HHS Public Access

Author manuscript

Curr Opin Virol. Author manuscript; available in PMC 2020 June 01.

Published in final edited form as:

Curr Opin Virol. 2019 June ; 36: 38–46. doi:10.1016/j.coviro.2019.02.010.

Virus capsid assembly across different length scales inspire the development of virus-based biomaterials

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Abstract

In biology, there are an abundant number of self-assembled structures organized according to hierarchical levels of complexity. In some examples, the assemblies formed at each level exhibit unique properties and behaviors not present in individual components. Viruses are an example of such where first individual subunits come together to form a capsid structure, some utilizing a scaffolding protein to template or catalyze the capsid formation. Increasing the level of complexity, the viral capsids can then be used as building blocks of higher-level assemblies. This has inspired scientists to design and construct virus capsid-based functional nanomaterials. This review provides some insight into the assembly of virus capsids across several length scales, and certain properties that arise at different levels, providing examples found in naturally occurring systems and those that are synthetically designed.

Introduction

Virus capsids are diverse and elegant examples of biomolecular nanostructures, which are hierarchically self-assembled from a limited number of macromolecular subunits. Self-assembly is a common mechanism for the construction of complex biological systems whereby smaller building blocks spontaneously come together to form larger, hierarchically organized, structures. Biology has evolved to assemble hierarchically ordered structures, which exhibit properties that arise from the collective interaction of the individual building blocks [1,2]. Bacterial microcompartments, for example, are cellular containers that self-assemble from protein subunits and encapsulate a series of enzymes [3]. These containers act as organelle-like compartments that segregate chemical reactions within prokaryotic cells leading to specialized catalytic function. Inspired by nature, materials with multiple levels of hierarchy have been synthetically constructed using modular approaches [4,5]; that is, the formation of individual virus-like particles (VLPs) through self-assembly of capsid subunits, and the assembly of these VLP building blocks into ordered three-dimensional arrays [6•]. The assembly behavior and resultant lattice structure are a consequence of inter-particle interactions mediated by the particle exterior and because this construction approach is modular, it holds the promise that a large diversity of functional cargos could be encapsulated inside of VLPs and assembled into superlattices using the same assembly

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approach. Thus, the construction of virus-based assemblies at multiple length scales presented here could be widely applicable for the formation of a range of complex materials.

Scaffold protein-mediated assembly

Both viral and non-viral assemblies often require macro-molecular scaffolds to template formation of the proper structure. Tubulin, for example, is essential for cell proliferation and its polymerization requires regulatory proteins that mediate the assembly and disassembly of the microtubule network [7–9]. Similarly, chaperone proteins behave as scaffolds to promote proper intracellular protein-folding, and prevent aggregation in the cytosol due to the high macromolecular concentrations found within cellular environments [10]. However, there are many more examples of scaffold-mediated assembly in the realm of viral capsid self-assembly.

The role of scaffold proteins (SP) in viral capsid assembly can be to prevent the formation of aberrant assemblies, act as a catalyst during nucleation, promote proper inter-subunit interactions between coat protein (or major capsid protein) subunits, and prevent formation of particles that may otherwise form due to the spontaneous radius of curvature of the CP subunits [11–13,14••]. In systems where SP is necessary, it is typically required for the proper formation of an initial assembly intermediate, the procapsid or prohead [12,15]. This assembly is accomplished via both long-range and short-range non-covalent interactions between the coat protein (CP) and SP, some of which can subsequently be disrupted during the maturation of the procapsid [5,11,15,16,17••]. Considering the critical role of SP and the environment in which viral particles assemble, the interactions between the CP and SP are often highly specific. The presence of a SP can also lower the threshold or critical CP concentration required for capsid formation making the overall assembly process more favorable [17••].

In general, large icosahedral viruses require scaffolding protein [14••]. A few bacteriophage examples such as P22 [18–21], λ [22–24], T7 [25–27], T4 [28–30], and ϕ29 [31–33] all require scaffolding proteins to template the assembly of the initial procapsid structure. Viruses from the *herpesviridae* also require an internal scaffolding protein, and assemble via a similar mechanism to these bacteriophages, where first a prohead structure is formed before the packaging of DNA [34,35]. Oligomeric forms of SPs (monomers, dimers, and tetramers) template CP assembly by either first forming a SP ‘core’ around which the CPs can accumulate (e.g.: T4) or the SP remains largely dissociated and co-assembles with the CP (e.g.: P22 (Figure 1a), λ, T7, and ϕ29). The conformational flexibility of many of these scaffolding proteins allows for structural adaptability, which is critical for driving interactions between non-equivalent capsid proteins.

In the case of bacteriophage T4, the essential scaffolding proteins form a core structure with at least four other proteins, even in the absence of the major capsid protein [28], before capsid assembly. In P22, the flexible nature of the internal scaffolding protein has allowed materials chemists to repurpose these viral capsids and drive the encapsulation of cargo molecules, not native to the P22 structure, into the capsid [36–40,41•,42•]. The SP binding domain is a structured helix-turn-helix (hth) located near the C-terminus, while the N-

terminus of the SP is largely disordered and can be truncated without losing the ability to template P22 assembly (Figure 1b) [20]. Fusing protein cargos, such as fluorescent proteins or catalytically active enzymes, to the truncated N-terminus or C-terminus, while preserving the integrity of the SP hth binding domain, has provided a general approach for encapsulating a wide variety of functional proteins for use in synthetic materials design and construction (Figure 1c).

Capsid–capsid interactions and collective behavior

The functional complexity achieved by biological systems often arises from global behavior that is the result of collective properties not present in the behavior of the independent components before assembly [1,2,43]. This can be observed in entire ecosystems as well as on a cellular level, where the individual sub-cellular compartments act together (i.e. the cell) to carry out reactions beyond the capabilities of each individual compartment [44••]. Furthermore, when individual cells come together to form specific tissues, additional functionality is achieved as a result of the collective cellular behavior [45]. In the case of viral capsids, emergent properties are evident upon assembly of a single capsid from individual protein subunits, including the ability to package cargo such as DNA and other macromolecules, provide a protective barrier for the interior components, and in infectious viruses the ability to infect host organisms [46•].

Adding complexity to the hierarchical organization, such as in the interactions between individual viral capsids, can lead to collective behavior not present in the individual capsid. When considering the processes of viral infection, the intracellular environment undergoes dramatic rearrangement due to the increasing concentration of capsids and other viral components [47–50]. For both bacterial and eukaryotic organisms parts of the cellular machinery migrate to the periphery of the cell altering cellular organization [51], and the cytoskeleton shifts in order to accommodate the viral replication sites, which often include electron-dense aggregates referred to as viral factories (Figure 2d) [49,52,53•]. Viral factories assist in the synthesis of viral components, fabrication of capsids, packaging of genomic material, and most importantly for this discussion, are associated with the high local concentration of viral particles within the intracellular environment [51,54].

Not only does the high viral-particle concentration result in cytopathic effects, but also there are several examples where the inter-capsid interactions give rise to new properties, something that has been exploited by material scientists. In one example, viral factories are associated with the paracrystalline arrays of iridovirus formed inside the cytoplasm of infected cells (Figure 2a and b) [48]. Though the mechanism of this assembly remains largely unknown, the result is the crystalline close packing of the iridovirus particles giving rise to the iridescent properties associated with high levels of infection [55,56]. The iridescence is indicative of infection; however, this feature has prompted the study and use of this virus toward the design and construction of bio-photonic crystals [57–59]. The rod-shaped Tobacco Mosaic Virus (TMV) also adopts similar crystalline packing densities, where hexagonal crystals have been observed in the cytoplasm shortly after infection (Figure 2c) [47]. These nematic liquid-crystal domains formed by TMV, exhibit intrinsic magnetic properties [60–62], show Bragg diffraction, and form iridescent gels [50].

Overall, the formation of these crystalline arrays is driven in part by shape complementarity, where the shape of the individual components determines the orientation, global entropic gain due to displacement of water molecules, the local concentration of individual particles, excluded volume effects, and factors dependent on ionic strength and other environmental conditions.

Synthetic higher-order assembly

Materials scientists increasingly draw inspiration for the design of new functional materials [5,64–67] from the multi-length scale assemblies found in nature. The study of these materials is important for understanding self-assembly in biological systems, which are often dynamic, complex, and difficult to study in their native forms. The synthetic use of directed self-assembly via non-covalent interactions, has highlighted the possibilities for nano-scale and micro-scale structures, unattainable via covalent bond formation. Designing synthetic systems provides an opportunity to limit and control the study to a few parameters. Exploiting some of the characteristics of self-assembled structures can lead to the synthesis of multicomponent materials designed for applications in the fields of biomedicine, energetics, and catalysis [68,69••,70–74,75••]. For example, similar to the photonic properties observed in the ordered lattices of iridoviruses, crystalline assemblies of individual synthetic nanoparticles have been shown to have unique magnetic, electronic, photonic, and plasmonic properties [76,77].

Virus and virus-like particles (VLPs) are attractive building blocks for the synthetic construction of higher order assemblies due to their monodispersity in size and shape [69••, 78,79]. Both isotropic and anisotropic viral nanoparticles have been studied for the design and synthesis of self-assembled nano-arrays. Tobacco mosaic virus (TMV) and M13 phage are two examples of anisotropic rod-shaped nanoparticles with a propensity to orient along their long axis and form liquid crystal-like domains, and therefore are appealing candidates for higher order assemblies. TMV has been used as a building block for the construction of superlattices [80–82], as a template for ordered silica mesophases [83], and the formation of 2-D/3-D assemblies [84–86] through non-covalent interactions including electrostatics [86], depletion forces [80,81], and metal coordination [82,84]. Similarly, the high aspect ratio and helical nanofibrous shape of phage M13 make it ideal for the development of both covalently and non-covalently assembled liquid-crystals [87,88], supramolecular structures [89], nanoporous networks [90], with very long range (cm length scale) order [91••], and hierarchically organized M13 phage-based nano-fiber materials with piezoelectric properties [92].

Symmetrical icosahedral virus particles such as those derived from bacteriophage P22 [6•, 93,94], Cowpea chlorotic mottle virus (CCMV) [95], Cowpea mosaic virus (CPMV) [96], and bacteriophage Qβ [97] have also been used for directed construction of synthetic higher-order assemblies via non-covalent interactions. CCMV and Qβ have been assembled into binary 3D superlattices using tunable electrostatic interactions with Au nanoparticles and poly-peptide functionalized bio-macromolecules (Figure 3a) [98], and complementary oligonucleotide interactions [95,97]. Complementary oligonucleotide-functionalized CPMV particles have been used to assemble 3D arrays with tunable melting temperatures by

varying the degree of complementarity between the nucleotides [96]. The icosahedral capsids additionally contain hollow interiors, capable of encapsulating functional cargo, highlighting the potential for user-defined functionalities of the resulting higher ordered assemblies. Functional CCMV VLPs have been used as building blocks in the formation of non-lattice higher-order 2D thin films and 3D hydrogels [99,100]. CPMV and Qβ have been utilized to encapsulate non-native cargo but lattice formation of these functional VLPs remains to be demonstrated [101–103].

However, studies using the VLP derived from the bacteriophage P22 have combined the capabilities of encapsulating active enzyme cargos, and the ability to design and construct protein cage superlattices. Utilizing the functionally active P22 VLPs as building blocks, the construction of catalytically active arrays using protein linkers and polymer-mediated assembly has been demonstrated [6•,93]. The exterior of the P22 VLPs was modified with a range of small peptides, to tune the surface charge. When allowed to interact with oppositely charged branched polymers (PAMAM dendrimers), the P22 variants assembled into ordered lattices with very pronounced ionic strength dependence (Figure 3c) [6•]. The resulting lattices were investigated by small angle X-ray scattering (SAXS) and electron microscopy that revealed ordered face centered cubic arrangements of VLPs. These higher order assemblies were driven by the nature of the exterior capsid surface and were independent of the encapsulated cargo, thus catalytic enzymes encapsulated within the P22 remained active when assembled in the higher order structures. This afforded the design and construction of extended materials with demonstrated multistep enzyme catalysis for the formation of isobutanol. Since the VLP-based lattice materials required less solvation than the individual capsids, this allowed for very high enzyme and substrate concentrations in the reactions thereby increasing catalytic efficiency considerably [6•]. To further enhance the robustness of this design and construction, a ditopic ‘cementing’ protein was used to lock the P22 lattice into place forming a Protein Macromolecular Framework (PMF) from which the dendrimer could be removed at high ionic strength without disrupting the lattice [93]. Higher order assemblies constructed from P22 VLPs demonstrated properties observed in the extended lattice that were different from those of the individual particles. This was shown when the assembled lattice incorporated and bound a charged macromolecule under ionic strength conditions where there was no interaction with individual P22 particles [94]. Collective behavior has also been observed in ordered domains assembled from M13 phage that displayed colors in the visible range due to light refraction (Figure 3b). Upon changes in humidity, or through specifically designed interactions with small molecules, the assemblies underwent a structural change that caused the inter-particle distances to shift and change color in an easily measurable way [104,105]. These properties are a result of the extended lattice and are not present in the individual virus particles.

Conclusion

The field of VLP-based materials assembly to create higher-order structures is an emerging area, even though the hierarchical organizations of assemblies such as TMV or iridovirus have been known for decades. However, the collective properties and the potential applications for synthetic higher order assemblies have not been fully realized for many of these systems. Virology has provided scientists with inspiration and a framework for using

virus-based building blocks to design and synthesize a new generation of functional biomaterials. Understanding self-assembly across multiple length scales has guided the development of these systems with the ability to tune the properties of individual particles, as well as new approaches for higher order assembly of functional materials.

Acknowledgements

The authors would like to acknowledge funding support from the U.S. Department of Energy, Office of Basic Energy Sciences, Division of Materials Sciences and Engineering (DESC0016155), the National Institutes of Health (R01 AI104905), and the National Science Foundation (NSF-BMAT DMR-1507282 and EEC-720625). E.S. was supported by the Graduate Training Program in Quantitative and Chemical Biology under Award Number T32 GM109825 and Indiana University. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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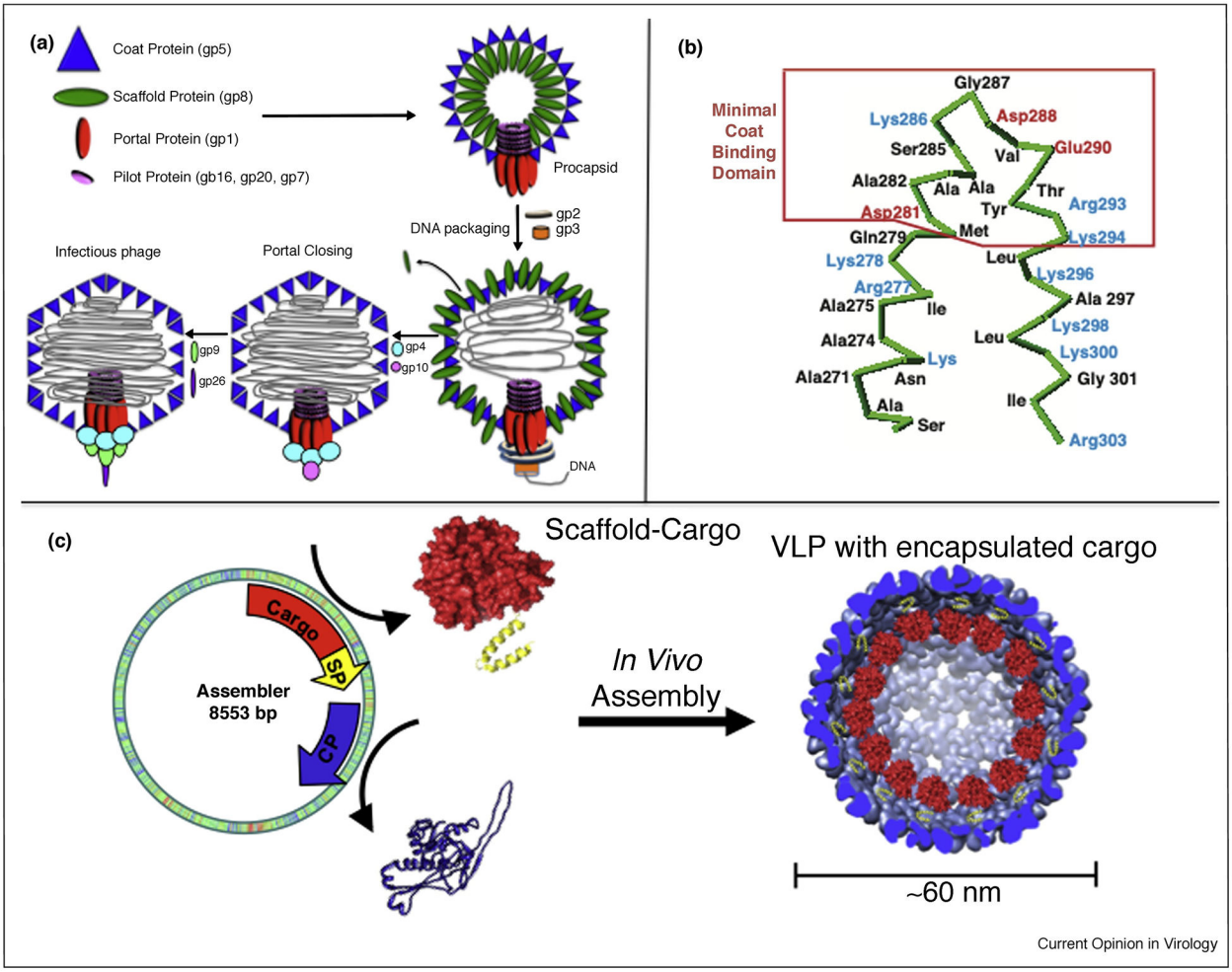

Figure 1.

Roles of bacteriophage P22 scaffolding protein (SP). (**a**) The assembly pathway of bacteriophage P22. A variety of gene products come together to form the capsid including coat protein (CP) gp5 and SP gp8. SP is responsible for co-assembling with CP and templating the procapsid structure. As DNA is packaged, the binding domain is lost due to a CP conformation shift and SP is ejected from the capsid. (**b**) The C-terminus of gp8 SP, including the 35 amino acids necessary for interacting with CP for assembly of the procapsid. The N-terminus is not required for templating capsid assembly [20]. (**c**) Truncating the N-terminus of SP and fusing a cargo to it allowed for the programmed encapsulation of cargo non-native to P22, including a variety of different enzymes [36].

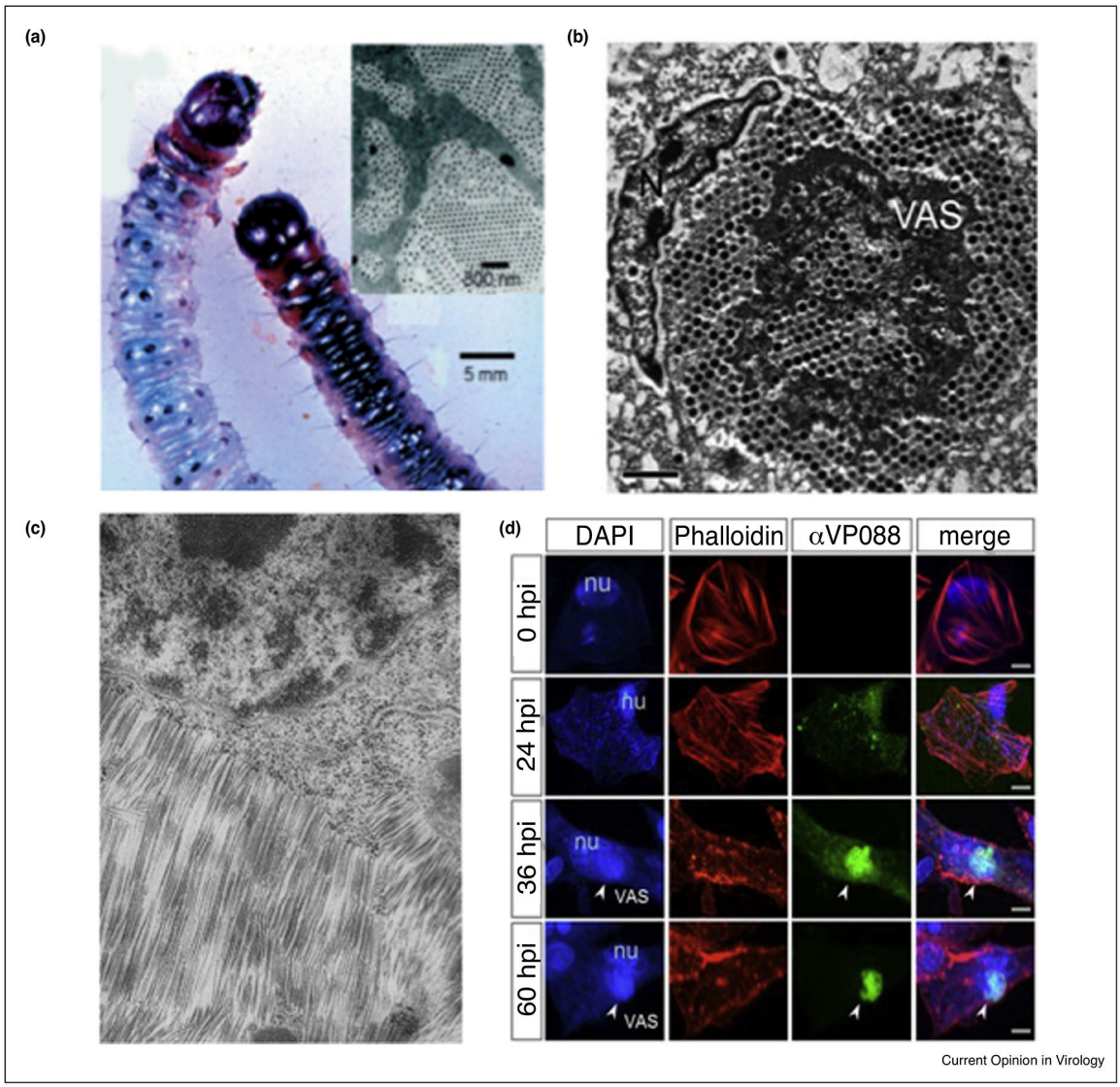

Figure 2.

Capsid–capsid interactions can induce structural changes. (**a**) A larvae infected (left) and not infected (right) with *Wiseana* Iridovirus. The infected larvae display iridescence and discoloration due to the crystalline packing arrangement of the virus capsid in the infected cells [57]. (**b**) The paracrystalline array formed by the Singapore Grouper Iridovirus in an infected cell [48]. (**c**) Hexagonally packed TMV crystals embedded in the cytoplasm [47]. (**d**) Confocal microscope fluorescence imaging of a cell upon formation of a virus factory, monitored after hours post infection (hpi). The nucleus (blue-DAPI stained) and the F-actin (red-phalloidin stained) both go through large conformation changes upon formation of a virus factory (green) [63•].

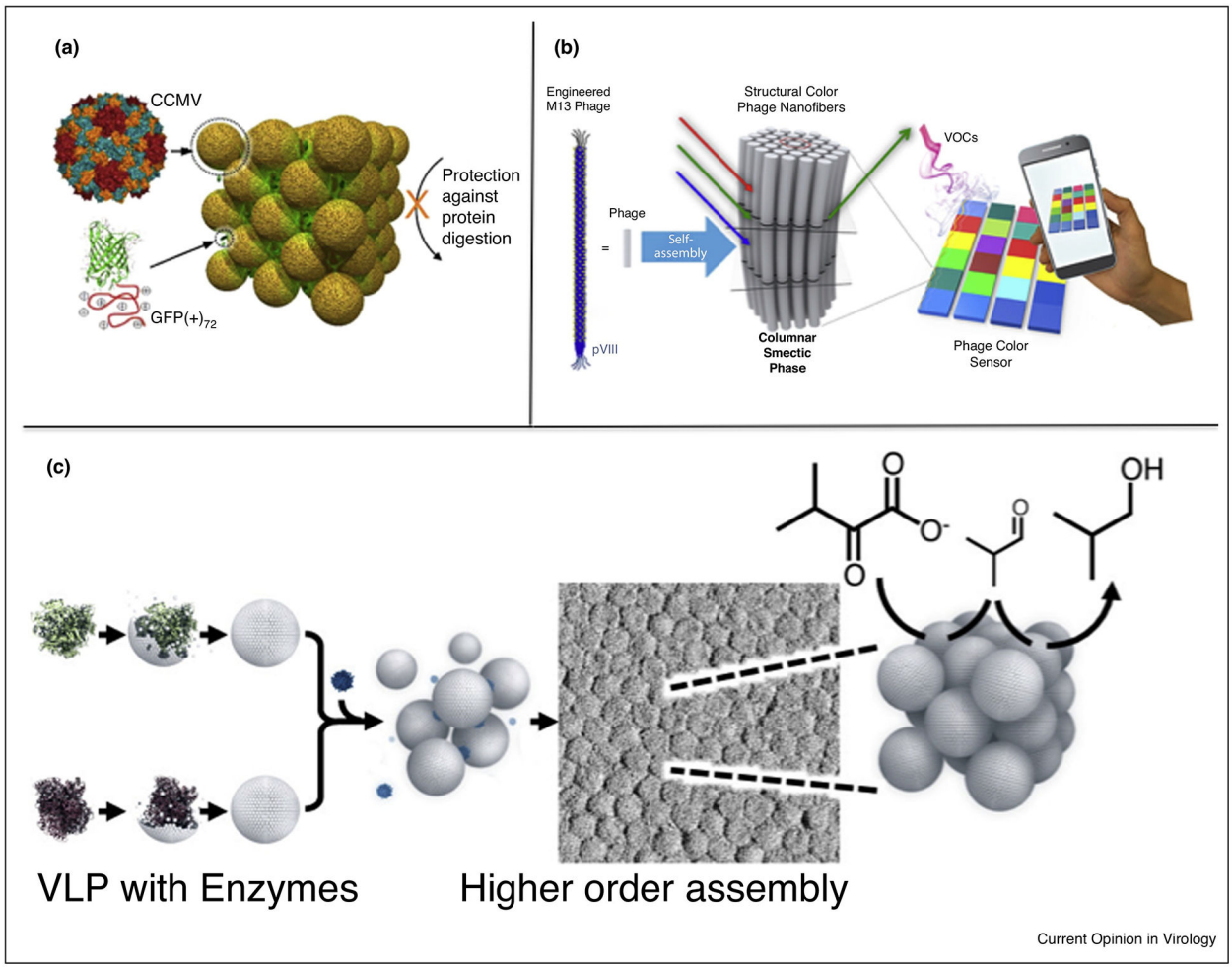

Figure 3.

Virus capsid-based synthetic high-order assemblies. (**a**) Electrostatically driven co-crystals are formed through the interactions between the negatively charged CCMV capsid and super-charged cationic polypeptide fused to a fluorescent protein [98]. (**b**) A sensor was constructed using M13 Phage where environmental stimuli triggered a change in the spacing between phages resulting in an optical response [105]. (**c**) Coupling the ability to encapsulate enzyme cargo and tune inter-particle interactions, bacteriophage P22-based fcc lattices were formed capable of multi-step catalysis toward the enzymatic synthesis of isobutanol [6•].