ECRONICON OPEN ACCESS

EC PHARMACOLOGY AND TOXICOLOGY

Mine Review

Antimicrobial Peptides: Importance in Biomedicine, and Future Directions

Sina Gerayli[1], Mohammad Delirrad[2], Mohammad Majidi[2] and Adel Ghorani-Azam[2]*

[1]*Immunology Research Center, Inflammation and inflammatory Diseases Division, Mashhad University of Medical Sciences, Mashhad, Iran*

[2]*Department of Forensic Medicine and Toxicology, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran*

***Corresponding Author:** Adel Ghorani-Azam, Department of Forensic Medicine and Toxicology, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran.

Received: October 21, 2021; **Published:** February 26, 2022

Abstract

Antimicrobial peptides (AMPs) are ancient immune components found in almost all classes of living organisms. They are biologically active supramolecules with strong antimicrobial, antiviral, and anti-tumor properties. They also have important role in various biological processes, and due to their unique properties and versatile structure, they are currently investigated for development of various biomedical applications, such as biomarkers or drug discovery in addition to developing peptide-based vaccines or diagnostic tools. In this study, we briefly reviewed some currently acknowledged applications of peptides in biology and medicine.

Keywords: *Antimicrobial Peptides; Importance in Biomedicine; Future Directions*

Introduction

Antimicrobial peptides (AMPs) are evolutionarily conserved components of the innate immune response, which have crucial role in the host defense system. Biologically active peptides vary from small regulatory peptides to peptides as large as 100 amino acids. Studies on pharmacological properties of therapeutic and regulatory AMPs show that they can play a crucial role in cell differentiation, various cellular processes such as cytokine secretion, angiogenesis, and wound healing, in addition to their antimicrobial, antiviral and anti-tumor activities [1]. AMPs have the capability to incorporate in various biomedical applications, including drug delivery, medical imaging, cancer therapy, and variety of diagnostic purposes [2]. Peptide-based medicines such as immunogenic peptide vaccines, peptides conjugated to other biologically active molecules, and non-immunogenic self-assembled peptide-based scaffolds are currently hot topics in drug targeting and developing biological tools for vaccine delivery. Some important biomedical applications of peptides are discussed below.

Therapeutic peptides

Ultra-structures containing peptides, especially those with D-amino acids or other peptide conjugates possess some unique advantages such as enhanced efficacy, acting through several mechanism, and more importantly, resistance to enzymatic digestion [3]. Peptide–drug conjugates are currently considered as an important class of peptide therapeutics, particularly in cancer therapy. Antimicrobial and antiviral peptides are the most important and known classes of therapeutic peptides. The emergence of new microbial, viral and fungal diseases in the world, which are mainly resistant to many drugs and antibiotics and pose a health risk in today's societies similar to what the world is currently facing with COVID pandemic crisis, raises the need for research on development of new drugs. As the conventional antibiotics are used against bacterial and viral infection, they become more resistant to these drugs; therefore, AMPs can be developed to combat with microbial, fungal and viral infections [4]. These peptides can be excellent candidates for developing as more potent therapeutic agents to conventional antibiotic therapy because in contrast to conventional antibiotics, they do not appear to induce antibiotic resistance [5]. Instead, they have a broad range of activity with mechanism that can hardly be blocked by the microorganisms. So far, more than 300 peptides have been reported that could combat the microbial infections, and most of them are FDA-approved or in different phases of human trials [6].

Regulatory peptides

Some peptides have regulatory acts and play roles in the regulation of many cellular processes such as transmission of inter- and intracellular information. These regulatory elements are produced by almost all classes of life from bacteria to mammals. These peptides have versatile structure with broad spectrum of biological effects, which are produced by many organs such as endocrine cells of the digestive tract or nervous system in response to a variety of stimuli [7]. They generally act as neurotransmitters, hormones and cytokines, and their production and release finally leads to physiological responses relevant to the stimulus, such as growth, change in metabolic rate, energy balance, and cytokine-assisted immune regulation [8]. They are also involved in control of many physiological and pathophysiological activities, such as Alzheimer's disease (Tau and amyloid β), stroke (cardiac natriuretic peptides), and diabetes (Amylin and insulin). In addition, regulatory peptides are the main target of many drugs in which many cellular responses are mediated via production or release of these regulatory elements, such as bradykinin potentiating peptide and angiotensin-converting enzyme (ACE) peptide inhibitors [9]. Majority of regulatory peptides act through G protein-coupled receptors (GPCRs), which are generally affected by a large proportion of the drugs, or through direct or indirect activation of intracellular signaling cascades. An important example of the last mechanism is suppressing the expression of age-related matrix metalloproteases and subsequent caspase-dependent apoptosis by short peptides [10]. These regulatory elements can also regulate gene expression and epigenetic modifications (i.e., romidepsin and nesiritide), which are mainly modulated through DNA methylation, histone acetylation/deacetylation and/or regulation of small non-coding RNAs [11].

Peptide-based vaccine

Vaccines had a profound impact on prevention of infectious disease and they are still the option of choice to control pandemics caused by novel viruses. Vaccines typically consist of one or several components or epitopes related to the infectious agent or even inactivated and live attenuated pathogens [12]. Since the introduction of peptides as therapeutic agents and immune modulators, peptide-based epitope vaccines have revolutionized vaccine development with several advantages to overcome the drawbacks associated with classical whole-organism vaccines, in which the immune response solely corresponds to the relevant epitopes, leading to rule out non-specific and non-protective responses in addition to many unwanted side effects [13]. Accordingly, peptide-based vaccines can be used as an alternative solution intelligent and practical ways for induction of innate and adaptive immunity, allergen specific tolerance, and stimulation of major histocompatibility complexes (MHC), which is the ultimate target for infection immune responses [14]. In recent years, the design of peptide-based vaccine prototypes is considered as the potential vaccine developing strategy in future, which is able to induce highest antibody level production with minimized side effects [15].

Peptides in analytical toxicology and diagnostic medicine

AMPs are highly flexible molecules, and various types of these molecules can be designed to fit the structure with high binding affinity to the target molecule. Accordingly, employing AMPs for diagnostic purposes can minimize false negative results and increase the accuracy of detection [16]. Using such a molecular specific tools can be useful for tracing a very small amount of the desired analyte in biological systems. In recent decade, various peptide-based tools and aptamers have been introduced, which have great molecular specificity to the target analytes [2]. Therefore, AMPs may be used in diagnostic medicine for detection and determination of a specific target inside the collected specimens. Due to specific interaction between the peptide and the desired analyte at molecular level, selectivity, specificity, and the accuracy of peptide-based detection methods are highly acknowledged [17]. Currently, peptide aptamers have been introduced as new diagnostic tools for detection of variety of molecules in biological specimens [18,19]. Interactions of the peptides with specific molecules in the cells, particularly when the peptide is exclusively designed for the probe molecule, can be used for selective trapping of the desired molecules and detection of a very small amount of substances in biological systems [2]. Due to specific and selective interaction of the peptides to their target molecules, peptide-based radio-florescent molecular probes are currently used for *In vivo* molecular imaging, which provide sensitive recognition of the target molecule with high affinity, and high specificity, and more importantly, can be designed for different target molecules [20]. Figure 1 represents a selective binding of a newly designed peptide to morphine in urine sample.

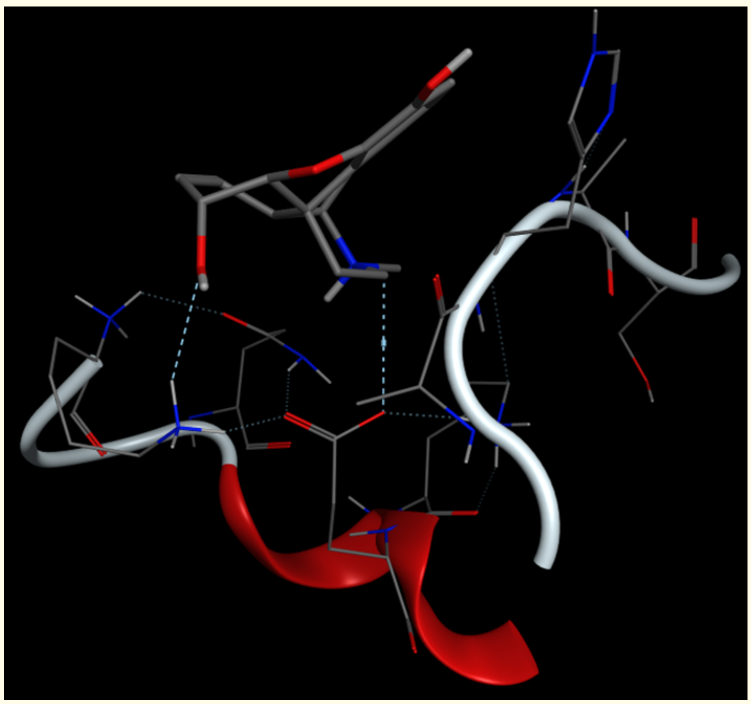

Figure 1: *Interaction between a putative peptide to a morphine molecule.*

Peptides for drug delivery

As smart functional motifs, peptides are currently used for assembling smart drug delivery systems [21]. These functional smart motifs deliver drugs to the pathological tissues selectively, thereby reduce the side effects associated with the drug and increase the efficacy of therapy. Responsiveness to pH, temperature, and ionic strength, biocompatibility, high capacity for drug loading, stability against enzymatic degradation, sustained drug release, and selective targeting through receptor recognition ligands, or peptide-based antigens are the most pharmacologically important features of peptide self-assembly drug delivery [22]. These peptide-based delivery systems are formed through intramolecular peptide folding and subsequent supramolecular self-assembly, which form assorted nanostructures such as nanotubes, nanowires, nanofibrils, spherical vesicles, and drug encapsulating organogels. Some of the FDA-approved peptide drugs, vaccine and peptide-based agents with various biomedical applications are listed in table 1 [23-25].

Name	Application	Target
Lixisenatide	Diabetes type (II)	Glucagon-like peptide 1 receptor
Plecanatide	Chronic idiopathic constipation	Guanylate cyclase-C
Etelcalcetide	Secondary hyperparathyroidism in adult chronic kidney disease	Calcium-sensing receptor
Abaloparatide	Anabolic agent	Parathyroid hormone 1 receptor
Semaglutide	Diabetes type (II)	Glucagon-like peptide 1 receptor
Liraglutide	Diabetes type (II)	Glucagon-like peptide-1 receptor agonist
Romiplostim	Chronic immune thrombocytopenic purpura	Thrombopoietin receptor agonist
PGT129 Fab	Viral infection	HIV-1 gp120 V3 glycopeptide
Tau fragment (Tau393–408)	Alzheimer's diseases	Activation of Fc receptor
Macimorelin	Diagnosis of adult growth hormone deficiency	Growth hormone secretagogue receptor type 1
Angiotensin II	Septic shock, diabetes mellitus, and acute renal failure	Type-1 angiotensin II receptor
Boceprevir	Chronic hepatitis C	NS3/4a protease inhibitor
Afamelanotide	Erythropoietic protoporphyria	Melanocortin 1 receptor
Carfilzomib	Multiple myeloma	Proteasome inhibitor
Bremelanotide	Hypoactive sexual desire disorder	Melanocortin receptors
Setmelanotide	Obesity	Melanocortin-4 receptor
[^{68}Ga]-PSMA-11	Diagnosis of recurrent prostate carcinoma by Positron emission tomography	Prostate-specific membrane antigen
Enfortumab vedotin-ejfv	Urothelial cancers	Nectin-4 receptor
Synthetic Brevinin-M1	Urine toxicology	Morphine
Belantamab mafodotin-blmf	Relapsed or refractory multiple myeloma	B-cell maturation antigen

***Table 1**: List of some peptides with various applications.*

Conclusion and future perspective of peptide

AMPs are key components of the immune system and are found in all organisms from prokaryotes to humans and plants. These peptides have a wide range of biological properties, including antimicrobial, antifungal, regulatory and hormonal, antitumor and antiviral properties [26]. These supramolecules represent a fascinating multidisciplinary area of research with strong potential for novel drug development as well as diagnostic medicine. These molecules have also strong potential for development of therapeutic modalities by modulating epigenetics, which can be translated into pharmaceutical products to treat diseases with an epigenetic basis, particularly some types of cancers and neurodegenerative disorders such as Alzheimer's disease [27]. Many efforts are also on the move to improve pharmacodynamics and pharmacokinetic properties of peptide-based drugs through conjugation with variety of molecules or through smart drug delivery. Due to their specific molecular targets, diversity, and ease of use, engineered peptides can also be considered as an important element in the diagnostic medicine to enhance the diagnosis as well as detection of a very small amount of analytes in biological samples. Development of various tools such as liquid chromatography with tandem mass spectrometry (LC-MS-MS) have also highlighted the significance of peptides, particularly in metabolomic screening for early detection of biomarkers [28]. Progress in computational biology has also strengthened the discovery of new peptide candidates for various purposes. Development of these tools altogether can help to identify new bioactive peptides with unique structural features, which can help to pre-assess the peptides for future modification [29]. Finally, peptide drug delivery approach is a new area for smart delivery of the drugs to the target site, which is an innovative approach to enhance the therapeutic efficacy and to minimize the side effects associated with chemotherapies [30]. Taken together, peptides are smart molecules and due to their role in various biological processes and broad-spectrum biomedical applications, deserve further investigations for development of therapeutics, biosensors, biomarkers, etc.

Bibliography

1. Bernard JJ and Gallo RL. "Protecting the boundary: the sentinel role of host defense peptides in the skin". *Cellular and Molecular Life Sciences: CMLS* 68.13 (2011): 2189-2199.
2. Riahi-Zanjani B., *et al*. "Molecular modeling and experimental study of a new peptide-based microextraction fiber for preconcentrating morphine in urine samples". *Journal of Molecular Modeling* 25.3 (2019).
3. Asoodeh A., *et al*. "Identification and Characterization of Novel Antibacterial Peptides from Skin Secretions of Euphlyctis cyanophlyctis". *International Journal of Peptide Research and Therapeutics* 18.2 (2011): 107-115.
4. Ahmed A., *et al*. "Human Antimicrobial Peptides as Therapeutics for Viral Infections". *Viruses* 11.8 (2019).
5. Asoodeh A., *et al*. "Purification and Modeling Amphipathic Alpha Helical Antimicrobial Peptides from Skin Secretions ofEuphlyctis cyanophlyctis". *Chemical Biology and Drug Design* 83.4 (2014): 411-417.
6. Usmani SS., *et al*. "THPdb: Database of FDA-approved peptide and protein therapeutics". *PloS one* 12.7 (2017): e0181748.
7. Vaudry H., *et al*. "Editorial: Trends in Regulatory Peptides". *Frontiers in Endocrinology* 9 (2018): 125.
8. Szekely M., *et al*. "Thermoregulation, energy balance, regulatory peptides: recent developments". *Frontiers in Bioscience* 2 (2010): 1009-1046.
9. Arendse LB., *et al*. "Novel Therapeutic Approaches Targeting the Renin-Angiotensin System and Associated Peptides in Hypertension and Heart Failure". *Pharmacological Reviews* 71.4 (2019): 539-570.
10. Davenport AP., *et al*. "Advances in therapeutic peptides targeting G protein-coupled receptors". *Nature Reviews Drug Discovery* 19.6 (2020): 389-413.
11. Janssens Y., *et al*. "Peptides as epigenetic modulators: therapeutic implications". *Clinical Epigenetics* 11.1 (2019): 101.
12. Nelde A., *et al*. "The Peptide Vaccine of the Future". *Molecular and Cellular Proteomics: MCP* 20 (2021): 100022.
13. Izumoto S. "Peptide vaccine". *Advances in Experimental Medicine and Biology* 746 (2012): 166-177.
14. Reche PA., *et al*. "Peptide-based immunotherapeutics and vaccines". *Journal of Immunology Research* (2014): 256784.
15. Purcell AW., *et al*. "More than one reason to rethink the use of peptides in vaccine design". *Nature Reviews Drug Discovery* 6.5 (2007): 404-414.
16. Dubois ME., *et al*. "Optimization of peptide-based ELISA for serological diagnostics: a retrospective study of human monkeypox infection". *Vector-Borne and Zoonotic Diseases* 12.5 (2012): 400-409.

17. Sfragano PS., *et al*. "The Role of Peptides in the Design of Electrochemical Biosensors for Clinical Diagnostics". *Biosensors* 11.8 (2021).
18. Xu X., *et al*. "Aptameric peptide for one-step detection of protein kinase". *Analytical Chemistry* 84.11 (2012): 4746-4753.
19. Johnson S., *et al*. "Surface-immobilized peptide aptamers as probe molecules for protein detection". *Analytical Chemistry* 80.4 (2008): 978-983.
20. Wang W and Hu Z. "Targeting Peptide-Based Probes for Molecular Imaging and Diagnosis". *Advanced Materials* 31.45 (2019): e1804827.
21. Lian Z and Ji T. "Functional peptide-based drug delivery systems". *Journal of Materials Chemistry B* 8.31 (2020): 6517-6529.
22. Tesauro D., *et al*. "Peptide-Based Drug-Delivery Systems in Biotechnological Applications: Recent Advances and Perspectives". *Molecules* 24.2 (2019).
23. Al Musaimi O., *et al*. "FDA TIDES (Peptides and Oligonucleotides) Harvest". *Pharmaceuticals* 14.2 (2021).
24. Malonis RJ., *et al*. "Peptide-Based Vaccines: Current Progress and Future Challenges". *Chemical Reviews* 120.6 (2020): 3210-3229.
25. Lau JL and Dunn MK. "Therapeutic peptides: Historical perspectives, current development trends, and future directions". *Bioorganic and Medicinal Chemistry* 26.10 (2018): 2700-2707.
26. De Mandal S., *et al*. "Antimicrobial Peptides: Novel Source and Biological Function With a Special Focus on Entomopathogenic Nematode/Bacterium Symbiotic Complex". *Frontiers in Microbiology* 12 (2021): 555022.
27. Galoian K and Patel P. "Epigenetic control of cancer by neuropeptides". *Biomedical Reports* 6.1 (2017): 3-7.
28. MacMullan MA., *et al*. "Quantitative Proteomics and Metabolomics Reveal Biomarkers of Disease as Potential Immunotherapy Targets and Indicators of Therapeutic Efficacy". *Theranostics* 9.25 (2019):7872-88.
29. Ghorani-Azam A., *et al*. "Effect of amino acid substitution on biological activity of cyanophlyctin-β and brevinin-2R". *Journal of Molecular Structure* 1158 (2018): 14-18.
30. Ghosh D., *et al*. "Peptides as drug delivery vehicles across biological barriers". *Journal of Pharmaceutical Investigation* 48.1 (2018): 89-111.

Volume 10 Issue 3 March 2022