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Are Peptides Truly Less Important than Proteins, or are Peptides and Proteins Mutually Inclusive of Each other?

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Editorial
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Editorial

In today's research world, peptides and related functions are mostly undermined, undervalued, underappreciated, and sometimes maybe marginalized. It could be mainly due to the fact that peptides are shorter in amino acid length (less sequence conservation or variation), less structured (more random structures i.e., many do not form defined secondary structures), single-functioned (not as dual or even multifunctional), more direct-action oriented (less indirect and consequently more complex effects, e.g., signaling cascade events), and less global impacts (e.g., peptidomes are far less characterized than proteomes to date, due to either lack of interest or lack of available and validated tools and methods). These factors make peptides less attractive for research studies than their protein counterparts.

These points of views are understandable. Thinking from a protein biochemist's or chemist's perspective, less sequence conservation or variation means less evolutionary comparison/contrast, phylogenetic determination, or in the worst scenario, not able to draw any association if no sequence similarity or contrast exists, unlike proteins which can offer all 3 of above. Peptides being less structured make them less attractive for structural studies. For those with structures, structural biologists are limited to mostly primary and secondary structures, whereas proteins offer many more structural varieties for studies, including primary, secondary, tertiary, and even quaternary structures, or combinations of any 2 or more of the above. In addition, proteins can be crystallized to be studied by X-ray crystallography in solid state form or solubilized in solvent to be studied by NMR in solution state form, whereas peptides are mostly limited to solution state NMR studies. The single functionality of peptides makes it easier to find their mechanisms of action and even biological (and/or therapeutic) target (s). However, the commonly acknowledged multi functionality of proteins make them more seemingly attractive to study, as many known functions and unknown, but parallel to the original, functions increase research question diversity and opportunities for a single protein of interest. Peptides are famously known for their direct actions, e.g., acting directly on a pathogen (antimicrobial peptides), internalized to bind DNA (cell penetrating peptides), and binding a receptor (antigen presentation and peptide hormones). While these direct actions are indeed fascinating, peptides seem to lack many indirect impacts and actions unlike their protein counterparts. These indirect effects can generate profound and complex research questions, leading to long-term research opportunities in order to fully understand the true impacts on atomic, molecular, cellular, systemic, and organismal levels. Lastly, even though peptidomics have progressed significantly in recent years, it is still far away from reaching the maturity level of proteomics, including robust methods, advanced tools, dedicated resources, previous knowledge and data accessibility. These factors would hinder researchers from accessing sufficient resources to enter and/or progress in the peptide research field.

While these may seem to be drawbacks on peptide research, todays research shows one fundamental (yet flawed in my opinion) assumption: Peptides and proteins are separate entities, so research on these biomolecules must also be independent of each other. While this view may seem

very convincing and must be very popular among protein researchers, as proteins are indeed more complex molecules than peptides, and peptides seem to be nothing but short chains of amino acids without sophisticated meaning, we should really ask ourselves this question: Are peptides and proteins really separate from each other? Theoretically, peptides could be synthesized using cellular machineries just like proteins, but this does not exclude other possibilities that peptides and proteins are intertwined in various modes or forms. For example, could peptides already exist as parts of circulating proteins?. That is, peptides can become available through different and carefully nature-designed proteolytic events for different immediate uses. This would significantly reduce the amount of time to synthesize peptides (and energy to store peptides (e.g., in granules) in some cases) to respond to various biological events and/or threats. In fact, there are still numerous proteolytic events in nature that we have not discovered or understood fully yet, and these could be some among those undiscovered and/or unanswered. In addition, could multi functionality of proteins be simply an additive and/or synergistic functional aspect of various peptide components in proteins? For example, if a protein can act on 2 different receptors to show 2 different biological functions, could this really be simply 2 different peptide components responsible for binding to 2 different receptors in different (or the same, which would be a scarily wild concept) biological events, and the rest of the protein sequence (may or may not include uninvolved functional peptide component(s)) just act as facilitator(s)?. Since oftentimes the interaction between a protein ligand and its receptor triggers the recruitment of additional receptor component(s) and/or other receptor(s), could additional peptide component(s) other than the one interacting with the receptor involve in this recruitment event? Furthermore, some peptides show moonlighting functionality just like some proteins. Moonlighting is somewhat different from multi functionality in that multiple functions are shown through a single biomolecule, whereas multi functionality can be shown through gene fusions or multiple proteolytic fragments [1]. In this case, could moonlighting functions of a protein be actually the moonlighting function of a peptide component in the protein, or even more strikingly, an additive or synergistic effect of multiple peptide components in the protein, without any proteolytic event?. Lastly, since a lot of proteins and peptides have precursors prior to some nature-designed proteolytic events to exert their functions (e.g., pro-protein and pro-peptide concept), could protein also act as a precursor that sequesters the biological effect of its peptide component(s) (until ready to use) prior to yet unknown and undiscovered proteolytic events, or even more disturbingly, vice versa? Even more provokingly, could protein act simply as a carrier for its peptide component(s) to protect these precious "cargos" from degradation (e.g., by proteases), or one or multiple peptide component(s) act as a "cushion carrier" to shield sensitive and vulnerable part(s) of a large protein component?

As you read along, you may now see that peptides and proteins are distinctive biomolecules but may or may not be mutually exclusive of each other. This is how I foresee and envision our peptide and protein research and related outcome concepts in the future. I want this editorial to be a mind provoking ground for the readers to re-think and challenge our views to re-evaluate the importance of peptides in all research fields, particularly that host defense peptides are now promising leads for future immunotherapy, anticancer peptides are now in the anticancer drug pipeline, and cell penetrating peptides are now re-designed to carry cargos intracellularly to act on biological and/or therapeutic target(s). We need to think outside the box to dare ourselves to march into different research territories and realms, and the mutuality of peptides and proteins is just one of many daring concepts to be discovered in the future by different scientific researchers and communities.

Reference

1. Constance J (2018) Protein moonlighting: what is it, and why is it important?. Phil Trans R Soc B 373: 1738.