Rationally designed chimeric solid-binding peptides for tailoring solid interfaces

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Abstract
Joining biology with materials science requires the ability to design, engineer and control biology/solid-state materials interfaces at the molecular level. The specific molecular interactions that take place among biomolecules, known as molecular recognition, enable all aspects of molecular processes in living systems prerequisite to the biological functions. Having the ability to establish specific biological interactions between the solid materials and biological constituents is essential for precise design of biologically viable soft interfaces that are molecularly tailored at solid surfaces. Solid-binding peptides offer excellent opportunities in surface biofunctionalization over the traditionally utilized chemical approaches which generally make use of covalent bonds for surface molecular attachments with limited flexibility. Solid-binding peptides are selected using directed evolution techniques using genotype to phenotype relationships and therefore referred also as genetically engineered peptides for inorganics (GEPI) and exclusively bind to solid materials using molecular recognition. Here, the peptide has weak interactions at multiple contact points that are established between the biomolecule and the solid lattice, and then folds into a conformation coherent with the underlying solid lattice through self-organization on the surface. Solid-binding peptides provide an unprecedented biological advantage as modular building blocks to couple biological and synthetic entities at the bio–solid interfaces. Taking full advantage of biology’s versatility, they can easily be engineered to form chimeric molecules with inherent multifunctionality displaying biofunctional molecular entities, such as enzymes, co-factors, antimicrobial peptides, antibodies, nucleic acids and molecular probes that target biomarkers. This minireview provides an insight into the key principles of solid-binding peptides for advancing surfaces biofunctionalization by a selected set of examples on chimeric functions built upon linking, displaying and assembling functional molecular moieties at solid surfaces ranging from enzymatic biocatalysis to antimicrobial coatings. Modular multifunctional peptide design offers to tune molecular processes with coupled biological functions for a wide variety of applications in biotechnology, nanotechnology and medicine.

Keywords
bionanosensors, bioreactors, enzyme immobilization, genetically engineered peptides for inorganics, GEPI, graphene FET, modular peptide design, self-assembled peptide coating, soft bio–nano interfaces, solid-binding peptides
Functional integration of biological molecules with solid materials (Ball, 2001; Fratzl & Weinker, 2007; Lowenstam & Weiner, 1989; Sarikaya, Tamerler, Jen, Schulten, & Baneyx, 2003; Seeman & Belcher, 2002) is essential to fabricate efficient medical devices ranging from diagnostics to therapeutics as well as plethora of other practical biotechnological and biosensing applications (Hammond, Formisano, Estrela, Carrara, & Tkac, 2016; Nair & Alam, 2006; Sepúlveda, Angelomé, Lechuga, & Liz-Marzán, 2009). A key to fabricate such devices is to develop an effective molecular tool in directing surface interactions at the bio–solid interface and, therefore, controlling inorganic material's behaviour as well as biomolecular events on the solid surface (Hammond et al., 2016; Liu & Yu, 2016; Muguruma, Iwasa, Hidaka, Hiratsuka, & Uzawa, 2017; Nair & Alam, 2006; Sarikaya et al., 2003; Seeman & Belcher, 2002; Sepúlveda et al., 2009). In an attempt to fabricate hybrid devices that incorporate both inorganic solids and biological components, an unresolved limitation is the lack of programmable surface tools that could enable precise control of species at a molecular level at the solid interface and, thus, allow to design of robust biological devices with predictable behaviour (Bolella & Gorton, 2018; DiBattista, Liotta, & Whitesides, 1996; Karyakin, Presnova, Rubtsova, & Egorov, 2000; Muguruma et al., 2017). Herein, the desired fabrication strategy would be an environmentally benign and biologically compatible approach that can be actively implemented for a wide range of bioactive molecules including proteins, peptides, DNA, RNA, peptide nucleic acids (PNA) and other small biomolecules (Khatayevich et al., 2010; Mach et al., 2019; Moehlenbrock & Minteer, 2011; Sarikaya et al., 2003; Tadimety et al., 2019; Tamerler et al., 2010; Tamerler & Sarikaya, 2008).

Traditional deposition methods were developed to fabricate multilayered films and molecular devices that include Langmuir–Blodgett films, multilayer deposition based on the use of various polymeric materials and self-assembled monolayers (SAMs) (Hnilova, Yucesoy, Sarikaya, & Tamerler, 2013; Scholl & Caseli, 2015; Whitesides, 1996). Although these processes have been shown to be useful to fabricate various multilayered films and nanodevices, they suffer from significant drawbacks due to their limited or lack of capability to provide spatial localization and orientation control of biological molecules on the support surface as well as complexity of the process, long stacking time and high cost (Hnilova et al., 2013; Sarikaya et al., 2003). Moreover, the required solvents and harsh processing conditions are often not compatible with biological molecules, limiting their utility in many practical applications in the biotechnology and, especially, in biomedical fields (Deng, Mrksich, & Whitesides, 1996; King & Lai, 2013; Rusmini, Zhong, & Feijen, 2007; Sajfutdinow et al., 2017; Sassolas, Blum, & Leca-Bouvier, 2012; Tamerler et al., 2010).

Covalent attachment and physical adsorption have so far been the primary methodologies for immobilizing biological molecules, for example, proteins, to the inorganic materials surfaces. (Rusmini et al., 2007). In both approaches, however, biological molecules are displayed on the support surface in a random orientation due to limited control over the chemical reactivity of the protein with the activated SAM or complex uncontrolled electrostatic interaction behaviour on the bare solid surface (Bhakta, Evans, Benavidez, & Garcia, 2015; Firestone, Shank, Sligar, & Bohn, 1996; Garcia-Galan, Berenguer-Murcia, Fernandez-Lafuente, & Rodrigues, 2011; Ramachandran et al., 2004; Sassolas et al., 2012; Tack, Schickle, Böke, & Fischer, 2015). Chemical surface modifications and/or cross-linking reactions often alter the conformation of the biological molecules, resulting in a loss of functionality or reduced stability due to non-specific binding of the functional biomolecule. It has been apparent for a long time, therefore, that efficient fabrication of advanced biomolecular devices and systems still require more robust coupling techniques and involvement of versatile bio-friendly linkers that are material-specific, modular and amenable to control over a prescribed structural architecture on the support surface (Hnilova et al., 2013; Khatayevich et al., 2010; Ramachandran et al., 2004; Sarikaya et al., 2003; Tamerler et al., 2010).

An ideal surface coupling approach should ensure minimum two functions when immobilizing molecular probes and other biologically active entities, such as enzymes, antibodies and other functional proteins, onto the surfaces of solid-state devices: Firstly, immobilization method should have a tailored adhesion with specificity to the solid surface of choice, and secondly, while acting as a bridge between the biological molecule and the solid, it should be flexible to display a chemically or genetically conjugated probe. Surface functionalized biomolecule can then physically exert its biological selectivity for targeting or enzymatic functions. The key to satisfy these requirements would be to use a biomolecular entity that undergoes a molecular interaction with the underlying solid structure similar to molecular recognition, a fundamental interaction taking place among the biomolecules, such as peptide–protein, co-factor-enzyme or protein-DNA.

A superior alternative strategy to overcome many of the limitations of conventional methods, therefore, can be the utilization of peptides that have specific binding affinity to inorganic solid surfaces (Brown, 1997; Naik, Brott, Clarson, & Stone, 2002; Sarikaya et al., 2003; Whaley, English, Hu, Barbara, & Belcher, 2000). Solid-binding peptide (SBP), also known as genetically engineered peptides for inorganics (GEPI), provides self-immobilization that is biochemically versatile, genetically tailorable and enabling the display of biological functionality effectively. Unlike the traditional approaches using covalent solid surface binding, (Karyakin et al., 2000; Rushmini et al., 2007) GEPI-surface binding offers a combination of weak interactions, including van der Waals, hydrogen bonding and Coulombic collectively resulting in high affinity due to peptide conforming onto the surface using multiple contact points (Corni, Hnilova, Tamerler, & Sarikaya, 2013; Hnilova et al., 2008). As a result, these short sequences (7-14 amino acids) have strong-binding capacity $k_\text{d} = 50 \text{nM}^{-1} \mu \text{M}$, exhibiting a wealth of chemical diversity with exquisite material specificity (Corni et al., 2013; Hnilova et al., 2008; So et al., 2012). GEPIs are particularly well suited for applications in medical and biological fields since they are produced and function under biological conditions, and have so far not shown any
The versatility of GEPIs as molecular tool set comes from their capacity to form modular constructs as well as biochemical and functional diversity which can be exploited through simple point and domain mutations as well as residue-based biochemical modifications, providing unique opportunities to control binding strength, chemistry and biofunctional display (Figure 1) (Naik, Stringer, Agarwal, Jones, & Stone, 2002; So et al., 2012; Wisdom et al., 2016). Successful design of a chimeric molecule requires retaining the functionality of each domain that is integrated into the final molecular construct. In the peptide-based design, the structural integration can be accomplished by using a short linker AA sequence that can be inserted between GEPI and its fusion partner genetically or chemically during the peptide synthesis. The linker sequence may be made flexible, for example, by using the multiple repeats of glycine, G, or rigid using proline, P, or combination of other AAs (Tamerler et al., 2010; Tamerler & Sarikaya, 2009). Different number of repeats of G or P can be used to tailor the physical spacing between the probe and the solid surface and customized through computational modelling with nanometre-scale accuracy (Tamerler et al., 2010; Tamerler & Sarikaya, 2008; Wisdom et al., 2016).

The principles of the solid-binding peptide technology outlined above constitute novel biological routes for biofabrication of various bio–nano devices with controlled surface organization and architecture. In this review, we summarize the utility of solid-binding peptides as a biofriendly modular technique for designing programmable functions at solid interfaces that can be integral part of bio/nano hybrid devices employing hierarchically assembled bioactive molecules for biosensing, molecular devices and functional coatings/films. The versatility, tunability and applicability of the GEPIs are demonstrated in selected set of examples from a wide variety of implementations in nanotechnology, biotechnology and medicine.

2 | SHORT PEPTIDES WITH SOLID AFFINITY AND SPECIFICITY—GENERAL PHYSICAL AND CHEMICAL CHARACTERISTICS

The authors’ laboratories and other groups have identified a large collection of peptides that are specific to different materials, for example, metals, ceramics and minerals such as Au, Ag, Pt, ZnO, TiO$_2$ and graphite, through phage- and/or cell-surface display libraries (Cetinel et al., 2012; Hnilova et al., 2008; Naik, Stringer, et al., 2002; Sedlak et al., 2012; Yazici et al., 2013; Yucesoy, Hnilova, et al., 2015). Many groups have studied mechanisms underlying their binding and self-assembly properties at soft interfaces on solid surfaces (Corti et al., 2013; Hnilova et al., 2008; So et al., 2012; Zhou, Schwartz, & Baneux, 2010). Solid-binding peptides have also been demonstrated as anchoring molecules onto different material surfaces providing functional integration between proteins and inorganic supports over a multi-length scales. For the last two decades, the authors have pioneered the utility of these inorganic-binding peptides as molecular building blocks in association with fusion partners, such as proteins, peptides and oligonucleotides and built multifunctional units for directed assembly applications. The solid-binding peptides have a sequence containing usually 7–14 amino acids and, therefore, have low molecular weight (~1,000 Dalton), tailorable isoelectric points with an average size of 1 nm diameter when folded on the surfaces (Sarikaya et al., 2003; Tamerler et al., 2010; Wisdom et al., 2016). As a consequence of the innate selection procedures, these peptides do not usually interact with each other in solution. When bound to the solid surfaces, they can surface diffuse and undergo intermolecular interactions with other peptides through templating and can lead to long-rage ordered self-organization for full surface coverage. These characteristics are desirable attributes for solid-binding peptides as highly versatile molecular building blocks for surface functionalization.
3 | MODULAR DESIGN OF BIO/NANO INTERFACES

Here, we use three case studies where the modular multifunctional molecular constructs are designed and demonstrated for surface bio-passivation and biosensing application; multi-enzyme immobilization; and antimicrobial molecular coatings. In all examples, multifunctional molecular constructs are self-assembled on the solid surfaces enabled by the solid-binding peptides (Hayamizu et al., 2016; Khatayevich et al., 2010; Khatayevich et al., 2014; Yazici et al., 2016; Yucesoy, Hnilova, et al., 2015).

3.1 | Surface passivation and functional display of molecular probes for bionanosensors

Direct detection of molecular biomarker, such as a small biomolecule, protein, oligonucleotide or a microorganism, is essential for diagnosis and monitoring of numerous diseases, including several types of cancer, trauma and neurodegeneration. These biomarkers can be detected using different resources including blood, tissues, saliva or urine of a patient (Vaisocherova et al., 2008). Conventionally, such biomarkers are detected in clinical settings by immuno- and electrochemical assays. The target detection in these assays is carried out using a variety of spectroscopic techniques, such as calorimetric assays, surface plasmon resonance spectroscopy (SPR) and quartz crystal microbalance (QCM). Unfortunately, many of these techniques provide high signal-to-noise ratio restricting their use for clinical practise (Chou, Hsu, Hwang, & Chen, 2002; Di Natale et al., 2003; Liu et al., 2008; Yu et al., 2006). The practical utility of these techniques remains limited as a result of their low sensitivity and specificity failing to detect the targeted markers in complex environments. Often, these biomarkers are present in low concentrations against a background of high abundance of serum, saliva, urine or tissue proteins, shadowing the required high selection efficiency of the sensor (Liu et al., 2007; Mani, Chikkaveeraiah, Patel, Gutkind, & Rusling, 2009).

During the last several years, two-dimensional single layer material-based field-effect transistor sensors (2D-FET) starting with the high interest in graphene have been employed for significantly enhanced sensitive detection of target molecules (Alam, Wang, Guo, Lee, & Tseng, 2005; Curreli et al., 2008; Ohno, Maehashi, & Matsumoto, 2010; Stine, Robinson, Sheehan, & Tamanaha, 2010). Compared to many other traditional materials, for example, gold substrates, biosensors based on 2D materials offer superior sensitivity by exceeding the detection thresholds with designs reported to detect femtogram per milliliter concentrations of analyte (Alam et al., 2005; Ohno et al., 2010; Stine et al., 2010). These levels of sensitivity are possible with the excellent electronic properties of graphene, resulting from delocalized π-bond structure, and zero band gap, which is highly sensitive to molecular doping and surface binding events (Balandin et al., 2008; Castro Neto, Guinea, Peres, Novoselov, & Geim, 2009; Novoselov et al., 2004; Page, Hayamizu, So, & Sarikaya, 2012). In particular, charge transfer resulting from the interactions of molecules with graphene substrate changes its Dirac point and, therefore, its resistance as output signal allowing specific detection of the surface binding events at the molecular level (Castro Neto et al., 2009; Page et al., 2012). In contrast to remarkable high sensitivity, however, the specificity of the sensor is significantly hampered with the surface functionalization techniques used. Robust immobilization and/or functionalization of target-specific biological probes would largely benefit from molecular tools that act as enablers to achieve controlled interaction at the sensor surface. To overcome this limitation, many graphene/graphite surface functionalization approaches have been developed (Alwarappan, Erdem, Liu, & Li, 2009; Besteman, Lee, Wiertz, Heering, & Dekker, 2003; Ratinac, Yang, Gooding, Thordarson, & Braet, 2011). These mostly involve covalent binding, for example, via the introduction of carboxylic groups, which, however, greatly alters the electronic properties of graphene such as electron mobility due formation of surface defects on hexagonal lattice via covalent interaction. To maintain the intrinsic properties of graphene, non-covalent functionalization methods using π−π stacking-based aromatic chemistry have been employed, which however lacks spatial organization control on the sensor surface as well as limited capacity for further functionalization with probe moieties (Hayamizu et al., 2016; Khatayevich et al., 2014).

Solid-binding peptides have been demonstrated as a biomimetic alternative to controlling the surface properties of graphitic materials as well as displaying the conjugated active biomolecules with a highly controlled spatial organization on the substrate surface. The peptides specific to 2D materials including graphite (GrBP) and MoS2 (MoSBPs) have been selected using combinatorial peptide libraries and further optimized using rational and computational design principles to a strong-binding affinity (kd = 50 nM–1 μM) and material specificity (Hayamizu et al., 2016; Khatayevich et al., 2014; So et al., 2012). Among these, the dodecapeptide WT-GrBPs (with amino acid sequence: IMVTESSDYSSY, affinity constant: Kd = 3.78 μM−1) upon binding to the graphene/graphite substrate, forms long-range ordered and self-organized nanostructures that uniformly cover the surface with a monomolecular thick layer, ~1 nm, and whose crystallographic organization is commensurate with the underlying graphene lattice (Hayamizu et al., 2016; So et al., 2012; Jorgenson, Yucesoy, Sarikaya, & Overney, 2019) (Figure 2). When bound to the surface, the structural modularity of the sequence domains of the WT-GrBPs peptide facilitates the exposure of predictable surface chemistry through the display of specific amino acids facing the analyte and, thereby; making it ideal for presenting molecular probes, ligands, anti-bodies and other sensing molecules in controllable means (Figure 1).

Here, we demonstrate selective detection of a streptavidin, a model protein, against a background of serum proteins using a graphene sensor functionalized by using WT-GrBPs (Khatayevich et al., 2014). With this aim, two specific graphite binding peptides are engineered, first one, for binding and displaying a probe molecule, namely biotin, dubbed bio-GrBPT5, while the second one,
SS-GrBP5, which co-assembles with the first, for preventing surface fouling. Because of the complete miscibility of the two peptides on the surface in the self-assembled surface layer, the bio-GrBP5 detects the target protein streptavidin (SA) while the second peptide passivates the surface and, therefore, prevents non-specific protein adsorption onto the device surface, ensuring specific target selectivity (Figure 2c,d). With a mixture of two modular peptides on the surface, it has been possible to detect SA against a background of serum bovine albumin that contains a plethora of background biomolecules with a sensitivity at less than 50 ng/ml (Khatayevich et al., 2014).

In a follow-up study, peptide-based gFET biosensor is aimed to detect cancer-specific biomarkers in order to facilitate the early diagnosis of cancer. In cancer biomarker detection in clinical settings, for example, pancreatic cancer, the level of detection of biomarkers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen (CA19-9), is required to be less than ng/ml concentrations against a background of complex protein mixtures in the serum. Using the same approach, it may be possible to detect the targets at these levels of low concentrations using a four-probe gFET with increased the electronic stability. Here, similarly, two modular peptides could be used both containing the same binding moiety, GrBP5, with the first one, that is, conjugated to SS, for surface passivation and the second, conjugated with antibody-binding peptide, for targeting that specifically aims the biomarker. As demonstrated, it is conceivable that multifunctional molecular constructs can be made for a variety of electronic-, photonic- and magnetic-based biosensors with the appropriate solid-binding peptide with two functions performing three tasks: binding the probe onto the sensor surface; displaying it effectively into the analyte; and forming a passivating layer on the sensor surface to preventing non-specific interaction and enhancing signal-to-noise ratio.

3.2 | Directed Immobilization of Enzymes using Solid-Binding Peptides

Enzymatic pathways that perform multi-step biochemical reactions in biological systems constitute a vital functions enabling life (Conrado, Varner, & DeLisa, 2008; Guterl et al., 2012; Schoffelen & Hest, 2012). Following the lessons from biology, (Sarikaya et al., 2003) biomimetic reconstruction of these biochemical reactions in a confined environment holds enormous promise for sustainable green synthesis of fine chemicals, for example, pharmaceuticals, biofuels and consumer products, as well as developing efficient biomolecular devices (Riva, 2006; Willner, 2002). A key limitation is to maintain the desired biomolecular orientation and consequently optimize the catalytic activity of the enzyme when it is at a close proximity to the solid surface. Traditional strategies, including physical adsorption, chemical coupling, cross-linking, entrapment or encapsulation, result with random protein immobilization often leading to decreased or lost activity due to blockage of the active sites or undesired reactions involving active functional groups (Liu & Yu, 2016; Muguruma et al., 2017; Rusmini et al., 2007). With Nature’s wide repertoire of proteins with different functions, folding patterns attained by their sequences, there is a need for a robust strategy to control the desired physical orientation while biomolecules are immobilized at the solid interfaces. In bionanotechnological applications, a reliable immobilization method should (a) enable spatial localization of enzymes or functional proteins in a desired proximity; (b) control the orientation and display of the structurally anisotropic biomolecules on the solid surface; (c) enhance the catalytic activity towards native function by minimizing the loss of catalytic activity upon immobilization; and (d) offer tunability at the bio–nanomaterial interfaces.
over a multitude of size scales, from the nanometre to 10s of micrometres (Cetinel et al., 2013; Tamerler et al., 2010; Yucesoy, Karaca, et al., 2015). Furthermore, sustainable green synthesis approaches will benefit immensely from incorporating multi-step biochemical reactions involving multi-enzymes; however, their success depends on the immobilization methods which can overcome the diffusion limitations by offering to control the desired proximity among the enzymatic couples for sequential functionality (Mani et al., 2009).

Solid-binding peptides when used as fusion partners to enzymes offer to overcome the immobilization challenges that involve biomolecules. The resulting multifunctional molecular constructs provide directed self-immobilization of enzymes within a desired proximity and preferred orientation at the bio–nano interfaces and enable retaining a high biochemical activity on the solid surface. Our prior research demonstrated the use of inorganic-binding peptides as specific fusion tag partners for immobilization of functional proteins including maltose-binding protein (Hnilova, Karaca, et al., 2012), green fluorescent protein (Hnilova, Liu, et al., 2012), alkaline phosphatase (Kacar et al., 2009), lactate dehydrogenase (Cetinel et al., 2013) and formate dehydrogenase (Yucesoy, Karaca, et al., 2015), on various inorganic surfaces including gold, silver and silica over different hierarchical architectures. The example presented here involves an enzyme system involving two different enzymes that are immobilized in spatial proximity to each other with a desired orientation. The selected enzyme couples are designed to carry out a cascade reaction that depends on the temporal activities of the two enzymes with respect to each other.

The constrained gold-binding peptide (cAuBP2) was genetically conjugated to Geobacillus stearothermophilus lactate dehydrogenase (LDH) (Cetinel et al., 2013) and Candida methylica formate dehydrogenase (FDH) (Yucesoy, Karaca, et al., 2015) enzymes. The selected enzyme couples, LDH and FDH, are two of the well-characterized model enzymes to study cascade reactions. In this model, LDH catalyses the biosynthesis of chiral lactate from pyruvate with concomitant oxidation of nicotinamide adenine dinucleotide, and FDH breaks down formate into carbon dioxide while reducing the NAD+ back to NADH (Kraragüler, Sessions, Binay, Ordu, & Clarke, 2007; Riva, 2006). When used together, these enzymes provide suitable model to study cascadic reactions for regeneration of a relatively expensive NADH co-factor during the lactate production.

Both fusion enzymes were designed to have His domain on their N-terminals for simplification of the purification process (Figure 3). A structurally constraint 18 amino acid long, biocombinatorially selected gold-binding peptide motif (cAuBP2) was inserted between His-tag and the N-terminus of the LDH and FDH (Corni et al., 2013; Hnilova et al., 2008). To prevent the non-specific interaction of the His-tag with the gold surface, a site-specific protease recognition sequence was inserted next to the cAuBP2 region to assist the removal of His-tag via specific proteases following the purification process. On both fusion enzymes, a structurally flexible <1 nm long spacer sequence, GGGG (glycine–glycine–glycine–serine), was integrated as an engineered linker between the peptide tag and enzyme to ensure peptide tag is freely exposed to the environment without any intermolecular interactions by either of the enzymes (Figure 3b). Next, catalytic activities of each fusion enzyme were quantitatively analysed by monitoring the production/consumption of NADH spectrophotically at 340 nm. The catalytic turn-over rates were reported to be 66.8 ± 3.7 s⁻¹ and 0.61 ± 0.02 s⁻¹ for cAuBP2-LDH and cAuBP2-FDH, respectively, demonstrating no significant reduction in the catalytic activities after the peptide tag insertion compared to wild-type LDH (78.5 ± 4.5 s⁻¹) and FDH (0.59 ± 0.02 s⁻¹) enzymes. On the other hand, the molecular affinity of cAuBP2-LDH and cAuBP2-FDH to gold surface, however, was shown to increase by ~8-fold and ~12-fold compared to wild-type enzymes. We then demonstrated the sequential immobilization of cAuBP2-LDH and His-FDH enzymes using a flow bioreactor fabricated using an aluminium oxide (AAO) monolithic membrane. Highly oriented nanochannels on the ceramic membranes are allowed to mimic biological cascade reactions.

The presence of genetically incorporated peptide tags facilitated the self-organization of fusion enzymes onto gold and Ni-NTA functionated surfaces in a spatially defined cascade geometry. Over 80% NADH regeneration was shown to be stable during a continuous operation at room temperature for 10 days with a ~15% gradual decrease over 10 days. The immobilization capability of the gold-binding peptide fused as a modular domain to the enzymes provided an unprecedented advantage compared to the traditionally immobilized enzyme reactors. Solid-binding peptides, as demonstrated herein, can be the key molecular design component in the construction of chemical and biochemical reactions that involve cascade bioprocesses in complex architectural and biochemical settings.

3.3 Biofunctional coatings/engineered protective molecular biofilms

Implants are common treatment modalities in medicine to replace a missing tissue and organ; they also are support materials to enhance damaged biological structures (Geetha, Singh, Asokamani, & Gogia, 2009; Khatayevich et al., 2010; Yucesoy, Hnilova, et al., 2015; Zhang & Webster, 2009). An ideal medical implant is anticipated to have biomechanical and structural properties comparable to those of autogenous tissues without causing adverse effects. A variety of materials, for example, titanium, zirconia and stainless steel, have desirable physical and mechanical properties and are available as implants. However, because of the differences in the intrinsic structures and functions of synthetic materials and biological tissue, there are still limitations in controlling the biological response at the tissue/implant interfaces that affect the life-time of the implant material (Geetha et al., 2009; Guillaume, 2016; Pye, Lockhart, Dawson, Murray, & Smith, 2009; Subramani, Jung, Molenberg, & Hammerle, 2009). Towards enhancing the success of the implant treatment, the materials should be carefully tailored according to the site and type of implantation for their intended use with desired performance and durability (Yazici et al., 2013). For instance, dental and orthopaedic implants are generally required to be bioactive to enhance tissue compatibility as well as
infection resistance to prevent bacterial invasion and colonization in the oral environment. On the other hand, materials for intravenous implants, for example, stents and pacemaker electrodes, need to be bioinert to limit undesirable interaction with the circulation environment and, thereby, be resistant to surface fouling (Narayana & Srihari, 2019). A common strategy to enhance implant’s biocompatibility and durability is to modify their surfaces with covalently attached molecules. Depending on the proposed use, these could be PEG (anti-fouling), roughness (cytocompatibility) and ceramic coatings (osseointegration) (Khatayevich et al., 2010). Even though these methods offer solutions, up to a certain degree, to address the issues associated with biocompatibility, biofunctionality and biodurability, many of the traditional surface functionalization methods, however, are either restricted to a limited range of materials or require the presence of specific functional groups to perform complex chemical coupling processes on material surfaces and therefore none offers permanent solution.

During the past decade, the utility of solid-binding peptides has been demonstrated as multi-purpose molecular tools for biofunctionalization of a wide variety of biomedical surfaces including development of anti-fouling gold surface (Khatayevich et al., 2010), engineered titanium surfaces with enhanced biocompatibility using titanium-binding peptide (TiBP) fused with RGD motifs (Yazici et al., 2016), and biofunctionalization of implant surfaces with antimicrobial peptides (Yucesoy et al., 2015).

**FIGURE 3** (a) Conceptual schematics of the modular peptide enabled enzyme immobilization strategy and spatially directed assembly of enzymes for cascadic production. (b) Sequence map of engineered His-cAuBP2-LDH, His-cAuBP2-FDH and His-FDH fusion proteins with His-tag, PreScission Protease recognition, linker and cAuBP2 domains. (c) SDS-PAGE gel image of cAuBP2-LDH and His-FDH proteins after purification; left lane shows protein weight marker with corresponding molecular masses while cAuBP2-LDH and His-FDH are shown in the middle and right lanes (dotted circles), respectively.

**FIGURE 4** (a) Conceptual schematics of the solid binding peptide based antimicrobial implant coating; one site binding to implant surface while the other end displaying antimicrobial peptide moiety that is penetrating into cell membrane. The bacterial adhesion on (b) bare (no peptide), (c) AMP coated, and (d) TiBP–AMP peptide coated titanium surfaces against Streptococcus mutans. Bacteria are labelled with SYTO9 Green fluorescent nucleic acid stain and visualized under fluorescent microscopy (adapted from refs (Yucesoy, Hnilova, et al., 2015; Yazici et al., 2016)).
et al., 2013) and infection-resistant implant surfaces (titanium and zirconia) using material-specific solid-binding peptides chimerized with antimicrobial peptides (Yazici et al., 2016; Yucesoy, Hnilova, et al., 2015).

The next example describes the development of peptide-based antimicrobial implant coatings to prevent implant-associated infections, which have severe effects on the longevity of implant devices, the major cause of implant failure (Yazici et al., 2016; Yucesoy, Hnilova, et al., 2015). With this aim, a novel chimeric peptide was constructed involving a solid-binding peptide and antimicrobial peptide (GEPI-AMP). The AMPs are a novel class of bacterial therapeutic agents with a capacity to stimulate innate immune responses, but with the difficulty to develop bacterial resistance. The engineered chimeric construct simultaneously presents two functionalities: one of the domains binding to the implant surface through a solid-binding domain while the second domain displaying the antimicrobial property (Figure 4a). The implant material could be either metallic, for example, Ti-based alloy, or oxide, zirconia-based ceramic, necessitating the use of Ti- or ZrO$_2$-binding peptides, respectively.

In the present example, the titanium implant surface was coated with TiBPS1-AMP1 chimeric peptide harbouring the respective solid-binding unit, titanium-binding peptide and an antimicrobial peptide unit, AMP1. The biofunctional unit was tested in an assay for its efficiency both in the solution and as absorbed onto the solid surface. The experiments were carried out under in vitro conditions against three common human host infectious bacteria, Streptococcus mutans, Staphylococcus epidermidis and Escherichia coli (Yazici et al., 2016; Yucesoy, Hnilova, et al., 2015). The in-solution activity tests demonstrated that antimicrobial activity of the AMP unit is conserved when combined with the solid-binding peptide. (Yazici et al., 2016; Yucesoy, Hnilova, et al., 2015) The implant surface was coated with the chimeric peptide (TiBPS1-AMP1) was found to provide a significant resistance against all three bacterial species compared to the bare implant (Yazici et al., 2016; Yucesoy, Hnilova, et al., 2015). On the other hand, the efficacy of AMP peptide alone as a coating material was not effective enough for bacterial adhesion and growth. This is most likely because of the non-specific and weak nature of the peptide-surface interaction demonstrating the necessity of a molecular linker enabling efficient display of antimicrobial peptides on the implant surface (Figure 4a-d).

Collectively, the engineered chimeric peptide-based antimicrobial implant coating approach offers advantages for developing infection-free implants. First, unlike the conventional, cumbersome and multi-step surface treatment processes, chimeric peptide-based implant coating does not require any chemical modification on the implant surface. Therefore, it provides a biofriendly way of implant coating by eliminating the use of harsh chemicals. Secondly, by eliminating the multi-step surface treatment processes, it enables the rapid fabrication of such implants in a step procedure offering practical chair-side clinical implementation, that is, simple dipping of the implant into chimeric solution for coating before the implant operation in the surgery room. Thirdly, the utilization of AMPs as an antimicrobial unit has a high potential to help combating with increasing bacterial antibiotic resistance. Finally, the modular nature of solid-binding peptides, which can be experimentally isolated on virtually any given implant material, holds a promise to develop new chimeric units using variety of desired AMP fusion partners. (Wisdom, Chen, et al., 2019; Wisdom et al., 2019; Yucesoy, Hnilova, et al., 2015) Principles laid out in this study can be applied to other implant materials and can lead to development of infection-free implant materials in simpler treatment modalities in the future.
CONCLUSIONS

Solid-binding short peptides offer versatile control over binding, full coverage and self-biofunctionalization of solids resulting in well-defined surface properties essential in building engineered, chemically rich, bio–solid interfaces for a wide range of applications. The short peptide sequences with solid-binding activity selected by directed evolution approaches offer unprecedented opportunities in tailoring solid interfaces when coupled with solid substrates forming a new generation of novel hybrid materials systems. Genetic control of linking and the resulting function of the hybrid material are key approaches with potential to overcome limitations encountered in a wide range of applications where traditional synthetic linkers, such as thiol or silane, have been used up until now with major limitations such as bio-incompatibility, instability and non-specificity. The adaptable capabilities of the GEPIs facilitate a biomolecular tool in creating tailored soft interfaces on solid surfaces in controlled enzyme immobilization, to developing antibacterial molecular coatings and highly effective assembly of molecular probes for biosensors (Figure 5). For instance, multi-functionalization is achieved by genetically fusing a GEPI to a functional protein, for example, enzyme or antibody, to form heterofunctional molecular construct, where the peptide enables the enzyme to be immobilized onto the solid surface effectively with the enzymatic moiety properly displayed for function. There is an arsenal of available coupling strategies that provide highly versatile ways of conjugating molecular entities of orthogonal functionalities, including peptide bond, side chain modification, and N- or C-terminal click chemistry. The peptide–peptide supramolecular backbone interactions make them universal tool for use in a wide range of bioactive molecules including DNAs, RNAs, PNA’s, glycans, lipids and other small biomolecules, such as co-factors in addition to peptides and proteins. Firstly, the GEPIs have specific affinity to bind to a given solid material that can be a metal (Au, Ag, Pt, Ti), ceramic (silica, alumina, calcite, hydroxyapatite) or a single atomic layer 2D solid (graphene/graphite, MoS₂, BN) to form highly biofunctional surfaces. As demonstrated, based on their specific affinity and assembly characteristics, the role of inorganic-binding peptides in hybrid structures is being an integral component of the overall structure providing functional (e.g., mechanical) durability, in addition to providing the essential molecular linkage between solid-only components. Mimicking functions of natural proteins, the intrinsic properties of solid-binding peptides, are highly potent in a broad range of applications from particle synthesis and assembly with genetically controlled physical and chemical characteristics in materials science to probing for biomolecular targets in molecular biology, biotechnology and medicine in the coming years.

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