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Short Peptides: On the Trail of Future Stem Cell-Based Regenerative Therapies

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Abstract

Stem cells therapy is a great hope for untreatable diseases, transplantology and cosmetology. What is more, with regenerative benefits of stem cells, prolongation of human life is real. Nevertheless, stem cell-based therapeutical defects, such as low efficiency of differentiation or poor immune compatibility, cannot be overlooked.

Short peptides, due to their unique features, play an important supporting role in culture medium to stimulate diverse activities of stem cells and provide a new glimpse into future regenerative biomedicine. These simple biomolecules, constituents of proteins, have relevance in the transmission of biological information, can penetrate the cell membrane or activate signalling pathways. They have immunomodulatory, gero-, neuro-, vaso- and skin-protective effects. They enhance proliferation and differentiation of stem cells. Utilizing of short peptides can be helpful in guiding stem cell fate, by mimicking native tissues, which leads to optimization of stem cell-based treatment. They are also important modifiers of scaffolds and modulators of biomaterials in relation to stem cells engineering. This mini review is a summary of the survey of the newest scientific findings, scattered across the world literature, focusing on short peptides as promising tool in seeking safe and effective stem cell-based therapeutical code.

Keywords: Short peptides; Stem cells, Regenerative therapies; Tissue engineering; Self-assembling peptides; Peptide-based bio-materials

Introduction

Stem-cell based therapeutical approach has the potential to revolutionize the treatment of currently untreatable and socioeconomically devastating diseases as well as organs transplantology and cosmetology. Short peptides, due to their specific properties, play valuable supporting roles in the therapies of diverse diseases. Nonetheless, in the face of prevalent problem worldwide in the context of ageing society on the one side and the need for finding the *Holy Grail* in reliable medicine on the other side, importance of short peptides in the advanced stem cell-based treatment of neurodegenerative disorders are discussed in more detail.

Stem cells: a short background

The beginning of stem cells was in 1960s, when Friedenstein isolated and differentiated bone marrow-derived cells from guinea pigs [1,2].

Stem cells are non-specialized cells of the organism. They have the ability of differentiation into any highly specialized cells (into either mature cells of the same organ or the other type of cell), excessive proliferation and self-renewal during age [2]. Stem cells occur either in embryos or adult cells. They can be classified as totipotent, pluripotent, multipotent, oligopotent and unipotent stem cells. Totipotent cells can divide to any type of cell in the whole organism. They have the greatest differentiation potential, leading to forming of embryo or extra-embryonic structures. A zygote is an example. Pluripotent cells can generate cells of germ mayers, but not extraembryonic structures. Embryonic stem cells are a good example. Pluripotent cells offer a promising tool for regenerative medicine [3]. Multipotent cells have lower differentiation potential. Discrete cells of specific cell lineages are a specialization of this type of stem cells. Haematopoietic stem cells are example. Oligopotent cells are able to differentiate into different types of cells. An example is a myeloid stem cell. Unipotent cells have the lowest differentiation potential, and form only one cell type, but can divide repeatedly. Muscle stem cells are the example. Therefore, they are good candidates in regenerative therapies [4]. The word 'uni' derived from Latin 'unus', which means one. However, these cells do not have the self-renewal property.

The extracellular matrix (a complex and dynamic 3D environment of cells) is the main part of the stem cell niche [5]. Notably, in niche, cell-cell and cell-extracellular matrix interactions inform stem cells to proliferation, whilst their stemness is stable. Extracellular matrix has impact on stem cell's fate [6]. Its composition depends on its tissue of origin. Adhesion proteins such as collagen, fibronectin, elastin, vitronectin, proteoglycan, groth factors or laminin should be mentioned. They bind to integrins (cell surface receptors, which are critical in cell-matrix interactions) on the cell surface *via* cell-binding epitopes [5]. The latter are short peptides originating in adhesion proteins.

The stem cells adapt the functions of the environment in which are embedded [7].

A milestone in stem cell therapy

In 2006, Japanese scientists, Yamanaka and Takahashi, discovered the possibility of reprogramming of multipotent adult stem cells

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to pluripotent cells [8-10]. This new form was named induced pluripotent stem cells. In consequence, a generation of the cells that can be biocompatible with the patient, became real.

Nowadays, stem cells are valuable strategy in biomedicine, either in development of regenerative therapies or as a source of knowledge on the complex events during human life. Stem cells are powerful and inexpensive tool in studies on both mechanisms of diseases and discovery new modern therapeutical agents. It is well-known that stem cells offer great promise and wide therapeutical opportunities in diverse diseases such as heart failure, cancer, wound healing, tooth and skin regeneration, osteoarthritis, haematological and neurodegenerative diseases, HIV, spinal cord injury, retinal and macular degeneration, tendon ruptures, diabetes type 1 and so on [2,4]. And, most importantly, clinical applications of cellular therapies in untreatable human diseases and can be possible.

Technically, stem cells can be divided into embryonic stem cells, adult stem cells and induced pluripotent stem cells. All of them have relevance in tissue regeneration [5]. Notably, use of adult stem cells overcome ethical and controversial problems concerning embryonic stem cells. Therefore, adult mesenchymal stem cells is called "gold standard" as target for tissue regeneration [5]. They can be isolated from the adipose tissue, next cultured and expanded *in vitro* and further used for cell transplantation in injured sites. They also have the immune regulatory properties [2].

On the other hand, therapeutical shortcomings such as low efficiency of differentiation, poor immune compatibility, high risk of teratoma formation cannot be neglected and further studies on stem cell biology towards therapeutical improvements are needed [11].

Short peptides

Short peptides, simple biomolecules constituting proteins, provide a valuable support for stem cell-based regenerative bio-medicine due to their unique advantages. They have small molecular weight, are stable, versatile, easily synthesized, cheap, easy to manufacture, noncytotoxic, biodegradable, biocompatible, thermoreversible, thixotropic, can cross the cell membrane and may be modified in a wide variety of ways to perform specific functions [12-16]. Peptides play a role of signalling molecules and regulatory factors *via* interaction with DNA and histone proteins [17]. They have importance not only in the transmission of bio-information (as autocrine hormones and neuropeptides) but also in modulation of transcription, „*restoring genetically conditioned alterations*", which occurr with age. Cyclic short peptides have additional extra features such as high specific affinity, specificity, selectivity or stability to protein targets [18]. Short peptides have geroprotetive, neuroprotective, vasoprotective, skin protective, reparative, immunomodulatory, retinoprotective or anticancer effects [19,20].

Relevance of short peptides in stem cells research

Short peptides are very helpful in development and behaviour of stem cells [19,21]. They can enhance the adhesion, expansion and proliferation of mesenchymal stem cells [22]. Short peptides are able to penetrate the cell membrane and activate signalling pathways regulating differentiation of gene expression through various ways such as „*interacting with proteins of histone, changing gene accessibility for transcription, regulating gene methylation status and activating/inhibiting their expression or directly interacting with the DNA"* [20,23-26]. Short and ultra-short peptides have relevance in stimulation of differentiation of diverse types of stem cells and tissues. The direction of differentiation depends on the structure and concentration of peptides [20]. More specifically, Ala-Glu-Asp-Gly tetrapeptide induces pluripotent cell differentiation into epidermis, mesenchyme and nervous tissue. Lys-Glu, Ala-Glu-Asp, Lys-Glu-Asp, Ala-Glu-Asp-Gly peptides activate neuronal differentiation. Ala-Glu-Asp-Leu and Lys-Glu-Trp-Asp peptides induce lung and pancreatic cell differentiation [20,27]. Glu-Glu-Glu tripeptide promotes osteogenic differentiation [28], while immune cell differentiation is stimulated by Lys-Glu dipeptide [20]. Gonearrestide is a scorpion venom-based peptide (including 18 amino acids), which can activate the proliferation of human embryonic stem cells and maintain their self-renewal *via* activation of specific signalling (receptors) pathways. Human embryonic stem cell therapy is good alternative for tissue replacement after injuries or diseases e.g. spinal cord injury, Parkinson's disease and diabetes [29].

Cell penetrating peptides are short and highly cationic peptides which have ability to penetrate the cell membrane and carry other molecules (biological cargos). They are useful delivery systems [25]. Another interesting issue, in the context of delivery system for mesenchymal stem cell transplantation, are self-assembling peptides [30]. They are short peptides that possess alternating hydrophilic and hydrophobic amino acids and can self-organize into a 3D nanofiber structures (e.g. stable hydrogels). They are versatile, easy to manufacture, cheap, biodegradable, biocompatible and noncytotoxic [31]. These peptides also can include amino acids covalently modified with a lipophilic group and are known as peptide amphiphiles. Self-assembling peptides and peptide amphiphiles can assemble into large structures which resemble components of native tissue. In other words, self-assembling peptides provide biomimetic synthetic microenvironment (and complex tissue-like structures) [32]. They represent a promising effective tool (reproducible 3D cell culture system) for stem cell differentiation and effective repair of damaged tissues [33]. Self-assembling peptides enhance either survival or action of stem cells, *via* interacting with them, leading to the desired effects. They weaken symptoms of Alzheimer's and Parkinson's disease, heart failure, and arthritis. They have potential to improve angiogenesis, for example in vascular diseases [7,31,33].

Peptide-based biomaterials

Recently, significant attention is focused on the development of functional biomaterials which mimic the natural environment of diverse cells. Peptides are ideal as mimetics of extracellular matrix and for the development of 2D and 3D cell-culture materials [7]. The incorporation of the receptor-binding peptides into synthetic biomaterials leads to their better signalling abilities [34]. Peptide-based biomaterials are useful in self-renewal of stem cells. Modified materials such as 9-Fluorenylmethoxycarbonyl(Fmoc)-protected peptide-based materials have increased relevance in neurogenesis [7,34].

Scaffolds, in regenerative medicine and tissue engineering, are 3D matrices, which mimic native extracellular matrix to support cell growth. Peptides, due to their beneficial properties, are important modifiers of scaffolds [5]. Peptide-based biomaterials have features

similar to protein-based scaffolds. However, peptides possess additional advantages such as simpler and more cost-effective production, easier modification, better resistance to environment conditions (e.g. pH and temperature), safety, low immunogenicity. And as a result, peptide-based materials are enriched with unique sequences promoting cell adhesion or inducing desired cell signalling pathways, which enhance cell-scaffold interactions and functionality of scaffolds. Arg-Gly-Asp peptide (occurring in collagen, gelatin, elastin, fibronectin, and laminin) is one of the most important modifiers enhancing cellular activities. Good examples are also Asp-Gly-Glu-Ala, Gly-Phe-HPro-Gly-Glu-Arg or Gly-Phe-Pro-Gly-Glu-Arg, Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val (PepGen P-15) derived from collagen. They promote cell adhesion, proliferation and differentiation. On the other hand, peptides have limitations, especially fast degradation. Therefore, they are combined with polymers. These biocompatible scaffolds are useful for *inter alia* regeneration of skin, nerves, muscles or bones [28,35,36].

Amyloid-like nanofibrillar biomaterials mimic extracellular matrix and are very attractive due to their biophysical advantages. Nevertheless, this positive aspect of amyloid-like peptide nanofibrils was underappreciated due to their specific function in neurodegenerative diseases. It should be emphasized that amyloid fibrils are nontoxic side products. In addition, functional amyloids are ubiquitous in nature, occurring also in human organisms [37].

Short peptides in the stem cell-based treatment of neurodegenerative diseases

The progression of disorders such as Alzheimer's, Parkinson`s and Huntington diseases, is characterized by a neuronal death, and consequently progressive loss of brain and the gradual cognitive functions.

Mesenchymal neuronal stem cells can be used in the treatment of not only neurodegenerative but also neurodevelopmental (autism spectrum disorders, Down syndrome, fragile X or Rett syndromes) diseases [38]. They stimulate neurogenesis as well as other physiological processes.

Short peptides support and activate the neuronal differentiation of stem cells, promote neuroplasticity processes [19]. Good examples are Lys-Glu, Ala-Glu-Asp, Glu-Asp-Ala, Glu-Asp-Pro, Lys-Glu-Asp, Glu-Asp-Arg, Ala-Asp-Glu-Leu, Lys-Glu-Asp-Trp, Ala-Glu-Asp-Leu or Ala-Glu-Asp-Gly, also know as epitalon. The latter regulates the function of the brain in the special way. It stimulates gene expression and protein synthesis during neurogenesis [39]. In consequence, either delay the progression of neurodegenerative diseases or elimination of the source of them is possible [4]. Another interesting issue of epitalon is „*induction of activity of telomerase and its elongation in fibroblast culture in relation to reactivation of the telomerase gene and indication of prolonging the life span of a cells*" [21].

Notably, short peptides from proteins of extracellular matrix, such as laminin-derived peptide Ac-Cys-Cys-Arg-Arg-Ile-Lys-Val-Ala-Val-Trp-Leu-Cys, help in the attachment, proliferation and direct human neural stem cells to differentiate into neurons. Conjugation the peptide with e.g. PEG hydrogel leads to enhanced cell migration. It is promising in artificial niche development towards human neural stem cells transplantation in future clinical therapies [16]. Fibronectin-derived peptides promote adhesion, increase pluripotency-related gene expression in stem cells [3]. Interestingly, vitronectin derived peptide allows for neuronal differentiation of astrocytes. The latter are numerous specialized non-neuronal cells in the central nervous system. They play various roles either in homeostasis of central nervous system or in disease. They maintain healthy neural tissue. They are mediators in response to traumatic injury and infectious agents. Dysregulation or death of astrocytes are implicated in pathologies such as multiple and amyotrophic lateral sclerosis, Alzheimer's and Parkinson's disease. Therefore, there is a need for study astrocytes in vitro and replacement of diseased astrocytes in vivo. Culture peptide-based system will probably allow for the use of human pluripotent stem cell-derived astrocytes in the future regenerative medicine [40].

Conclusion

Taken together, scientific findings indicate a promising peptide-based approaches for the improvement of stem cell-based therapies and potential clinical applications. Short peptides play diverse supporting roles, namely peptide-based biomaterials either for the study of diseases pathogenesis or application in human neural regeneration. Short peptides are important modifiers of scaffolds. Self-assembling peptides, cell penetrating peptides or peptide-based delivery systems cannot be overlooked. Short peptides stimulate differentiation of stem cells and have gero- and neuro-protective effects. Conjunction of stem cells with short peptides leads to improvement of the repair of damaged tissues.

To sum up, these simple biomolecules can have big impact on future regenerative biomedicine and tissue engineering.

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