Journal of Molecular Immunology

Zhu et al., J Mol Immunol 2016, 1:1

Short Communication Open access

Prothymosin Alpha (ProTα) and Thymosin Beta (Tβ): Conserved Immune-related Genes from Teleost to Mammals

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Received date: July 8, 2016; **Accepted date:** July 8, 2016· **Published date:** July 27, 2016

Abstract

Prothymosin alpha (ProTα) and thymosin beta (Tβ), members of the thymosin family, consist of a series of highly conserved peptides capable of stimulating immune responses in different species. Our recently published report discussed an issue of the conserved roles of ProTα b and Tβ-like (Tβ-l) in common carp (Cyprinus carpio L), which suggested that the highly-conserved carp ProTα b and Tβ-l can ultimately enhance immune response during viral infection and modulate the development of T lymphocytes in Teleost. These results enthusiastically pilled more evidences of evolutionary conservation of thymosins.

Keywords: Prothymosin alpha; Thymosin beta; Teleost; Immune responses

Introduction

Thymosin, a mixture of small polypeptides ranging from 1 to 15 kDa [1], were classified into three categories: α-thymosins (Tα) (PH<5.0), β-thymosins (Tβ) (5.0<PH<7.0), and γ-thymosins (Tγ) (PH>7.0) according to different isoelectric points [2]. ProTα is the precursor of α-thymosins, and is a highly acidic, intrinsically disordered protein containing 109-113 amino acids varying among the species. It was characterized by consisting mainly of aspartic and glutamic acid residues (more than 50%) with few hydrophobic amino acids and without any aromatic or sulfur amino acids [3]. Tβs are highly conserved polar 5-kDa polypeptides consisting of 40-44 amino acid residues. ProTα and Tβ genes have been well studies in mammals, but little is known in zeleost. ProTα was reported to be duplicated in Zebrafish (Danio renio) (ProTα a and ProTα b) as they showed different expression patterns [4]. Two thymosins of ProTα b and Tβ-l were studied in carps. It has been clearly demonstrated that ProTα b presented a thymosin α domain and a KKQK nuclear location signal motif well conserved from fish to mammals. Tβ-l gene revealed the existence of conserved actin binding LKKTET motif and two helix motifs indicated in all known Tβs [5]. The conserved motifs are supposed to anchor conserved functions of thymosins in different species.

Although thymosins were firstly discovered during the investigation of thymus in mammals, they were later found to be widely distributed in various organs [6] and played important roles in regulation of immunity. Studies, especially in mammals, gradually revealed that ProTα functioned well in regulating immune response and apoptosis, while Tβ4, one member of Tβs, may promote lymphocyte proliferation and differentiation [7]. Our study in carps filled the knowledge gaps of their immune roles in teleost. By examining the expression levels of Tβ-l in different carp organs, highest expression was detected in skin and intestine [5], which were important entry sites of pathogens [5]. In SVCV-infected carp models, with introperitoneal injection of virus we successfully demonstrated elevated ProTα b expression in kidney, peripheral blood, spleen, and intestine. At the same time Tβ-l shared the similar expression changes in kidney, peripheral blood, and liver [5]. These results suggested that carp ProTα b and Tβ-l played important roles in antiviral defense, with Tβ-l perhaps functioning as a key activator of NK cell cytotoxicity similar to Tβ4 [7]. Besides, over-expression of carp ProTα b and Tβ-l genes in zebrafish obviously induced the expression of Rag 1, TCR-γ, CD4, and CD8 [5], all of which were essential for cell-mediated immune response and the development of T lymphocytes. Thus, consistent with their conserved structures, ProTα b and Tβ-l indeed exhibited conserved immune-related roles from fish to mammals.

Besides regulation of immunity, ProTα and Tβ also played conserved roles in development. Knockdown of ProTα was reported to lead to apoptosis and developmental defects in zebrafish embryos early in 2013 [8], which was considered as the first evidence that ProTα regulate early embryogenesis. By analyzing the expression levels of ProTα b and Tβ-l at early developmental stages of carps, ProTα b was found to gradually increase starting from 4 h pf, reach maxmium at 16 h pf, and then decrease and keep at a certain stable level, whereas Tβ-l started to increase at 24 h pf and gradually increased up to 72 h pf, and then began to decrease at later developmental stages [5]. Therefore, ProTα b and Tβ-l played important roles in carp's development, with ProTα b exhibiting a clearer role in cell proliferation and/or differentiation, for ProTα b showed the highest expression in carp liver which was considered as an organ with a strong regeneration and recovery capabilities [9]. Moreover, early studies have already pointed out that higher expression of ProTα was found in proliferative cells than in quiescent cells, and more proliferative tissues exhibited higher expression of ProTα in adults [10]. Similar changes were also found in zebrafish as transient expression of ProTα on zebrafish epidermal cells promoted cell proliferation and attunated UBV-induced apoptosis [11]. However, little is known about the role of Tβ-l in development. In consideration of the highly-conserved structures, zeleost can be an effective model for further studying the role of thymosins in development.

Studies of thymosin genes have already progressed from labs to clinics in mammals. As a proliferative protein during development, ProTα is now considered as an oncoprotein and can be an indicator of poor prognosis in human cancers [12]. For example, ProTα was found to protect hepatocellular carcinoma cells against sorafenib-induced apoptosis [13], and targeting ProTα by miR-1 successfully induced apoptosis in nasopharyngeal carcinoma cells [14]. Tβ4, as one member of Tβs, was also reported as an oncoprotein in glioblastoma to promote mesenchymal signature by modulating P53 and TGFβ signaling networks [15]. And it was also found to be co-localized with CD133 in ovarian cancers to induce the patterns of cancer stemness [16]. However, not all thymosins function as oncoproteins during carcinogenesis. Tα 1 was reported to exert its anti-cancer effects through PTEN-mediated inhibition of PI3K/Akt/mTOR signaling pathway to suppress proliferation and induce apoptosis in breast cancer [17]. And a successful treatment case of stage Wilms tumor with integrative medical therapy of hyperthermia and Tα 1 combined with herbal remedy was reported in Korean, with liver metastasis successfully disappeared and lung metastasis stably maintained after nine months of treatment [18]. Suppression of Tβ10 was reported to activate Ras and ERK1/2, upregulate Snail and MMP2 [19], and finally induce metastasis of cholangiocarcinoma, which also indicates the anticancer role of Tβ10. Besides the carcinogenic roles, Tβ4 was reported to be successfully used in several clinical trials involving tissue repair and regeneration [20], and could reduce dryness in autoimmune disease of dry eye syndrome [21], which was consistent with its conserved immune-regulating roles and diversely expanded its clinical application. And Serum Tα 1 was supposed to expand its clinical application of regulating disordered immune system in patients with chronic inflammatory autoimmune diseases [22].

Conclusion

In conclusion, thymosins are extremely conserved during evolution, and share similar functions of immune-regulation and developmental modification in different species. Now the clinically therapeutic and prognostic importance of thymosins has been admitted by more and more studies.

Acknowledgement

Supported by Grants from the National Natural Science Foundation of China [Grant No. 81503093].

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