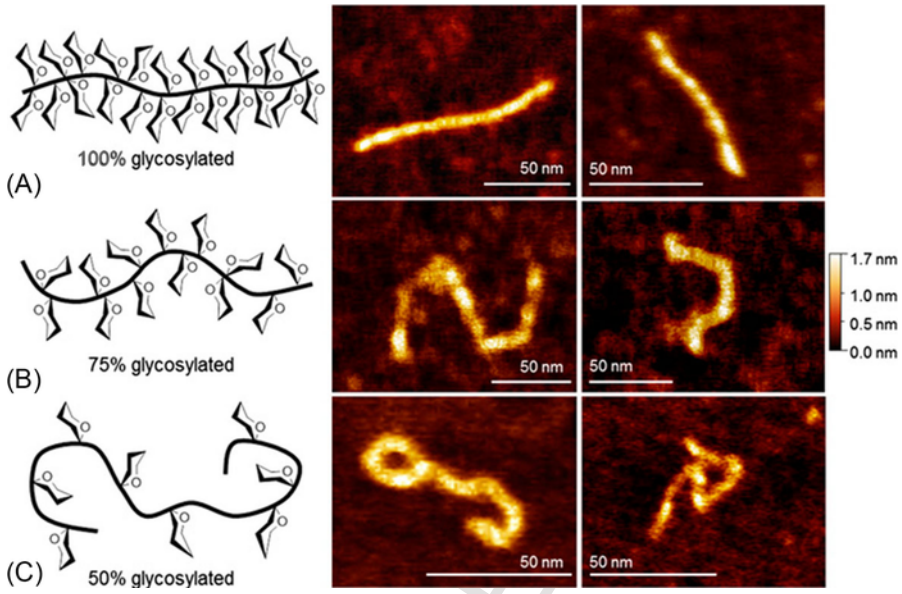

Fig. 5.1 The glycosylation of biomolecules has multiple roles: it instructs conformation of the respective biomolecules, e.g., proteins; protects and/or stabilizes them; and also activates them by creating specific scripts readable in recognition events.
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combination of interaction forces allowing their self-assembling into dynamic structures that are a better mimic of the extracellular matrix (ECM).

Below, we present several approaches and designs that have been developed within the last years to overpass the abovementioned challenges into the emerging area of carbohydrate-based supramolecular biomaterials.

5.2 Supramolecular systems using unmodified sugars

Within the biological systems, carbohydrates regulate different biochemical process mainly by interacting with proteins (carbohydrate-protein interactions, CPI) and other carbohydrates (carbohydrate-carbohydrate interaction, CCI). These interactions are generally weak, multivalent, and noncovalent ones, usually H-bonding (CCI and CPI) and/or carbohydrate-aromatic stacking (CPI), also called dispersion, apolar, or CH/π interactions [5,6]. Several biomimetic systems have been developed inspired by these natural supramolecular carbohydrate networks.

5.2.1 *Self-assembly of glycosaminoglycans (GAGs) and proteins*

The simplest carbohydrate supramolecular systems involve the use of unmodified components of the ECM, e.g., proteins and glycosaminoglycans (GAGs). There are numerous examples of hydrogels prepared using these components [7]. However, most of these systems are based on simple electrostatic interactions between GAGs (negative charge) and proteins bearing positively charged amino acids, and thus, they are generally instable at physiological conditions. The preparation of such materials, therefore, involves cross-linking step for the stabilization of the system. While this step is beneficial in terms of stability, it has also several drawbacks related with the dynamics/responsiveness of the system and the bioinformation that is transferred [8]. Usually, the cross-linking process involves modification of functional groups such as —COOH and —NH_2 that are crucial in recognition events and bioinformation transduction. Once modified, these functional units are not available for cross talk with other bioentities in the extracellular milieu. Recently, we demonstrated that these drawbacks can be overpassed by a process named interfacial complexion [9]. The process makes use of the specific interactions between the GAG (chondroitin sulfate or heparin) and collagen. When solutions of these polymers are brought into a contact, the biomolecules at the interface form a complex that acts as a viscous barrier preventing the mixing of the solutions (Fig. 5.2A2).

This complex can be isolated as a hydrogel or a fiber that can be drawn in the following step. During the drawing process, the integrity of interfacial complex is perturbed, and individual, scattered complexes are formed (Fig. 5.2A3). These complexes act as nuclei from which nanofibers grow (Fig. 5.2B, white arrows) and coalescence to form the final microfiber. Of note, when the components interact only electrostatically but not specifically (e.g., hyaluronan/collagen), the process is not reproducible, and the formed fibers are not stable at physiological conditions. The

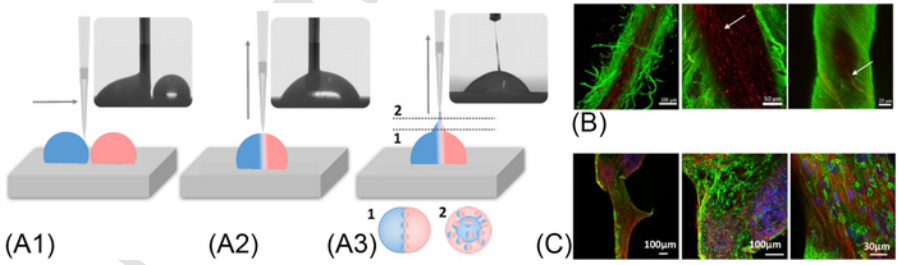

Fig. 5.2 Formation of collagen-GAG fibers by interfacial complexation: (A) schematic presentation of different processing steps, (B) confocal micrographs of the obtained fibers showing the incorporation of collagen *(green)* and glycosaminoglycan *(red)*, (C) adipose-derived stem cells adhere on the fibers and remodel them after 7 days of culture. Figure adapted from Carretero A, et al. Extracellular matrix-inspired assembly of glycosaminoglycan-collagen fibers. J Mater Chem B 2017;5(17):3103–3106.

fibers obtained by this method are flexible in wet and dry state, and their properties such as stability and diameter can be tailored by the choice of the complexing biopolymers and the processing conditions, e.g., viscosity of the polymer solutions and the drawing rate. Because the fiber components are unmodified ECM molecules, stem cells adhere readily to them and align with the smaller fibers that build the microfiber. Moreover, the reversible interactions between GAG and collagen allow remodeling of the fibers by the attached cells.

5.2.2 Self-assembly of carbohydrates and peptide amphiphiles

This approach also copycats the specific interactions between GAGs and proteins in the ECM. The methodologies involve the use of natural, unmodified GAGs and peptide amphiphiles, which are designed to self-organize and bind to the GAG via the specific sequence incorporated in the peptide portion. The role of the GAGs in this approach is to enhance the biofunctionality of the peptides' supramolecular structures either by driving different organization of the peptide amphiphiles (Fig. 5.3A) or by adding specific interactions with other bioentities (Fig. 5.3B) [10,11].

All GAGs have linear structure and intrinsic negative charge. These properties allow their application as molecular wires that can guide directional self-assembly. An example of such application is the formation of hierarchically organized sacs and membranes when a solution of hyaluronan of high molecular weight is added to a solution of peptide amphiphile (Fig. 5.3A). These sacs can be used to create discrete

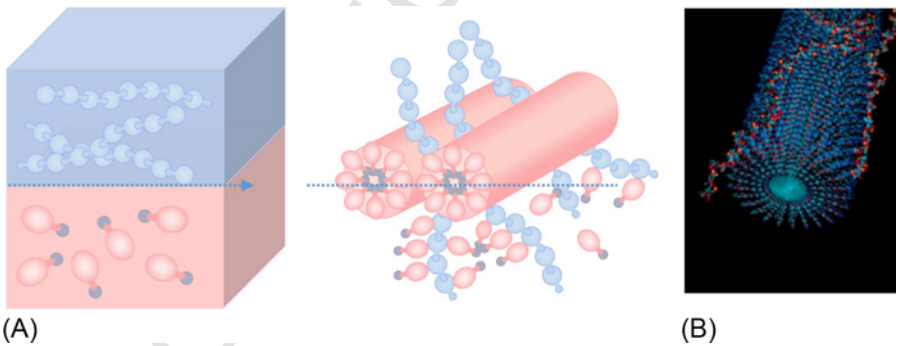

Fig. 5.3 (A) Schematic presentation of the formation of ordered membranes from hyaluronan *(blue)* and peptide amphiphile *(pink and gray)*: initial mixing of two components; formation of fibers at the solution interface followed by reptation of the hyaluronan macromolecules through the barrier and nucleation of new fibers on the hyaluronan templates that are perpendicular to the interface and the initially formed fibers. (B) Nanofiber formed by the aggregation of positively charged peptide amphiphile molecules and nucleated by the negatively charged heparin chains. The heparin chains presented on the surface of the fiber can bind different growth factors and thus enhance the bioactivity of the core structure. Adapted from Rajangam K, et al. Heparin binding nanostructures to promote growth of blood vessels. Nano Lett 2006;6(9):2086–2090; Capito RM, et al. Self-assembly of large and small molecules into hierarchically ordered sacs and membranes. Science 2008;319:1812.

cellular environments because they are semipermeable and allow exchange of nutrients and metabolites. In a different design, heparin, a GAG that binds various growth factors, was used to nucleate and biofunctionalize self-assembled nanofibers from peptide amphiphiles (Fig. 5.3B). As heparin is exposed on the fiber surface, the obtained assemblies bind VEGF and FGF-2 and stimulate extensive angiogenesis in vivo [10].

5.3 Supramolecular systems with glycopolymers and carbohydrate amphiphiles

Generally, the design of supramolecular building blocks with modified carbohydrates is challenging as subtle changes in the chemical structure of the carbohydrates can affect their specificity that is orchestrated by different intermolecular interactions. The synthesis of the respective building blocks is also quite demanding: carbohydrates have many hydroxyl groups that must be protected in order only specific one to react.

5.3.1 Peptides decorated with biofunctional carbohydrates

In the cellular environment, biofunctional carbohydrates are often presented as molecular conjugates such as proteoglycans and glycoproteins. These natural conjugates have inspired different designs based on self-assembling peptides decorated with carbohydrates. Usually, the self-assembly is driven by the peptide portion, while the carbohydrate moiety is presented on the surface of the formed peptide core, thus allowing sugar involvement in recognition events with other bioentities such as proteins (e.g., lectins and enzymes) and cells (Fig. 5.4).

So far, only simple monosaccharaides such as Man [12], glucosamine (GlcN) [13–15], N-acetylglucosamine (GlcNAc) [16], and glucuronic acid (GlcA) [16] have been exploited for the functionalization of self-assembling peptides of different complexity (Fig. 5.5). This monosaccharide unit can be bound directly or via linker (black, Fig. 5.5A, B, and E) to a bioactive peptide (pink, Fig. 5.5). The designs also

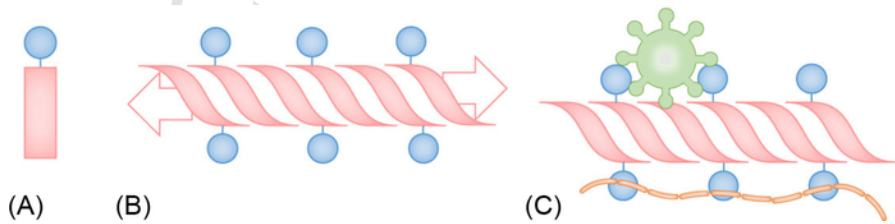

Fig. 5.4 Schematic presentation of (A) carbohydrate *(blue)*-functionalized peptide amphiphiles *(pink)* and (B) their assembly. (C) The obtained assemblies have pendant carbohydrate moieties that can participate in multivalent biorecognition processes with, e.g., proteins *(orange)* and cells *(green)*.

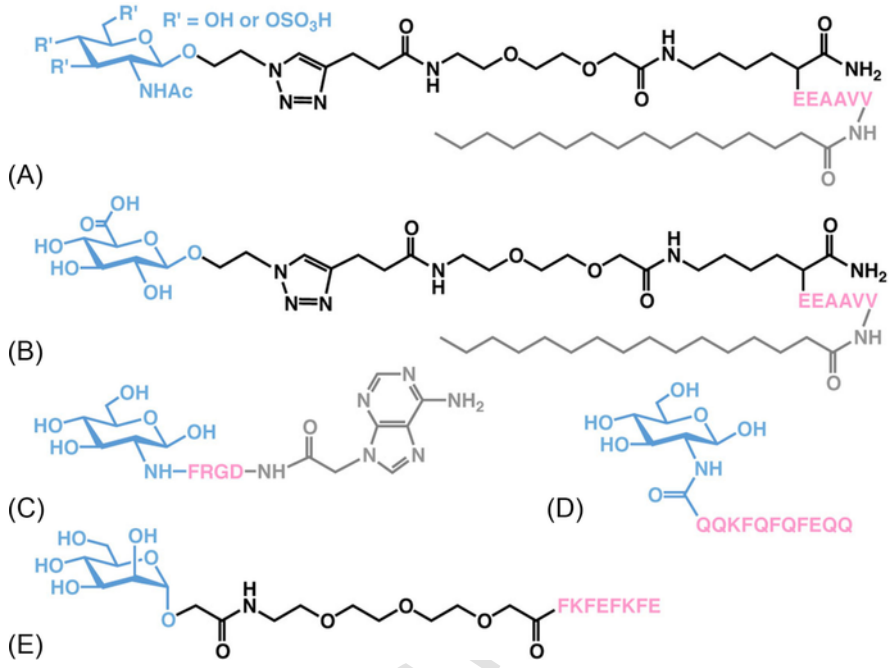

Fig. 5.5 Examples of synthetic glycopeptides that self-assemble into nanofibers with multivalent carbohydrate presentation on the surface. Different molecular functionalities are colored: carbohydrate *(blue)*, peptide *(pink)*, linker *(black)*, and amphiphile enhancer *(gray)*.

differ by the peptide unit that is incorporated within the structure—it can be a sequence that forms β-sheet or any other bioactive sequence that is additionally functionalized (gray, Fig. 5.5A–C) with aliphatic or aromatic units to add/enhance the amphiphilic properties of the molecule.

Similar to the native glycoprotein, the developed synthetic glycopeptides can play different bioroles and thus can have different biomedical applications. They can be used in regenerative medicine to either promote cell proliferation by interacting with different cell receptors or to prolong the lifetime of growth factors and/or augment their availability to the cells [13,16]. Immunomodulation materials can be also designed by exploring specific carbohydrate-antibody interactions [17]. Targeted interactions between specific lectins and tailored glycopeptides are explored for cancer and immunotherapy [14]. Bacterial adhesion and control of biofilm formation have been also envisioned as possible applications and supported by preliminary results: carbohydrate-functionalized β-sheet nanostructures reduce bacterial motility and agglutinate bacterial cells [12,18].

Of note, all these applications are based on specific multivalent interactions with proteins, i.e., the individual unassembled molecules do not have any bioactivity as they are not able to bind the respective proteins. In fact, this peculiar behavior is very useful in the design of responsive systems as described below.

5.3.2 Glycopolymers

This is the largest class of glycan-based building blocks for self-assembling biomaterials. In fact, these amphiphiles are very similar to the above-described molecules in which the peptide portion is replaced by a synthetic unit. This difference in the building components of the amphiphiles has the drawback of a reduced biological information/bioactivity due to the discarded peptide portion. However, the design has several advantages mainly related with versatility and feasibility of the systems. As an example, the synthetic portion can be easily tailored to give rise to different architectures such as micelles, vesicles, and wires of different sizes and with the carbohydrate moieties exposed on the surface (Fig. 5.6) [19–22]. The carbohydrate moiety has a multiple role: it adds amphiphilic properties to the molecule that drive the self-assembly; it stabilizes the formed assembly via CCIs, and it targets specifically a bioentity, e.g., protein or cells. The glycan portion can also influence the assembly process: different stacking was observed in the presence of monosaccharide (left-handed helix) or disaccharide (right-handed helix) [23]. The interactions of *Escherichia coli* with mannose-functionalized self-assembled nanostructures are the most explored in the field [20–22,24,25]. The selectivity of the assembly can be tuned by controlling the density of the carbohydrate on the surface. This can be done by coassembly with an amphiphile that does not contain the functional carbohydrate unit [24,25].

Besides linear amphiphiles, branched structures such as Janus dendrimers can be also used as synthetic cores (Fig. 5.6D) [19,26–32]. In such designs, multivalent presentation of the carbohydrate is already available within the monomer, but their density is usually not enough to trigger specific interactions with proteins. Studies with large libraries of Janus glycodendrimers functionalized with monosaccharides (e.g., mannose and galactose) or disaccharides (e.g., lactose) demonstrated that lectins do not recognize always the sugars presented on the surface of different assemblies. The recognition depends on both density of the sugar and its topological conformation: soft and adaptive assemblies as glycodendrimersomes interact stronger with lectins as compared with the less flexible lamellas. These results suggest that glycoassemblies stabilized by covalent bonds are in disadvantage when compared with supramolecular materials: in the covalently stabilized systems, the carbohydrate units are with reduced mobility, and thus, they are not prompt to recognize and interact with proteins at low surface density. Different biomedical applications have been proposed for the systems based on Janus dendrimers: they can be used as lectin targeted drug delivery systems [33] or when labeled as optical sensors for bacterial detection [27].

Metal-directed self-assembly is another means for the preparation of libraries with structurally defined saccharide clusters (Fig. 5.7) [34–36]. The method allows precise clustering of carbohydrates at the periphery of a nanosphere whose exact size depends on the chosen metal. The clustered saccharides are biofunctional: they efficiently bind to lectins that recognize the conformation of the carbohydrates. The combination of the protein recognition at the periphery and the possibility for

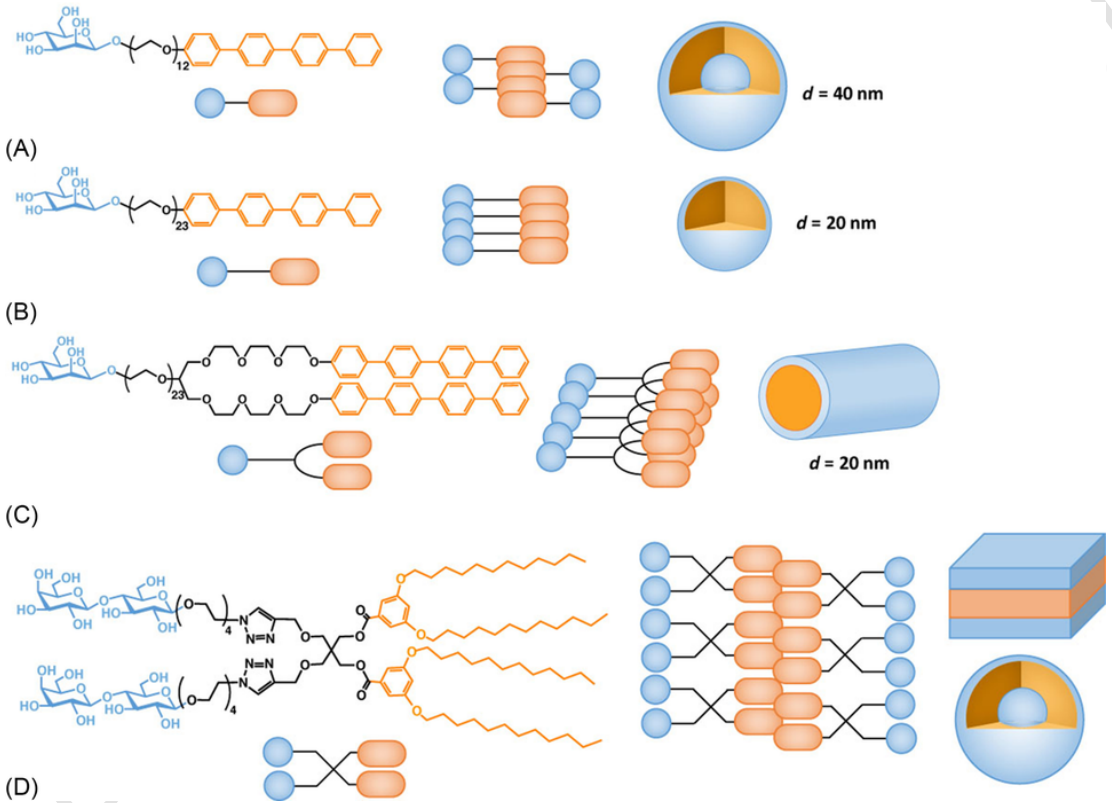
(A)
d = 40 nm
(B)
d = 20 nm
(C)
d = 20 nm
(D)

Fig. 5.6 Carbohydrate *(blue)*-functionalized supramolecular structures with different architectures generated in a function of the length and branching *(black)* of the synthetic unit within the amphiphile: (A) polymersomes; (B) micelles; (C) nanofibers; (D) lamellas and glycodendrimersomes.

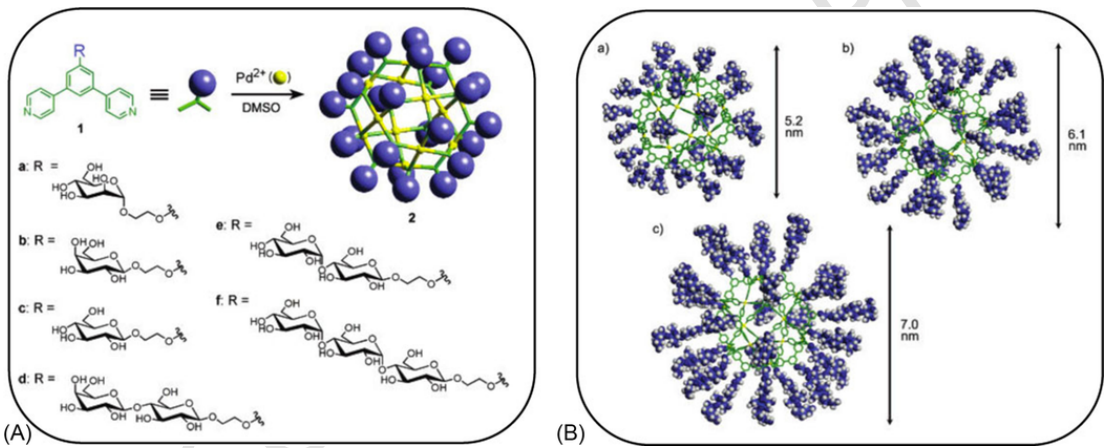

Fig. 5.7 Library of metal coordination complexes with surface-exposed saccharide clusters: (A) chemical structures of carbohydrate-functionalized ligands and (B) molecular models for the obtained assemblies.
Reprinted with permission from Yadav R, Kikkeri R, Carbohydrate functionalized iron(III) complexes as biomimetic siderophores. Chem Commun 2012;48(11):1704–6.

molecular encapsulation at the interior of the spheres are compatible with many biomedical applications.

5.4 Systems responsive to targeted external stimuli

One of the main advantages of the supramolecular systems is their inherent capacity to respond to external stimuli. Responses to stimuli such as pH, temperature, or ionic strength are intrinsic for such systems as they are based on weak interactions often involving polar and charged groups, and thus, small changes in the environment can affect dramatically the assembly process (Fig. 5.8) [37].

With the advancements of precision and personalized medicine, however, a specific (time, site, and rate) response to a targeted stimulus, e.g., overexpressed protein associated with a certain disorder, is desired. The design of such systems requires the introduction of an additional unit that can cross talk with the targeted marker. Moreover, this cross talk should affect the properties of the system: change in color, gel-to-sol transitions, gel-to-gel or sol-to-gel transitions, isomerization, or changes in morphology are some of the most common responses.

5.4.1 Sweet building blocks in biocatalytic self-assembly

As referred by the name, biocatalytic self-assembly (BSA) uses biomolecules, usually enzymes to trigger or accelerate the self-assembly process. It is a well-established approach for substrates as peptide amphiphiles that are decorated with enzyme-sensitive functionalities impairing the self-assembly process. The mode of action of BSA involves enzymatic cleavage of this functionality, resulting in rebalance of various supramolecular forces within the substrate and eventually self-assembly of the generated monomers (Fig. 5.9) [38–42]. Thus, it merges the efficiency and selectivity of an enzymatic transformation with the sensitivity of the self-assembly process.

Recently, it was demonstrated that this approach is valid also for short aromatic carbohydrate amphiphiles (Fig. 5.9A) [43]. When such amphiphile is functionalized with a phosphate group (orange in Fig. 5.9), it is soluble in aqueous media and assembles in micellar structures. Upon removal of this functionality by alkaline phosphatase, an enzyme that is overexpressed in different cancers, the solubility of the generated compound is reduced, and it assembles into fibers that are then organized into a supramolecular gel. This transformation can be used either for identification of cancer or for its treatment as the formation of the gel occurs only in close proximity of the cells overexpressing the phosphatase. These cells, thus, are entrapped in the gel formed in situ; they can't migrate and ultimately enter in apoptosis.

Glycosidases are another class of enzymes that can be useful in manipulating self-assembly process [17]. They catalyze the catabolism of complex carbohydrates and their conjugates and thus can be used as markers in many biological processes including pathogenic contaminations and pathological disorders [3,44]. Several high-

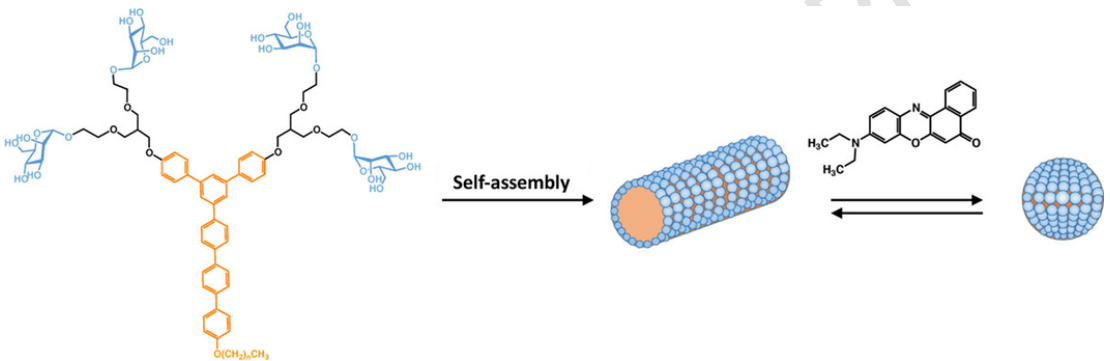

Fig. 5.8 Reversible transformation of cylindrical into spherical micelles in response to Nile red addition.
Adapted from Kamiya N, et al. Saccharide-coated M12L24 molecular spheres that form aggregates by multi-interaction with proteins. J Am Chem Soc 2007;129(13):3816–7.

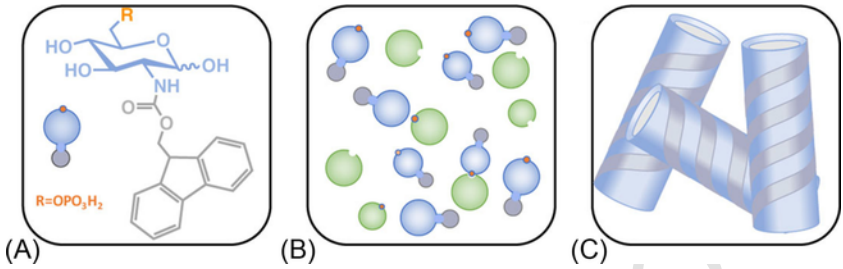

Fig. 5.9 Schematic presentation of biocatalytic self-assembly: substrates with enzyme-sensitive functionality (A) are transformed upon enzymatic action (B), and the generated monomers are able to self-assemble (C). Carbohydrate is presented in *blue*, the enzyme in *green*, and the enzyme-sensitive functionality in *orange*.

throughput platforms for the detection of glycosidases have been developed using glycopolymers with incorporated fluorophore unit [44,45]. Supramolecular hydrogels with glycosidase-dependent chromism have been assembled from glycolipids and functionalized with Man, Gal, or Glc (Fig. 5.10). The yellow-to-orange color change is visible with naked eye, and it is enzyme-specific—Man-functionalized glycolipid changed the color only in the presence of mannosidase but not when galactosidase or glucosidase were used. Besides color change, gel-to-sol transition occurs concurrently in response to the specific glycosidases. These responses have been applied to develop a colorimetric sensor array chip for sensing glycosidases [44]. This approach can be extended to other enzymes glucokinase and glycosyltransferase.

5.4.2 Photoresponsive systems

Light is a noninvasive trigger that can induce different responses of a supramolecular system. Azobenzene has been extensively used as an optical trigger in order to

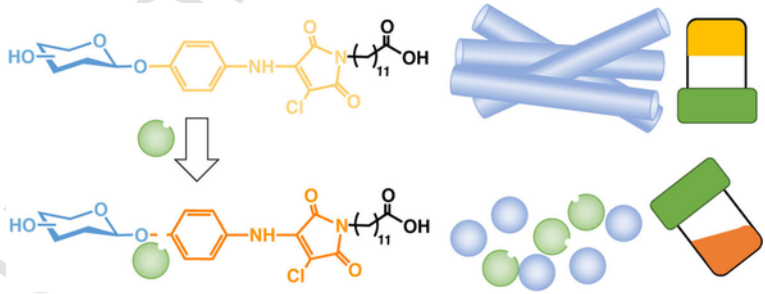

Fig. 5.10 Chemical structure of self-assembling glycolipids and schematic presentation of their glycosidase response.
Adapted from Pires RA, et al. Controlling cancer cell fate using localized biocatalytic self-assembly of an aromatic carbohydrate amphiphile. J Am Chem Soc 2015;137(2):576–9.

develop a diverse range of supramolecular photoresponsive systems [46–49]. It has several advantages: (i) it is a chromophore, and thus, changes can be easily followed by different spectroscopic techniques; (ii) it is hydrophobic, and thus, amphiphiles can be generated easily upon its functionalization with hydrophilic carbohydrates; (iii) it can form supramolecular structures via π-π interactions because of the planar benzene units; (iv) reversible *trans*-to-*cis* isomerization can occur upon irradiation with light. *Trans*-isomers are more stable than *cis*-ones, and thus, UV irradiation is needed to power this transition. On the other hand, the *cis*-to-*trans* isomerization can occur in the presence of visible light or heat. The most common response to this isomerization is gel-to-sol transition that is associated with changes in π-π stacking (Fig. 5.11) [46].

Azobenzene derivatives functionalized with simple carbohydrates (mono- and disaccharides) have been already developed and tested under this approach. As an example, lactose and maltose functionalized azobenzene self-assemble spontaneously into entangled helical nanofibers [47]. These supramolecular carbohydrate scaffolds are biofunctional as they can host cells and bind lectins. They are also light-responsive—photoisomerization resulted in a gel-sol transition demonstrating that the system can be useful as photoswitchable lectin inhibitors or cell delivery systems [49].

5.5 Future perspectives

Supramolecular systems involving carbohydrates are of great and widespread interest, given the involvement of carbohydrates in multitudinous crucial functions of different biological systems. Undoubtedly, during the last years, we have witnessed great advances in the field. Nowadays, we have an access to stable carbohydrate assemblies and extended supramolecular networks of different size, morphology, and complexity. These systems are functional in physiological relevant

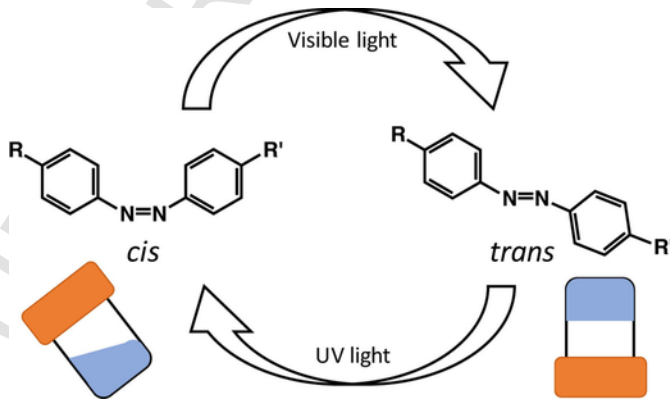

Fig. 5.11 Schematic presentation of the isomerization of azobenzene derivatives and associated with this isomerization sol-to-gel transition.

media as demonstrated by their binding to different targeted proteins. They can be used in dynamic experimental modeling to obtain valuable qualitative and quantitative information of CPIs. It seems, however, that the field is currently in a standby. While many supramolecular complexes have been prepared, most of them are based on the simplest carbohydrates: monosaccharides, mainly Man, Gal, and Glc. Keeping in mind that the cells are surrounded by complex polysaccharides, novel concepts that create supramolecular assemblies with sophisticated sugars must be developed. Another direction to be explored is CCIs. We still know very little about these interactions and about their physiological importance. Most of the currently available systems target or exploit only CPIs. Thus, important findings can come up from studies involving CCIs.

References

[1] A. Varki, Biological roles of glycans, Glycobiology 27 (1) (2017) 3–49.
[2] I. Pashkuleva, R.L. Reis, Sugars: burden or biomaterials of the future?, J Mater Chem 20 (40) (2010) 8803–8818.
[3] D.S. Costa, R.L. Reis, I. Pashkuleva, Sulfation of glycosaminoglycans and its implications in human health and disorders, Annu Rev Biomed Eng 19 (2017) 1–26.
[4] M. Delbianco, et al., Carbohydrates in supramolecular chemistry, Chem Rev 116 (4) (2016) 1693–1752.
[5] A.P. Davis, R.S. Wareham, Carbohydrate recognition through noncovalent interactions: a challenge for biomimetic and supramolecular chemistry, Angew Chem Int Ed 38 (20) (1999) 2978–2996.
[6] L.S. Birchall, et al., Exploiting CH-pi interactions in supramolecular hydrogels of aromatic carbohydrate amphiphiles, Chem Sci 2 (7) (2011) 1349–1355.
[7] U. Freudenberg, et al., Glycosaminoglycan-based biohybrid hydrogels: a sweet and smart choice for multifunctional biomaterials, Adv Mater 28 (2016) 8861–8891.
[8] H.Y. Wang, S.C. Heilshorn, Adaptable hydrogel networks with reversible linkages for tissue engineering, Adv Mater 27 (25) (2015) 3717–3736.
[9] A. Carretero, et al., Extracellular matrix-inspired assembly of glycosaminoglycan-collagen fibers, J Mater Chem B 5 (17) (2017) 3103–3106.
[10] K. Rajangam, et al., Heparin binding nanostructures to promote growth of blood vessels, Nano Lett 6 (9) (2006) 2086–2090.
[11] R.M. Capito, et al., Self-assembly of large and small molecules into hierarchically ordered sacs and membranes, Science 319 (2008) 1812.
[12] Y.B. Lim, et al., Glycoconjugate nanoribbons from the self-assembly of carbohydrate-peptide block molecules for controllable bacterial cell cluster formation, Biomacromolecules 8 (5) (2007) 1404–1408.
[13] X.W. Du, et al., Supramolecular assemblies of a conjugate of nucleobase, amino acids, and saccharide act as agonists for proliferation of embryonic stem cells and development of zygotes, Bioconjug Chem 25 (6) (2014) 1031–1035.
[14] A. Restuccia, et al., Self-assembled glycopeptide nanofibers as modulators of galectin-1 bioactivity, Cell Mol Bioeng 8 (3) (2015) 471–487.
[15] D. Yuan, et al., Supramolecular glycosylation accelerates proteolytic degradation of peptide nanofibrils, J Am Chem Soc 137 (32) (2015) 10092–10095.
[16] S.S. Lee, et al., Sulfated glycopeptide nanostructures for multipotent protein activation, Nat Nanotechnol 12 (2017) 821–829.
[17] F. Zhao, et al., L-Rhamnose-containing supramolecular nanofibrils as potential immunosuppressive materials, Org Biomol Chem 12 (35) (2014) 6816–6819.

[18] Y.B. Lim, et al., Tunable bacterial agglutination and motility inhibition by self-assembled glyco-nanoribbons, Chem Asian J 2 (11) (2007) 1363–1369.
[19] V. Percec, et al., Modular synthesis of amphiphilic janus glycodendrimers and their self-assembly into glycodendrimersomes and other complex architectures with bioactivity to biomedically relevant lectins, J Am Chem Soc 135 (24) (2013) 9055–9077.
[20] B.S. Kim, et al., Controlled self-assembly of carbohydrate conjugate rod-coil amphiphiles for supramolecular multivalent ligands, J Am Chem Soc 127 (46) (2005) 16333–16337.
[21] B.S. Kim, et al., Carbohydrate-coated nanocapsules from amphiphilic rod-coil molecule: binding to bacterial type 1 pili, Chem Commun 15 (2005) 2035–2037.
[22] D.W. Lee, et al., Multivalent nanofibers of a controlled length: regulation of bacterial cell agglutination, J Am Chem Soc 134 (36) (2012) 14722–14725.
[23] K.R. Wang, et al., Synthesis and predetermined supramolecular chirality of carbohydrate-functionalized perylene bisimide derivatives, Chem Asian J 10 (5) (2015) 1204–1214.
[24] M.K. Muller, L. Brunsveld, A supramolecular polymer as a self-assembling polyvalent scaffold, Angew Chem Int Ed 48 (16) (2009) 2921–2924.
[25] F. Wu, et al., Functionalization of DNA-dendron supramolecular fibers and application in regulation of Escherichia coli association, ACS Appl Mater Interfaces 7 (13) (2015) 7351–7356.
[26] S.D. Zhang, et al., Mimicking biological membranes with programmable glycan ligands self-assembled from amphiphilic janus glycodendrimers, Angew Chem Int Ed 53 (41) (2014) 10899–10903.
[27] K. Petkau, et al., Pre- and postfunctionalized self-assembled pi-conjugated fluorescent organic nanoparticles for dual targeting, J Am Chem Soc 133 (42) (2011) 17063–17071.
[28] G. Thoma, et al., Novel glycodendrimers self-assemble to nanoparticles which function as polyvalent ligands in vitro and in vivo, Angew Chem Int Ed 41 (17) (2002) 3195–3198.
[29] G. Thoma, et al., Non-covalent polyvalent ligands by self-assembly of small glycodendrimers: a novel concept for the inhibition of polyvalent carbohydrate-protein interactions in vitro and in vivo, Chemistry 12 (1) (2006) 99–117.
[30] M. Paolino, et al., Self-assembly of poly(propylene imine) glycodendrimers: role of aromatic interactions in the formation of necklace- and donut-like nanostructures, Polym Chem 3 (12) (2012) 3239–3242.
[31] S.D. Zhang, et al., Dissecting molecular aspects of cell interactions using glycodendrimersomes with programmable glycan presentation and engineered human lectins, Angew Chem Int Ed 54 (13) (2015) 4036–4040.
[32] S.D. Zhang, et al., Unraveling functional significance of natural variations of a human galectin by glycodendrimersomes with programmable glycan surface, Proc Natl Acad Sci U S A 112 (18) (2015) 5585–5590.
[33] L. Sun, et al., NIR-responsive and lectin-binding doxorubicin-loaded nanomedicine from Janus-type dendritic PAMAM amphiphiles, Biomacromolecules 13 (11) (2012) 3581–3591.
[34] R. Roy, J.M. Kim, Cu(II)-self-assembling bipyridyl-glycoclusters and dendrimers bearing the Tn-antigen cancer marker: syntheses and lectin binding properties, Tetrahedron 59 (22) (2003) 3881–3893.
[35] R. Yadav, R. Kikkeri, Carbohydrate functionalized iron(III) complexes as biomimetic siderophores, Chem Commun 48 (11) (2012) 1704–1706.

[36] N. Kamiya, et al., Saccharide-coated M12L24 molecular spheres that form aggregates by multi-interaction with proteins, J Am Chem Soc 129 (13) (2007) 3816–3817.
[37] J.H. Ryu, et al., Carbohydrate-coated supramolecular structures: transformation of nanofibers into spherical micelles triggered by guest encapsulation, J Am Chem Soc 129 (15) (2007) 4808–4814.
[38] Z.M. Yang, et al., Enzymatic formation of supramolecular hydrogels, Adv Mater 16 (16) (2004) 1440.
[39] Y. Gao, et al., Enzyme-instructed molecular self-assembly confers nanofibers and a supramolecular hydrogel of taxol derivative, J Am Chem Soc 131 (38) (2009) 13576.
[40] A.R. Hirst, et al., Biocatalytic induction of supramolecular order, Nat Chem 2 (12) (2010) 1089–1094.
[41] R.V. Ulijn, Enzyme-responsive materials: a new class of smart biomaterials, J Mater Chem 16 (23) (2006) 2217–2225.
[42] J.K. Sahoo, et al., Biocatalytic self-assembly cascades, Angew Chem Int Ed 56 (24) (2017) 6828–6832.
[43] R.A. Pires, et al., Controlling cancer cell fate using localized biocatalytic self-assembly of an aromatic carbohydrate amphiphile, J Am Chem Soc 137 (2) (2015) 576–579.
[44] R. Ochi, et al., Supramolecular hydrogels based on bola-amphiphilic glycolipids showing color change in response to glycosidases, Chem Commun 49 (21) (2013) 2115–2117.
[45] Y. Koshi, et al., A fluorescent lectin array using supramolecular hydrogel for simple detection and pattern profiling for various glycoconjugates, J Am Chem Soc 128 (32) (2006) 10413–10422.
[46] E.R. Draper, D.J. Adams, Photoresponsive gelators, Chem Commun 52 (53) (2016) 8196–8206.
[47] Y. Ogawa, C. Yoshiyama, T. Kitaoka, Helical assembly of azobenzene-conjugated carbohydrate hydrogelators with specific affinity for lectins, Langmuir 28 (9) (2012) 4404–4412.
[48] Y.X. Hu, R.F. Tabor, B.L. Wilkinson, Sweetness and light: design and applications of photo-responsive glycoconjugates, Org Biomol Chem 13 (8) (2015) 2216–2225.
[49] O. Srinivas, et al., Photoswitchable cluster glycosides as tools to probe carbohydrate-protein interactions: synthesis and lectin-binding studies of azobenzene containing multivalent sugar ligands, Glycobiology 15 (9) (2005) 861–873.

Further Reading

[1] J.R. Kramer, et al., Chemically tunable mucin chimeras assembled on living cells, Proc Natl Acad Sci U S A 112 (41) (2015) 12574–12579.