Short Peptides

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Short peptides should not include more than 45 amino acids.

Short Peptides amino acids

1. Introduction

Recently, short peptides have attracted increasing attention in biology, chemistry, and medicine due to their specific features. They are appreciated as novel and more efficient therapeutical agents with reduced side effects. Their structural diversity combined with the conformational flexibility is used to control interactions with particular receptor sites. Peptides display high selectivity due to specific interactions with their targets. Moreover, the number of short peptides involved in important biological processes is steadily growing by far exceeding that resulting from the traditional mimetic approach. Unfortunately, peptides also have profound medical limitations, namely the development of oral peptide-based therapeuticals that modulate cellular processes via high affinity binding is like a search for the Holy Grail [1].

In 1902, two distinguished German chemists, Hermann Emil Fischer and Franz Hofmeister, proposed that proteins are constituted by amino acids linked by bonds between the amino group of the proceeding amino acid and the carboxyl group of the following residue [2]. However, proteins were initially characterized by the Dutch chemist Gerardus Johannes Mulder, but their name was coined out by the Swedish chemist Jöns Jacob Berzelius, in 1838 [3][4]. The term “protein” is derived from the “proteios” (“primary”) i.e., representing the first position in living organisms [4][5][6]. Nevertheless, proteins do not exist without peptides. A name “peptide” comes from “peptós” (in Greek “digested, digestible”) and reflects the fact that peptides are generated by the proteolytic cleavage reaction. The first peptides and amino acids were discovered at the beginning of 19th century [7][8]. The first amino acid, asparagine, was isolated from asparagus by French chemists Louis-Nicolas Vauquelin and Pierre Jean Robiquet in 1806 [9][10]. Their chemical category was recognized by the French Charles Adolphe Wurtz, in 1865, but the expression “amino acid” was used for the first time in 1894, in German as Aminosäure [11][12]. Interestingly, the first peptide, benzoylglycylglycine, was synthesized by the German chemist Theodor Curtius, in 1881 [13]. However, a more efficient synthesis was described by Fischer and the French chemist Ernest Fourneau in 1901 [14][15]. In consequence, Fisher is known as the “father” of peptide chemistry [16].

Peptides exist in all terrestrial living organisms and are indivisibly related to the origin of life [17]. Cooperative interactions among peptides and other molecules (amino acids, proteins, nucleic acids, lipids) were the driving

forces at all stages of chemical evolution [18]. Nowadays, a chemical peptide synthetic biology approach facilitates theories on the creation of life, in particular in the eyes of scientists who believe that historically chemistry proceeds biology [19][20][21].

2. Advantages vs. Disadvantages: SWOT Analysis

Peptides as a unique class of bio-molecules have filled the therapeutic niche due to their specific biochemical and therapeutic features. They explore the “middle space” between small chemical molecules and biologics because of their molecular weight. They have the intermediate nature extending “beyond size”, combining the advantages of both small molecular drugs (e.g., better permeability) and therapeutic proteins (selectivity, target potency) and exluding their disadvantages, such as adverse side effects, drug-drug interactions, and membrane impermeability, respectively.

Short peptides have evolved as a very promising scaffold for diverse applications either in diagnosis or therapies. The current status of their strengths, weaknesses, opportunities and threats (SWOT analysis) [22] is briefly discussed (Table 1).

Table 1. SWOT analysis of short peptides.

Strengths	Weaknesses
essential bio-molecules with a broad range of activities & functionalities in vivo	instability in vivo (easy degradation in plasma, protease sensitivity)
bio-chemical diversity, easy availability	short half-life
structural simplicity	low (oral) bioavailability
easy design & cost-effective synthesis with high purity	difficult membrane permeability in the case of greater peptides *
easy modification, scaling up	low binding affinity *
mechanical stability	high conformational freedom *
high: modularity, flexibility *, selectivity, target specificity, affinity *, absorbability, potency, tolerability, efficacy, safety, biocompatibility, biodegradibility	
low toxicity, antigenicity, immunogenicity	
easy recognition by bio-systems	
ability to penetrate the cell membranes (but only very short peptides) *, high	

brain penetration in systematical administration	
versatility as both targeting moieties and therapeutic agents	
specific interactions with various bio-systems	
predictable metabolism: degradation products are amino acids (non-toxic, natural entities used as nutrients or cellular building blocks)	
lack or fewer secondary off-targets (side) effects (peptides do not accumulate in kidney or liver)	
low unspecific binding to the structures other than the desired target, minimisation of drug-drug interactions, less accumulation in tissues (low risk of complications due to intermediate metabolites)	
Opportunities	**Threats**
development of peptide-based delivery systems: - cell-penetrating peptides - nano-cyclic peptide-based micceles, vesicles as gene or drug carriers - conjugations with non-peptidic motifs	oncogenicity of endogenous & synthetic peptides
supramolecular peptide-based biofunctional materials	immunogenicity (related to greater peptides)
formulations development (e.g., subcutaneous injections)various forms of using (drugs, vaccines, hormones, radioisotopes)	
development of the peptide-based safe & effective vaccines	
diveristy of well-ordered, robust, long-lived self-assembled nanostructures	
vital tool for neurodegenerative diseases studies & various applications in anticancer therapy	
peptoids or peptidomimetics	

* Bivalent property which may be either strength or weakness depending on particular species.

First of all, short peptides have numerous advantages in comparison with their larger analogues. In particular, cost-effective synthesis both on a small- and large-scale, wide chemical diversity, easy modification, high bio-activity, absorbability, accessibility, tunable functionalization, high selectivity and specificity, biodegradability and biocompatibility, high safety, low toxicity (due to their safe metabolites-amino acids, the limited possibility for accumulation in the body), or low immunogenicity should be emphasised [23]. Peptides have diverse bio-functionalities of their components (amino acids) and good biomolecular recognition [24][25]. As a consequence, they have high binding affinity for a wide range of specific targets.

On the other hand, short peptides have limitations, such as high conformational flexibility (can result inter alia in the lack of receptor selectivity) or problems in permeability of greater peptides via physicological barriers (due to the strong interactions of peptide backbone with water molecules) [26]. Moreover, there are other important factors, e.g., short half-life in vivo (due to the susceptibility to rapid digestion by protolytic enzymes in the gastrointestinal tract and serum, proteases/peptidases) and fast clearance from the circulation (first-pass metabolism) by the liver and kidneys (lasting from minutes to hours after administration). In spite of approvement of over 60 peptide drugs, nearly none can be orally administrated [27]. Market placement of effective peptides as oral medications is still the “Holy Grail”. Furthermore, the risk of immunogenic effects is the main threat of peptide therapies [26]. Cyclisation of short peptides is of outmost importance in the architecture of designing mimetic drugs which overcome the proteolytic limitations of peptides. Cyclisation of a peptide reduces the vast possible conformations it can take pointing to and confirming the active conformer, the basis for a non peptide mimetic or peptide conjugate selective drug [31][32][33][34].

Peptides and aminoacids are now more than ever the key to understand the molecular basis of SARS Cov 2 structural mutations which would allow to design strategies to battle infection and the world pandemic [35][36][37][38][39][40].

3. Conclusions and Future Outlook

Short peptides exhibit a remarkable array of biological functions, which may be used by innovative therapies in almost all branches of medicine. They are synthesized and investigated by research groups spread all over the world. The number of publications and patents in the subject has been growing enormously over the last years. This global review reflects this situation. It is written by scientists from all continents of the world who tried to unveil “fifty shades” of short peptides with the emphasis on biomedical, diagnostic, pharmaceutical, and cosmeceutical applications. In particular, peptides can play either a leading role as drugs or a supporting role in diagnosis, treatment, cell penetration, or targeting, and many more. Peptide-based vaccines are an expected breakthrough in cancer, microbial, or allergen immunotherapies. Natural and synthetic short peptides, including peptidomimetics, find numerous applications in nanotechnology and are thoroughly investigated by structural bio-informatics and supramolecular chemistry. Moreover, the development of comprehensive in silico techniques combined with efficient advanced synthetic methods facilitates the production of peptide based chemical species of almost unlimited applicabilities.

To sum up, short peptides can be a secret of idealized smart therapies.

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