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Redox-active host-guest supramolecular assemblies of peptides and proteins at surfaces

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ABSTRACT

The cell machinery is very complex, precisely regulated by cues in space and time. Fine tuning bioactive cues on surfaces has shown to be a crucial design criterion for cell interactions with materials. Stimuli-responsive surfaces of biomaterials and devices open up new opportunities to steer cellular fate and study cellular mechanisms. Supramolecular host-guest interactions are in itself dynamic in nature due to the noncovalent nature of the interactions between molecules, and in addition they allow for the incorporation of guests, controlled using external stimuli. This tunable reversibility makes them highly attractive for the exploration of cell-interactive surfaces for biological applications. In this feature article strategies to anchor bio- and redox-active peptides and proteins employing supramolecular host-guest chemistry are presented and discussed in the context of these surfaces interacting with cells.

1. Introduction

Assemblies of peptides and proteins on arrays, beads, chips, scaffolds and aggregates play an increasingly important role in the development of bioanalytics and biomedicine [1,2]. Protein-modified surfaces are also of interest for the study of cell growth and cell differentiation [3]. The interaction of cells with modified surfaces plays an important role in tissue engineering and the design of materials for the fabrication of medical implants. In addition, the controlled immobilization of enzymes is crucial to optimizing catalytic activities [4]. Supramolecular chemistry is a versatile tool for the assembly of peptides and proteins on surfaces, as it, in principle, allows for reversible attachment of biomolecules to the surface, not accessible via covalent immobilization techniques [5]. Additionally, supramolecular anchoring of peptides and proteins provides access to controlling the dynamics of the interaction through selecting the valency and type of interaction motifs. Furthermore, the density of biological ligands on the surface can be controlled through using photons, electrons, protons or other chemicals (Figs. 1 and 2), since often a change in e.g. a redox potential can lead to a change in affinity of the bioactive ligands with the surface.

While interfacing static, non-living systems with dynamic, living matter is an essential step in applying biomaterials in tissue regeneration, finding the optimum interface is a formidable task [1]. The highly complex composition of the extracellular matrix (ECM) and its complex interaction with the so-called molecular fingerprints on cell membranes make it a highly challenging task to create model systems. Since natural interfaces between the cell and its interacting ligands are built on

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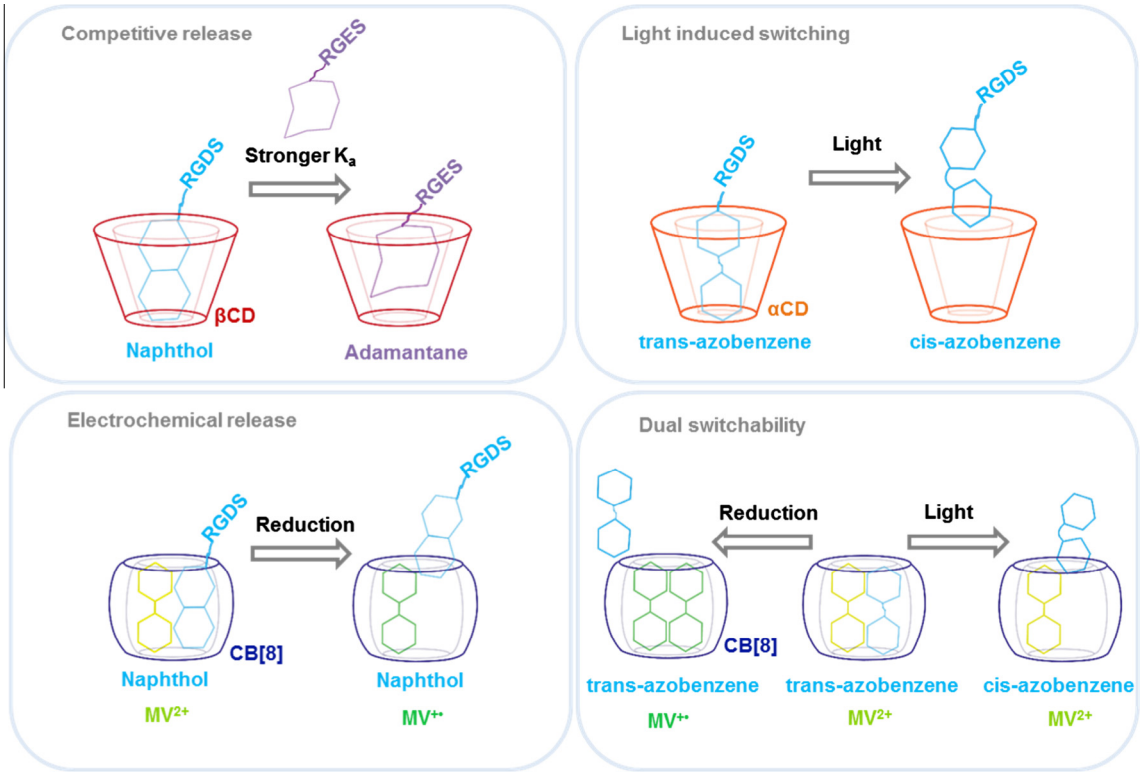

Fig. 1. Triggered change in host-guest affinity by (a) chemicals, (b) photons, (c) electrons or (d) a combination of photons and electrons. (A) Competitive release of the first guest by the second guest based on differences in binding strength to a cyclodextrin host. (B) Switching from *trans* to *cis*-azobenzene limits the interaction with the cyclodextrin host. (C) Electrochemical reduction of methylviologen leads to weakening of the charge-transfer complex with naphthol inside the CB[8] cavity. (D) *trans*-azobenzene and methylviologen can simultaneously interact with CB[8]. Electrochemical reduction of methylviologen or light causes release of the azobenzene from the CB[8] cavity. Host molecules are schematically depicted.

non-covalent interactions, chemical systems relying on non-covalent binding such as hydrophobic, van der Waals, ion-dipole or hydrogen bonds are being explored and representing a promising approach to mimic natural cell-ECM interactions [1]. Self-assembly is an attractive tool and an efficient bottom-up strategy to govern thermodynamic control aiming to position ligands at predefined locations and the modulation of those positions [1]. An appealing self-assembly strategy to create interfaces to cells is the use of supramolecular host-guest chemistry based on cucurbit[n]urils (CB[n]) and cyclodextrins (CD). They are highly attractive due to their ability of binding various guest molecules in physiologically relevant milieu. Moreover, these host-guest interactions are sensitive to e.g. redox-triggered affinity changes (Figs. 1 and 2).

2. A triggered change in host-guest affinity

CB[*n*]s are macrocyclic pumpkin-shaped molecules made of *n* individual glycoluril monomer units. Their hydrophobic core and electronegative carbonyl rim allows for highly specific interactions with small hydrophobic guest molecules [6,7]. CB[7] recognizes hydrophobic and electroactive guests, such as ferrocene and methylviologen, with dissociation constants in the nM to pM range (Fig. 2). CB[8], having a larger core diameter, has the unique ability to simultaneously bind two aromatic guest molecules. It can for instance incorporate an electroactive methylviologen (MV^{2+}) as the first guest along with naphthol, N-terminal tryptophan or azobenzene as the second guest. While in the former case oxidation of ferrocene is expected to yield a moderate change in affinity to the CB[7] cavity, in the latter case, reduction of methylviologen to its radical monocation weakens the ternary complex yielding a release of the second guest (Fig. 1).

CDs are nonsymmetrical cyclic oligosaccharides, interacting with hydrophobic guest molecules such as naphthol, ferrocene, adamantane and azobenzene with dissociation constants in the μM to mM range (Fig. 2) [8]. Exploration of these types of host-guest interactions has led to various designs of supramolecular hydrogels, polymers and nanoparticles and are reviewed elsewhere [9,10]. When ferrocene guests are oxidized the affinity with CD is expected to be lost.

This feature article focuses on reviewing our work dealing with bioconjugating peptides and proteins with redox-active moieties and their interaction with different types of host-functionalized surfaces (Section 3). Their use as bioactive interfaces to study electro-responsive interactions with cells will also be described (Section 4).

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