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Modular self-assembling biomaterials for directing cellular responses

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Abstract

Self-assembling biomaterials are promising as cell-interactive matrices because they can be constructed in a modular fashion, which enables the independent and simultaneous tuning of several of their physicochemical and biological properties. Such modularity facilitates the optimization of multi-component matrices for use in complex biological environments such as 3-D cell culture or scaffolds for regenerative medicine. This Highlight will discuss recent strategies for producing modular self-assembling biomaterials, with a particular focus on how ligand presentation and matrix mechanics can be controlled in modular ways. In addition, it will discuss key hurdles that remain for employing these materials as cell-interactive scaffolds in biomedical applications, particularly those that relate to how they may interface with the immune system.

Introduction

A cell's behavior is regulated by the complex milieu of signals in which it resides. Whether a cell finds itself in culture, in a native tissue, in an engineered tissue, or in suspension, its decision to apoptose, proliferate, differentiate, migrate, or subtly change its phenotype will always be made by integrating all of the available signals at hand.¹ When designing cell-interactive biomaterial scaffolds for applications such as defined 3-D culture or tissue engineering, a long and growing list of such signals may be relevant, including the density and spatial positioning of different ligands, the mechanics of the matrix, the time course of matrix degradation, the release of soluble signaling factors, and others. In cell-material interactions, relationships between these parameters may be additive, synergistic, or antagonistic, and they depend on the context of all signals present. Moreover, these relationships almost always vary with time. This incredibly large, convoluted, and time-dependent parameter space presents a challenge for engineering biomaterials that can predictably and controllably interface with biology.

Self-assembling biomaterials can be constructed in a modular fashion, which enables the independent and simultaneous tuning of many of these physicochemical and biological factors. The term modularity can take on different meanings in different contexts and fields; in the context of self-assembling biomaterials, it indicates both a multi-component segmental construction and a capability to orthogonally adjust many of these components at once (Figure 1). These features promise to facilitate more systematic explorations of the multidimensional parameter space of cell-material interactions than have been previously possible. Modularity arises from both the non-covalent architecture of self-assembling biomaterials as well as their chemical definition, enabling the precise integration of different components simply by mixing and inducing assembly. In this way, combinations of parameters may be systematically fine-

tuned while observing biological outcome (Fig. 1). This optimization is more difficult in other biomaterials such as tissue-derived biopolymers or covalent polymer networks, which can be more polydisperse, incompletely defined especially in the case of biologically derived materials, and which tend to confound multiple physicochemical properties with each other. Given the exceedingly multifunctional and complex microenvironment that determines cell behavior, the orthogonal modularity exhibited by self-assembling systems is advantageous.

This brief Highlight is an account of recent advancements in self-assembling biomaterials designed to promote specific cellular responses, both in vitro and in vivo, and it emphasizes work that extends these materials' modularity. It will also discuss a few areas of challenge and opportunity that exist as self-assembling biomaterials move closer to biotechnological and biomedical applications, including how these materials may interface with the immune system. For more detailed discussions of other aspects of self-assembling biomaterials, including stimulus-responsiveness,² protein delivery from self-assembled scaffolds,³ polypeptide-based materials,^{4, 5} biomaterials for controlling stem cell phenotype,⁶ nanofibrous biomaterials,^{5, 7, 8} peptide-amphiphiles,^{8, 9} and the cell-surface interface,¹⁰ the reader is referred to other recent reviews. In addition, for more extensive discussions of modularity in supramolecular biomaterials, please see the comprehensive reviews published recently by Dankers and Meijer¹¹ and Weck and coworkers.¹²

Modular ligand presentation in self-assembled biomaterials

Although modularity can take on many dimensions, several recent approaches to construct self-assembling biomaterials have particularly emphasized the modular integration of various ligands for cell binding. For example, Meijer and co-workers designed ureido-pyrimidinone (UPy)-functionalized polymers able to incorporate a variety of peptide ligands.^{13, 14} Backbone polymer networks of UPy-functionalized polyesters provided sites where UPy-functionalized peptides could dock via four precise hydrogen bonds. The usefulness of this approach lies in its simplicity, as one can envision a nearly endless combination of UPy-functionalized peptides immobilized simply by mixing them together and applying them to the polymer matrix. A variety of UPy-functionalized peptides have already been produced, demonstrating the potential breadth of this approach.¹³ An analogous strategy has also been utilized to decorate collagen matrices with peptides able to co-assemble non-covalently into the collagen triple helix.¹⁵ Other recent advances in modular self-assemblies have sought not to decorate a base scaffold but to construct the entire material from self-assembling small molecular weight components. For example, Stupp and coworkers recently extended their previous work with peptide-amphiphile biomaterials^{16–18} by investigating the assembly and bioactivity of new peptide-amphiphiles capable of presenting additional ligands such as biotin,^{9, 19} RGD,^{20, 21} and others.²² In these systems, the ligands are effectively displayed and bioactive, enabling future work where complex combinations of them are tuned. Other recent work with β -sheet fibrils has demonstrated that such peptides can also be functionalized with a variety of pendant peptide sequences so as to integrate different ligands into a gel network of peptide fibrils.^{23–26} Expressed α -helical coiled coil systems have also been designed where cell-binding domains may be integrated into backgrounds of non-functionalized protein gels in a modular way.²⁷ It is expected that the continuing refinement of modular strategies for ligand incorporation such as these will enable increasingly systematic fine-tuning of these scaffolds for applications ranging from 3-D cell culture scaffolds to tissue engineering. Encouraging successes have already been reported using ligand-presenting self-assembling biomaterials to influence a variety of cell behaviors. Representative examples include the differentiation of neural progenitor cells,¹⁶ the adhesion and spreading of fibroblasts,²¹ the proliferation and protein expression of endothelial cells,^{26, 28} the proliferation, differentiation, and migration of osteoblasts,²⁴ and the intracellular uptake of the material itself.²⁹ However, the modularity of

these materials has not yet been fully exploited, as many simultaneously co-assembled factors have yet to be systematically tuned and optimized.

Orthogonal modularity: Matrix mechanics and ligand presentation

The concept of modularity can be extended beyond the incorporation of various different ligands to include other physicochemical aspects such as matrix viscoelasticity.²⁸ It is increasingly appreciated that the mechanical environment surrounding a cell profoundly influences its behavior³⁰ (for recent reviews, see 31). Given that self-assembled biomaterials are constructed predominantly from non-covalent interactions, recent work has focused on ways to adjust these materials' covalent connectivity and therefore their viscoelasticity. For example, we sought to develop a means for controlling the mechanical properties of β -sheet fibrillar matrices in a way that would be modular, chemically specific, and independent of ligands co-assembled within the matrix. We employed native chemical ligation³² as a chemoselective way of accomplishing this by designing short peptide thioesters capable of self-assembling and then oligomerizing into covalently stabilized networks (Figure 2).²⁸ Other laboratories have also recently utilized chemical ligation in combination with peptide self-assembly to produce long collagen-mimetic³³ or α -helical fibrils.³⁴ In the case of β -sheet fibrillar gels studied in our laboratory, native chemical ligation led to as much as a six-fold stiffening of the gels without significantly altering the morphology of the self-assembled fibrils.²⁸ Ligation could be performed in a range of peptide concentrations, providing a way of decoupling matrix stiffness from peptide concentration, and therefore presumably from porosity. The chemistry was also cytocompatible in cultures of primary human endothelial cells, and matrix stiffening by ligation led to a significant increase in cell proliferation over non-ligated gels (Figure 2c). In addition, co-assembling an RGD-functionalized peptide into the matrix could specifically enhance proliferation further. This latter example demonstrated the modularity of this approach, in which mechanical properties and cell binding could be controlled in separate, orthogonal, easily combined ways. Matrix mechanics in self-assemblies of peptides or peptide-amphiphiles have also been controlled through the formation of disulfide bonds,¹⁸ through primary sequence variations,³⁵ by ion complexation,³⁶ and by adjusting the concentration of the self-assembled species,³⁷ though the latter example is less modular because cell attachment points, porosity, and other biophysical aspects may change with varying peptide concentration. It is expected that advancing sophistication in the ability to regulate the mechanical environments surrounding cells will continue to improve the ability to direct desirable cell and tissue responses. Those approaches that enable the modular tuning of viscoelasticity may be particularly useful for systematically mapping how combinations of mechanical and biological stimuli promote specific biological outcomes.

Challenges and opportunities for implementation in biotechnology and biomedicine

The full implementation of modular self-assembling biomaterials *in vitro* and *in vivo* faces a number of challenges arising from biology's ability to remodel such scaffolds. However carefully or cleverly a self-assembled biomaterial is constructed, as soon as it is placed in a biological environment, its molecular features will start to be remodeled by proteolytic degradation, soluble protein adsorption, the deposition of new extracellular matrix, and in the case of *in vivo* environments, possible inflammatory or immune responses (Fig. 3). All implanted biomaterials must appropriately interface with the natural inflammatory processes that result from implantation,³⁸ but in the case of self-assembling biomaterials constructed from peptides or proteins, the possibility of immunogenicity must also be considered. In fact, several recent approaches for producing synthetic vaccines resemble many of the approaches described above for producing modular biomaterials, indicating a potential for self-assembled biomaterials to interact with the immune system for good or for bad. For example, a peptide-

lipid was recently reported that forms spherical self-assemblies, and the repetitive display of a peptide sequence on the surface of the assemblies produced an immunogen capable of producing high antibody titers without even the presence of any adjuvant.³⁹ Spatial repetition of antigens has long been recognized as a means for enhancing immune responses.⁴⁰ One mechanism by which this occurs is through the clustering and cross-linking of B cell receptors by multivalent ligands, which can stimulate IgM production without the help of T cells (Figure 3e). It is also known that fibrillization and aggregation can significantly increase the immunogenicity of commercially available protein therapeutics even for fully human proteins.⁴¹ Such studies indicate that in the case of self-assembling biomaterials, which also display multivalent and repetitive ligands, care must be taken to ensure that the chosen ligands are exceptionally nonimmunogenic while at the same time capable of exerting their desired biological effects (e.g. integrin binding). However, even the most common and popular biomaterials modifications such as the RGD motif have been found to raise the immunogenicity of other peptides in some cases,⁴² and biomaterials surfaces themselves are capable of adjuvanticity,⁴³ further adding to the difficulty of predicting how a particular self-assembled biomaterial will be tolerated. In addition, many self-assembling biomaterials exhibit some degree of heterogeneity in lateral aggregation, potentially making it difficult to draw connections between self-assembled structure and immunoreactivity. Recent advancements in controlling lateral aggregation⁴⁴ or network topology⁴⁵ may prove helpful in this regard. It is also encouraging that many self-assembling biomaterials have not demonstrated evidence of cytotoxicity^{24, 25, 28, 46, 47} or elicited obvious inflammatory responses in immunocompetent animals.^{16, 47–49} However, with a few exceptions,^{16, 49} most *in vivo* studies to date have been performed with non-functionalized self-assemblies, so the range of possible ligands that will be tolerated is not yet clear.

Questions about how materials interact with the immune system are not unique to supramolecular structures, as a great deal of current research in the field of Biomaterials as a whole is concerned with the careful spatial positioning of molecular features (peptides, engineered proteins, growth factors, protein-polymers, biofunctionalized supports) that could also be recognized immunologically to various degrees. Perhaps self-assembling biomaterials, with their precise and modular control over multiple aspects of the material, will prove to be useful platforms for systematically intervening in these responses so that relationships between ligand antigenicity, spacing, co-presentation, matrix stiffness, and other factors may be more clearly understood. Given that the immune and inflammatory systems are intimately involved in tissue remodeling and healing, it is possible that elucidating these relationships may help provide novel strategies for regulating regenerative processes in tissue engineering.

Conclusions

This Highlight has attempted to provide a brief discussion of self-assembling biomaterials and how orthogonal modularity is an essential and useful characteristic of them. Modularity is being exploited to greater and greater degrees, particularly with different cell-binding ligands and matrix viscoelasticity. It is expected that such modular approaches will facilitate more rapid and systematic explorations of the complex parameter space of cell-materials interactions. The potential for these materials to engage immune responses presents a challenge for fully implementing them in biomedical applications, but if such interactions can be understood and controlled in the coming years, these materials may prove highly advantageous in regenerative medicine.

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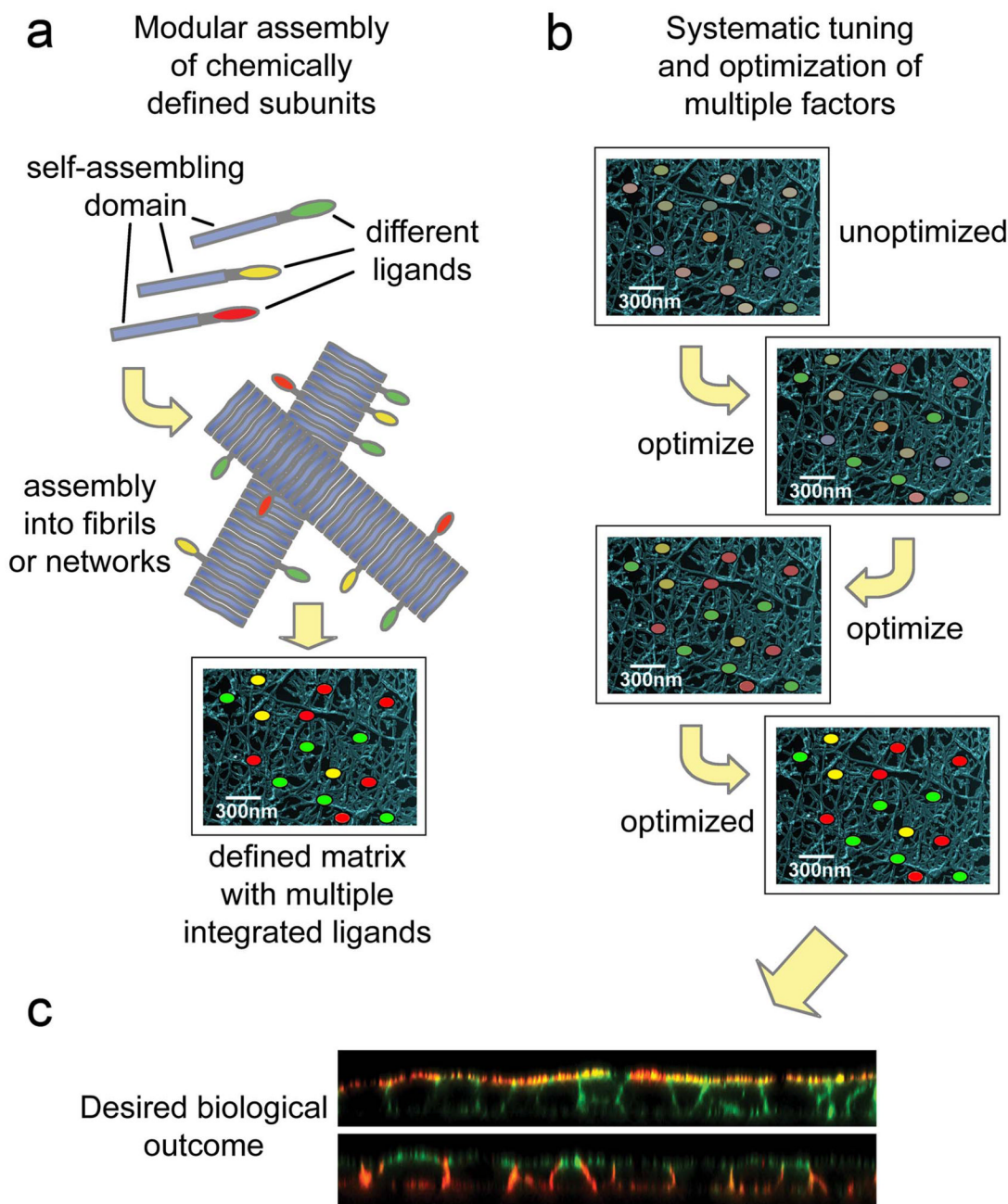


Figure 1.

Self-assembly enables a modular approach to biomaterials construction. The co-assembly of chemically defined molecular elements (a) promises to facilitate more systematic optimization and efficient exploration of the large parameter space of cell-biomaterials interactions (b) in order to experimentally identify those combinations of parameters that most effectively drive a desired biological response, for example the formation of a polarized epithelium (c). In panel (c), polarized MDCK epithelial cells are shown with confocal microscopy. The top image shows apical staining (red, gp135), and the bottom image shows basolateral staining (red, E-cadherin). In both images, F-actin is counterstained with phalloidin (green).

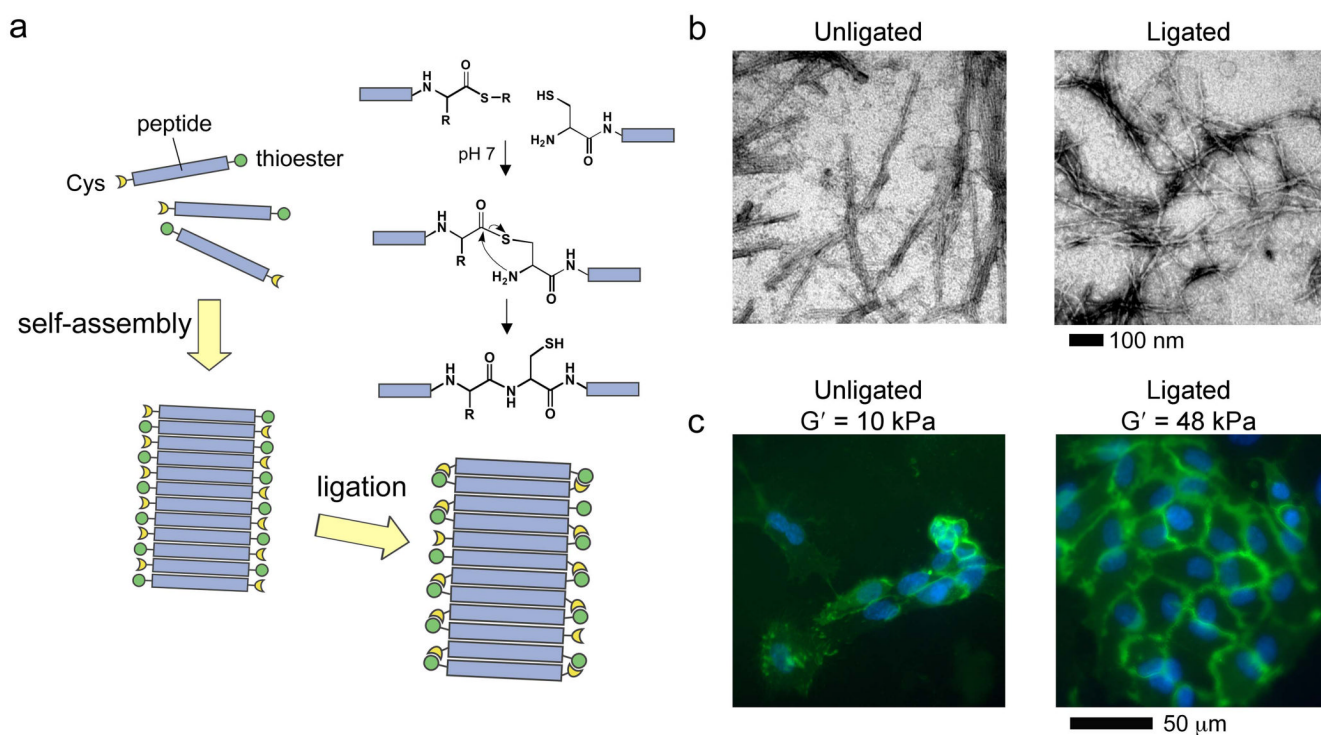


Figure 2. Matrix mechanics as a modular aspect of biomaterials. β -sheet forming peptide-thioesters self-assemble into fibrils and undergo native chemical ligation, leading to matrix stiffening (a). Ligated peptides retain the ability to fibrillize (b), and stiffening leads to significantly improved proliferation of human endothelial cells over un-stiffened matrices (c, blue DAPI, green CD31). Reprinted with permission from Jung et. al, *Biomaterials*, 2008.²⁸

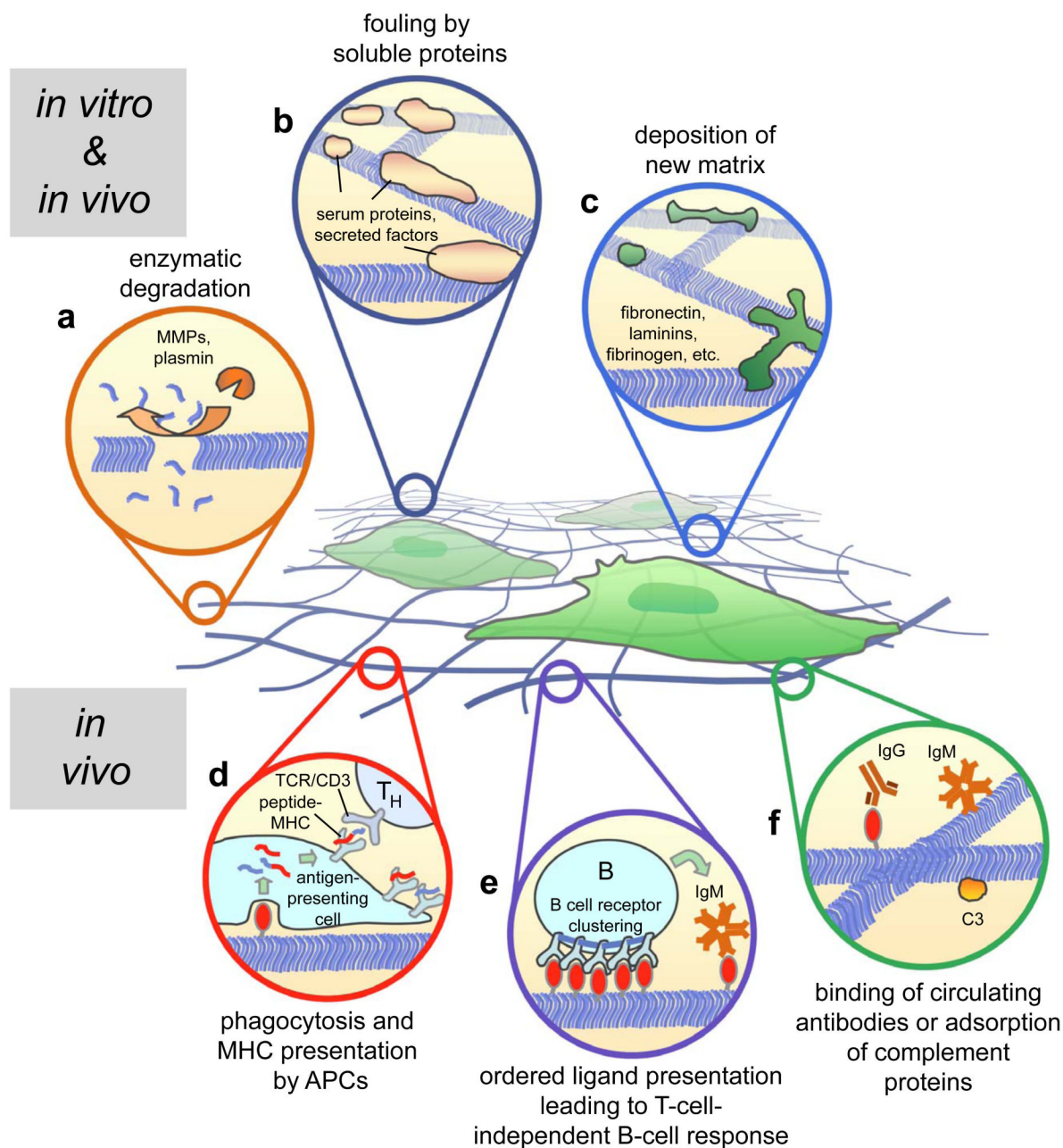


Figure 3.

Biological mechanisms that can modify self-assembling biomaterials construction *in vitro* (a–c) and *in vivo* (a–f). Processes at work in both environments include enzymatic degradation (a), fouling by serum-derived or other soluble proteins (b), and the deposition of new extracellular matrix by cells in contact with the material (c). Processes at work *in vivo* include phagocytosis of the matrix by antigen-presenting cells (APCs) and presentation in the MHC to potentially stimulate T-cell-dependent immune responses (d, note, many accessory and co-stimulatory proteins are not shown for simplicity), T-independent IgM responses induced by multivalent ligand display and B cell receptor clustering (e), and the binding of low-affinity circulating antibodies or complement proteins (f).