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The promise of peptides

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Introduction

Let us consider how to formulate a single molecular frame work for modulating polynucleotides, proteins and cell membranes. In accomplishing this, we might seek chemicals that can reliably self - assemble into modular nanostructures such as tethers, pores and other structural networks. Given such diverse targets, we may further desire facile synthesis of molecules over quite a range of different sizes (from under 100 a.m.u. up to several kiloDaltons) and charge states (from polycation to polyanion, including various different zwitterionic structures and environmentally inducible valences). Addressing our targets may dictate an arsenal of different functionalities such as salt bridges, H-bond networks, hydrophobic cores and even redox-sensitive covalent cross-linkages. To facilitate *in situ* delivery, we may wish to engineer small units that, in one conformation, are soluble in polar media such as plasma or cytosol, but may rearrange to prefer lipid media. Finally, we may wish to specify a range of different metabolic stabilities, ranging from strong persisting to rapidly cleared.

Requesting all such specifications within a single scaffold may seem outlandish, yet the scaffold is already available and ready to use. I speak, of course, of peptides [1,2].

Peptides are 'bioinspired', which means that an exceptional array of natural templates exist, as manifested by signaling molecules [3], cell-penetrators [4] and host defense effectors/mediators [5,6]. Other peptide formulations may be perceived from small functional domains (or sub- domains) within the extensive proteomes of any living creature. Furthermore, the synthetic flexibility and facility of peptides gives us access to far more chemical entities than are present in nature, ranging from simple mutational variants to completely unheralded formulations. Chemical, structural and functional diversity can be further amplified (without greatly impinging on synthetic accessibility) with non-canonical amino acids and stereoisomeric variation. Further functionalization can be included through convenient attachment to glycans and lipids [7,8].

Regardless of one's familiarity in peptide design or protein structure recognition, discerning readers should appreciate the practical implications of such scaffold versatility. To spur the imagination, one may review a scope of known applications that includes specification of drug candidates for protein-protein interaction targets [9] and adjuvants for optimizing drug transport and localization (including membrane-transit facilitors) [10]. Peptides can also be tailored for assembly into many different

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forms and sizes of transmembrane pores, including compact helical bundles with inward- facing amino acid side chains for monoatomic ion transport, slightly larger analogs for transit of small molecules (e.g., water, small metabolites, signalling molecules and amino acid monomers), all the way up to large beta barrel structures capable of admitting polynucleotides and even proteins [11]. Other natural applications include immunogenic roles such as membrane permeabilization (pores that disrupt pathogenic homeostasis, complex bleach-like networks, etc.) [12], antibodies [13], and immunogenicity [14]. An extensive additional array of biotechnology tools also emerge, including membrane anchors, cell labels, biosensors and related diagnostics, as well as environmental modulators such as surfactants and even antifreezes [15].

Peptide design obviously begins with specifying an amino acid sequence, which dictates a standard backbone that avails a small set of predictable secondary structure elements, including helices, hairpins, sheets, stable turns, and disulphide-anchored coils. Each structural element can be reliably dictated from sequence specification. Sequence choice furthermore enables the tailoring of specific charge distributions, surfaces (lipophilic vs. Hydrophilic), and H-acceptors/donors for intramolecular stabilization or intermolecular coupling. Subtler amino acid recipes can select for flat beta sheets as opposed to curved ones, and straight helices versus bent or curved structures.

Synergy between such residue-customizable features is what drives some of the most uniquely valuable adaptive capabilities of peptides: environmentally-dependent confomational variation and self-assembly. Conformational adaptation arises in part from pH-sensitive polar interactions (e.g., anion-anion repulsions that may alleviate under acidic conditions; cation-histidine couplings that modulate via the multiple pH-dependent valences of the imidazole), but the most crucial physicochemical effect that drives structural rearrangement and oligomeric assembly is amphiphilicity–the spatial segregation of exposed hydrophobes and polar surfaces [16]. Peptide helices with a high degree of radial amphiphilicity have a strong tendency to form hydophobe-inward-facing bundles in polar solvent that then restructure to produce stable polar-inward/hydrophobe-outward pores within lipid membranes. These pores maximizing the favorable lipid-lipophile coupling, while opening a membrane-spanning polar channel capable of sustaining transort that is either passive (in the case of a fairly rigid channel of fixed width) or active (semi-flexible side-chains whose vibrational modes can effect directional pumping). Analogous sheet structures, with predominant polarity on one side of the sheet and hydrophobicity on the other, tend to minimize lipophile solvent exposure in polar solvent, but will then form a strong lipophile-lipid interfaces within the membrane. Secondary structure stability and deviations from regular amphiphilicity enables control over the extent of membrane insertion for peptides that are designed to present both membrane spanning and extracellular functionality [17].

The design of monomer-active peptides is frequently intuited by mimicking domains within proteins that the peptide is intended to imitate or supplant. For example, the best DNA-binding [18] and RNA-binding peptides [19] share some structural analogy with known nucleotide binding domains on proteins. Artificial peptidic antibodies may be conceived by examining the host-cell proteins that known pathogens target [14]. Similar strategies can foster disruption of physiological protein-protein interactions for which there are prospective therapeutic or analytical motives for modulating [9]. Of course, in all of the above cases, a combination of rational design principles and combinatorial variation can be applied to effect a great likelihood that artificially-conceived peptides can achieve interaction profiles significantly enhanced over what nature has achieved, thus procuring therapeutic or analytical advantage.

The above peptide attibutes, as well as generally low toxicity and minimal environmental impact, position the scaffold exceptionally well for addressing many biomedical and biotechnology applications. As with any great chemical framework, however, there are practical drawbacks. For peptides, the primary challenges lie in *in vivo* deliverability, and chemical stability (metabolic decomposition *in vivo*, and redox degradation in any environment) [20].

In terms of *in vivo* ditribution, some peptides have excellent distribution characteristics but, when one has carefully refined the characteristics of a peptide to perform a very specific role upon delivery, the practical matter of the transport and distribution itself may suffer. In such cases, one may need to rely one one of the many tissue-specific delivery technologies that are emerging for drug development. These include (ironically) peptide-facilitated delivery, functionalized nanoparticles, micelles, liposomes, platelet-mimics and viral capsids [20].

When peptides are developed for *ex vivo* applications, the amide chain is generally stable, however various side chains are suspectible to chemical degradation within normal environmental conditions. The most susceptible moieties are cysteine and methionine, however tryptophan, tyrosine and arginine may also be modified by reactive intermediates generated under redox stress [21]. Thus, optimizing peptide lifetime may be pursued through minimizing the instances of vulnerable amino acids. The precise strategies for doing so are highly application-dependent and are thus beyond the scope of this brief synopsis, but the general options include swapping out problematic entities for more stable variants (potentially within the set of canonical proteinogenic amino acids, but potentially also from non- natural analogs) that maintain steric and charge profiles comparable to those of originally desirable residues. Methionines may thus be replaced by structurally analogous hydrocarbon side chains, while cysteine linkages may be replaced by more chemically stable cross-linking schemes such as inducible glycine-serine linkages [22].

Peptide stability *in vivo* poses significantly greater challenges, because biological systems interpret many peptides as fragments of partly degraded proteins, and thus subject them to a battery of mechanisms for proteolytic recycling or clearance. One basic scheme for slowing peptide degradation entails co-administration of protease inhibitors for the period during which efficacy is required [20]. It is possible to achieve additional stability enhancements through a variety of structural choices, such as the use of non-natural amino acid variants (e.g., norvaline, norleucine, ornithine, citrulline, etc.) [23]. Isomeric chiral variation at peptide alpha carbons [23] also substantially enhances metabolic stability, without impinging on pore formation. Chiral variation may also not interfere with polynucleotide binding, but it frequently does negate signalling effects and protein-protein-interaction modulation.

Conclusion

In conclusion, peptides provide a wealth of chemical functionality for many biomedical and biotechnology applications, with key virtues being synthetic facility and tremendous func-

tional diversity. Key challenges include tissue-specific delivery and chemical stabilization, however a number of technologies (already devised for drug development and other pursuits) provide reasonable mitigation for many of these obstacles. As more robust strategies avail, there is little reason to doubt the continued maturation of a framework that will prove exceptionally valuable for discovering and optimizing revolutionary new biotechnologies.

References

1. Sánchez A, Vázquez A. Bioactive peptides: A review. Food Quality and Safety. 2017; 1: 29–46.
2. Fosgerau K, Hoffmann T. Peptide therapeutics: current status and future directions. Drug Discovery Today. 2015; 20: 122-128.
3. de Bang TC, Lay KS, Scheible WR, Takahashi H. Small peptide signaling pathways modulating macronutrient utilization in plants. Curr Opin Plant Biol. 2017; 39: 31-39.
4. Giulia Guidotti G, Brambilla L, Rossi D. Cell-Penetrating Peptides: From Basic Research to Clinics. Trends in Pharmacological Sciences. 2017; 38: 406–424.
5. Hancock REW, Haney EF, Gill EE. The immunology of host defence peptides: beyond antimicrobial activity. Nature Reviews Immunology. 2016; 16: 321–334.
6. Lo, JCY, Lange D. Current and Potential Applications of Host-Defense Peptides and Proteins in Urology. Bio Med Research International. 2015.
7. Yim G, Thaker, MN, Koteva, K, Wright G. Glycopeptide antibiotic biosynthesis. The Journal of Antibiotics. 2014; 67: 31–41.
8. Rabana, F, Grau-Campistany A, Vila-Farrés, X, Gonzalez-Linares J, Borràs M, Vila J, Manresa A, Cajal Y. A bioinspired peptide scaffold with high antibiotic activity and low in vivo toxicity. Scientific Reports. 2015; 5: 10558.
9. Helmer D, Schmitz K. Adv Exp Med Biol. 2016; 917: 147-83.
10. Arosio, D, Casagrande C. Advancement in integrin facilitated drug delivery. Adv Drug Deliv Rev. 2016; 97: 111-143.
11. Fuertes, G, Giménez D, Esteban-Martín, S, Sánchez-Muñoz, OL, Salgado J. A lipocentric view of peptide-induced pores. Eur Biophys J. 2011; 40: 399–415.
12. Wimley WC. Describing the Mechanism of Antimicrobial Peptide Action with the Interfacial Activity Model. ACS Chem Biol. 2010; 5: 905–917.
13. Trier NH, Hansen PR, Houen, G. Production and characterization of peptide antibodies. Methods. 2012; 56: 136-144.
14. Pisitkun T, Hoffert JD, Saeed F, Knepper MA. NHLBI-Ab Designer: an online tool for design of peptide-directed antibodies. Am. J. Physiol. Cell. Physiol. 2012; 302: C154–C164.
15. Koutsopoulos S. Peptide Applications in Biomedicine, Biotechnology and Bioengineering, 1st Edition. Wood head Publishing Series in Biomaterials, Chennai, India. 2017.
16. PLOS Computational Biology. Tipping the Scale from Disorder to Alpha-helix: Folding of Amphiphilic Peptides in the Presence of Macroscopic and Molecular Interfaces. 2015.
17. Eiríksdóttir E, Konate M, Langel U, Divita G, Deshayes S. Secondary structure of cell-penetrating peptides controls membrane interaction and insertion. Biochimica et Biophysica Acta. 2010; 1798: 1119-1128.
18. Kubo T, Yokoyama K, Ueki R, Abe S, Goto K, Niidome T, et al. Structure and affinity of DNA binding peptides. Nucleic Acids Symp. Ser. 2000; 44: 49-50.
19. Kazuo Harada K, Martin SS, Frankel AD. Selection of RNA-binding peptides *in vivo*. Nature. 1996; 380: 175–179.
20. Di L. Strategic Approaches to Optimizing Peptide ADME Properties. AAPS J. 2015; 17: 134–143.
21. Young-Mi Go YG, Jones DP. The Redox Proteome. The Journal of Biological Chemistry. 2013; 288: 26512-26520.
22. Chen YJ, Chen JC, Yao WH, Yao WH, Chen CC. Cross linking of cotton cellulose in the presence of serine and glycine. II. Pore structures and agent distribution. Journal of Applied Polymer Science. 2006; 102: 1578 - 1584.
23. Groß A, Hashimoto C, Sticht H, Eichler J. Synthetic Peptides as Protein Mimics. Front. Bio eng. Biotechnol. 2015; 3: 211.