

The Research Progress of Immunomodulatory Peptides

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Keywords: Immunomodulatory Peptides; Preparation; Mechanism

Abstract. Immunomodulatory peptides play an important role in immune response. Researchers acquired activity peptides from natural food protein by enzymatic hydrolysis and the most commonly used enzymes are Alcalase. In this paper, the mechanism of immunomodulation was summarized briefly. The peptides charge, hydrophobicity and the length of peptide chain have great influences on the immunomodulating activities of peptides.

Introduction

It has been reported that more than 1500 different bioactive peptides were found and more than 1250 peptides with different functional significances [1], immunomodulatory peptides was one of them. These bioactive peptides could be used for anti-oxidative, antifungal, antithrombotic, sensory physiological activities and can enhance the nutritional value of food [2]. Immunomodulatory peptides modulate [3] the immune response through improving the antibody production of secretory IgA and epithelial barrier function, modulating apoptosis and TLR4 binding, inducing regulatory T cells and B cells, and controlling cytokine production. The immunomodulatory peptides generated from natural sources usually have varieties of functions but not only for immunomodulatory. Peptide fraction from the larvae of *Musca domestica* not only has the ability of immunomodulatory, but also plays an important role in anti-tumor [4]. Dipeptidyl peptidase 4 inhibitors could stimulate the immune system 1 and 2 and also be used in the treatment of type 2 diabetes mellitus [5]. It has reveal immunomodulatory peptides not only for immunoregulation, but also could be used for other fields.

Preparation of immunomodulatory peptides

Enzymatic hydrolysis.

Since Jolles acquired a sort of immunomodulatory peptides from milk protein by trypsin for the first time [6], a growing number of people have paid attention to generate peptides from natural sources such as milk, grain and shark meat. It was focused on the use of by-products of food protein bio-processing for immunomodulatory peptides which could enhance the production value and reduce the cost of waste disposal [7]. Immunomodulatory peptides show no activity when contained with the whole protein sequence, but can be released by enzymatic proteolysis. The enzymes used for hydrolysis could be divided into digestive system or microbial origin [8]. Microbial fermentation and food processing could also be used for producing immunomodulatory peptides separated from enzymatic proteolysis. As shown in Table 1, several enzymes had been successfully applied to hydrolysis kinds of natural protein sources to acquire bioactive peptides like whey protein, soy protein, corn protein, oyster protein. It can be found that from these data, the most common enzymes are Alcalase, trypsin and pepsin. The immunomodulatory peptides generated by enzymatic hydrolysis *in vitro* probably be absorbed more effectively than released from dietary proteins during the digestive process in the gut [9]. In recent years, food-hydrolyzed peptides enriched were added to immunomodulatory diets, like whey- hydrolyzed peptides enriched used to prevent fibrosis.

Table 1 Immunomodulatory peptides derived from sources

Source of peptides	Conditions				Indicator	References
	enzymes	pH	T/ °C	Time/min		
Labeorohita roe	Pepsin	2	37	120	ABCDEF	[10]
	Trypsin	8	37	150		
	Alcalase	8	55	180		
Alaska pollock frame protein	Trypsin	8	20	290	A	[11]
Whey protein	Alcalase	8	50	-	A	[12]
Soy proteins	Alcalase	8	60	225	AB	[13]
Oysters protein	Protease	7.5	50	300	ABC	[14]
Corn protein	Alkaline	8.5	55	180	G	[15]
	Neutral	7	45	120		
Green microalga	Pancreatin	7.5	45	240	B	[16]

A-splenic lymphocyte proliferation, B-phagocytosis capacity of peritoneal macrophages, C-natural killer (NK) cell activity, D-splenic T lymphocyte, E-small intestine mucosal immunity (secretory-IgA), F-serum immunoglobulins (IgA, IgM & IgG), G-antihypertensive activity.

Separation and purification.

It has been reported that the molecular weight of most immunomodulatory peptides were less than 2 kDa, so the separation and purification of immunomodulatory peptides play an important role in analyzing immunomodulatory peptides activity. Milda obtained peptides of less than 3 kDa with significantly decreased the basal nuclear factor (NF)- κ B activity in Caco-2 cells through Ultracel regenerated cellulose ultrafiltration membrane [17]. Chromatographic separation, especially high-performance liquid chromatography (HPLC), and gel electrophoresis were also widely used in the separation and purification of immunomodulatory peptides, but the HPLC was more effective than gel electrophoresis when be used in industry because of different throughput and costing.

The mechanism of immunomodulation

It is well-known that the composition of amino acid, sequence and special structure influences the immunomodulation of protein peptides. So the factors influenced immunomodulatory activities have aroused increasing interests among researchers. Bioactive peptides were composed of 3 to 20 amino acids and have a positive impact on human health. As show in Table 2, immunomodulatory peptides are usually consist of hydrophobic amino acid, such as Ala, Val, Met, Ple, Ile, Leu, Pro, Trp, is in agreement with report of Easton. However, it has been postulated that overall ability of immunomodulatory must be attributed to comprehensive effects of a lot of factors rather than to the individual effect of the hydrophobicity of amino acid. Three structurally related small molecular weight peptides with limited sequence similarity to frenatin were compared and demonstrated to the C-terminal α -amidation, which plays an important role in immunoregulation [18]. It also has been observed that lower molecular weight and positively charged peptides plays the key role when it stimulated lymphocyte proliferation at much lower concentration [19].

Table 2 Amino acid compositions and their immunomodulatory activity

Source of peptides	Amino acid sequence	Activity	References
Bursa of Fabricius	ALPVVVII	increased the numbers of cfu pre-b, enhanced aiv-specific antibody and cytokine production	[20]
	DRATHGGE		
	GANEVEEER		
Alaska pollock Frame protein	Tyr-Gly	lymphocyte proliferation rates were improved to 35.92%, 32.96%, and 31.35%, respectively	[11]
	Asn-Gly-Met-Thr-Tyr		
	Asn-Gly-Leu-Ala-Pro		
Soy protein	His-Cys-Gln-Arg-Pro-Arg	exhibitd phagocytosis stimulatory effect	[8]
	Gln-Arg-Pro-Arg		
	GLVGTLLEGHIGKAILG.NH2(2.1S)		
Skin secretions	GLVGTLLEGHIGKAILS.NH2(2.2S)	2.1s($lc_{50}=80\pm6\mu m$) and 2.2($lc_{50}=75\pm5\mu m$) for cytotoxic against non-small cell but less hemolytic against human erythrocytes	[18]
	GLVGTLLEGHIGKAILG(2.3S)		

Today, more and more people try to synthesis peptides identified as potential modulators of immune system function and selected on the basis of physicochemical characteristics [21]. On one hand, the chemical synthesized peptides could replace the matrix peptides to evaluate the immunomodulating properties. It also can be explored the mechanism of modulate immune response was also explored. More and more advanced technologies have been used to explore the mechanism of immunoregulation like HPLC. The peptides charge, hydrophobicity and the length of peptide chain have great influences on the immunomodulating activity of peptides [19].

Summary

An increasing number of immunomodulating peptides are prepared by enzymatic hydrolysis from all kinds of natural resources. However, we only know that immunomodulating peptides from natural proteins could modulate immune system but the mechanism of modulate immune system through protein peptides was rarely showed. As the application of immunomodulating peptides are widely used in preventing and inhibiting the proliferation of pathogenic bacterium, it becomes an urgent mission for us to reveal the mechanism of immunoregulation.

Acknowledgements

The authors acknowledge the financial support provided by the Key Projects of Jilin province Science & Technology Program (20150204032NY) and the Youth Scientific Innovation Leading Talent and Team Building Project of Jilin Province (20140519014JH).

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