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Thymosin β4 structure – multiple biological functions and potential therapeutic applications

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Introduction

Since thymosin was first isolated from the fetal bovine thymus by Goldstein and White in 1966, it was thought to be a thymic hormone consisting of a single 14-kDa polypeptide (Goldstein et al., 1966). But later it turned out that thymosin consists of a mixture of small polypeptides ranging in molecular weight from 1 to 15 kDa. Preparation of this peptides required five steps, so the final product was named thymosin fraction 5. It is divided into three groups due to the isoelectric points into isoforms: α (pH<5), β (5<pH<7) and γ (pH>7). The numerical subscript means the chronological order of isolation and the determination of its amino acid sequence. The first two peptides isolated from thymosin fraction 5 were α_1 and β_1. The α_1 was classified as thymosin, but the second one, polypeptide β_1 in spite of being most remarkable in this fraction does not show any activities in the biological analysis. After few years this polypeptide β_1 was described as a 74-amino-acid residue fragment of ubiquitin lacking two glycine residues at the C-terminus (Schlesinger et al., 1975). Ubiquitin takes part in numerous cellular functions and is the adenosine triphosphate ATP-dependent proteolysis factor essential to the proteasome formation (Hershko and Ciechanover, 1998). The next peptides isolated from thymosin fraction 5 were named β_2 and β_3. And another one named β4 (Tβ4) was isolated by conventional ion-exchange chromatography and gel filtration (Low and Goldstein, 1982; Goldstein et al., 2012).

The family of thymosin β contains 40–44 amino acids, having molecular weight about 5 kDa and it comprises about 20 polypeptides. This protein occurs in very simple organisms as an echinoderm and in higher organism but it does not exist in microorganisms and bacteria (Sanders et al., 1992; Stoeva et al., 1997). There are several different types of thymosin. Thymosin β4 and β_9 or β_{10} occur in mammals. Thymosin β_{10} can be found in rats, rabbits, mice and cats, thymosin β_9 in sheep, calves and pigs. Thymosin β_{15} is observed in some kinds of tumors in high concentration (Lere et al., 1998).

Different functions of thymosin β4

During past years, several reports have shown that thymosin β4 may be involved in many processes. Tβ4 plays an important role in apoptosis (Iguchi et al., 1999; Niu and Nachmias, 2000; Zhao et al., 2011), inflammation (Wang et al., 2003), preserves the balance of actins (Stark et al., 2012), is involved in tumor invasion and metastasis (Wang et al., 2003; Can et al., 2012; Xiao et al., 2012), angiogenesis, wound healing and other physiological and pathological processes (Grant et al., 1995; Frohm et al., 1996; Malinda et al., 1997; Philp et al., 2004 a; Ye et al., 2013). This multi-functional protein consists of 43 amino acids, has a mass of 4.9 kDa and its pI is 5.1. This peptide contains 79–80% of thymosin β family (Huff et al., 2001; Goldstein et al., 2005; Kuzan, 2016). The Tβ4 is located in many tissues and cells. We can find it in macrophages, blood cells, tumor cells and also in serous fluid of blister, wound, blood serum, urine ulcers. At the cellular level, it is mainly located in the cytoplasm.

The β-thymosins play an important role in organization of the cytoskeleton. But we do not understand why cells often express more than one β-thymosin and whether these β-thymosins do the same job. It is possible that the differences in their properties (e.g. stability of the complex with G-actin) are rather small but nevertheless critical to their biological function. The fact that they are differentially regulated in several cells and tissues under normal and pathological conditions may show they have different functions. The increasing number of reports about participation of β-thymosins in physiological events such as angiogenesis, inflammation, wound healing, apoptosis, and cancerogenesis also put the question whether these are based on the G-actin complex or on cytokine-like activities. At least in some cases, it seems obvious that β-thymosins may undergo such a change of function when released from cells by either secretion or cell death or cell lysis. It will be a very big problem to search for the molecular mechanisms mediating the effects attributed to extracellular β-thymosins. A basic problem will be the identification of receptors for this peptide family (Carlier et al., 1996; Huff et al., 2001).

Tβ4 has been shown to stimulate angiogenesis by differentiation and directional migration of endothelial cells and tube formation. The reason for this activity was determined to be the central actin-binding domain, 17LKKTETQ23 of Tβ4. Interaction with G-actin by way of the 17LKKTETQ23 sequence induces the formation of structured N- and C-terminal helices. This interaction with G-actin, forming a 1:1 complex, is a process by which Tβ4 controls the assembly and disassembly of actin filaments that regulate the dynamics of the actin cytoskeleton. That is how Tβ4 control cell differentiation, migration, morphogenesis and organogenesis and probably it is how thymosin β_4 is related to hold a dynamic equilibrium between G- and F-actin, important for the rapid reorganization of the cytoskeleton (Crockford et al., 2010). The interaction between β-thymosins and G-actin also depends on the nucleotide ADP or ATP bound to G-actin. The relationship of thymosin β4 to ATP–G-actin is about 50-fold higher than that to ADP–G-actin (Carlier et al., 1996). Profilin, another G-actin binding protein, increases nucleotide exchange, whereas thymosin β4 inhibits this exchange (Goldschmidt-Clermont et al., 1992). The different influence of thymosin β4 and profilin on actin nucleotide exchange is discussed as a potential regulatory mechanism for actin polymerization inside of the cells (Kang et al., 1999; Korenbaum et al., 1998).

It was observed that in mammalian tissues Tβ4 is often present by a small amount of its sulfoxide. As we know the cells produce reactive oxygen species (H_2O_2) during their metabolism and as signal transducing molecules. Thymosin β4 can be easily oxidized to its sulfoxide *in vitro* in millimolar concentration of H_2O_2. It is happening because Tβ4 is losing its affinity to G-actin (Huff et al., 1997). Reduction of thymosin β4 sulfoxide restores the initial affinity to G-actin. Oxidation of thymosine β4 to its sulfoxide as well as its reduction by a methionine sulfoxide reductase could regulate its actin binding activity and could affect the intercellular equilibrium between G- and F-actin *in vivo* (Tang et al., 2011; Tokura et al., 2011).

Grant et al. (1995) found the mRNA of thymosin β4 to be 5-fold higher in endothelial cells after growing on Matrigel and also found out an increased rate of capillary-like tube formation after transfection with thymosin β4 (Grant et al., 1995). The same group reported that thymosin β4 exhibits chemoattractant activity by stimulating the directional migration of human umbilical vein endothelial cells into the scratch wounded area, promoting angiogenesis *in vitro* and *in vivo* (Malinda et al., 1997). Frohm et al. (1996) determined a concentration of 13 μg thymosin β4 per milliliter of wound fluid and speculated that it may act as a wound healing factor (Frohm et al., 1996). Tβ4 promotes coronary vessel development and collateral growth not only during embryonic development but also from the adult epicardium by stimulating epicardial vascular progenitors, which migrate and differentiate into smooth muscle and endothelial cells.

The mesenchymal stem cells (MSCs) play a promising role in the field of tissue reconstruction As it is known it is extremely difficult to obtain sufficient numbers of MSCs for implantation from a single donor site. MSCs must be expanded

prior to their use in tissue regeneration. In many laboratories standard methods for MSC expansion have not been fully established for either allogenic therapies or autologous therapies. Recent studies using small animals indicate that most transplanted cells do not survive and are lost within a month, especially in tissue grafts. The use of growth factors and other trophic factors may increase MSC expansion and survival (Byung-Joon et al., 2013). When cultured on substrates with different surface hardness, the MSCs differentiate into different lineages without induction. This suggests that the altered physical cues caused by different cell-matrix interaction, can significantly affect cell fate choice and direct differentiation. Besides, cell-cell contact has also been reported to regulate cellular behavior in MSCs (Ho et al., 2010). In her research Ho et al. demonstrated that Tβ4 inhibited osteogenic differentiation through cytoskeleton reorganization by inhibiting F-actin formation and reducing the F-actin/G-actin ratio. They also show that during early osteogenic differentiation, F-actin formation was highly increased and Tβ4 significantly reduced F-actin formation as well as the F-actin/G-actin ratio, and was accompanied by the immature phenotype. On the other hand, Tβ4 has been shown in various rodent models to promote stem cell migration and differentiation into keratinocytes and hair follicles in the bulge region, inducing dermal repair and increased hair growth, respectively (Philp et al., 2004 a,b).

Tβ4 can be also found in tumor cells (Can et al., 2012). Several research groups have found that aberrant expression of Tβ4 is associated with metastasis (Cha et al., 2003) and penetration of tumor cells (Caers et al., 2010) as it was found in colorectal carcinoma (Wang et al., 2004; Cierniewski et al., 2010), gastrointestinal stromal tumors (Can et al., 2012), breast cancer cells (Yoon et al., 2011), melanoma, and lung tumors in mouse (Cha et al., 2003). Tβ4 promotes the growth of cancerous tumors by increasing new blood-vessel formation (Marx, 2007). But in different studies we can see contrary conclusions. For example, the expression of Tβ4 is significantly lower in multiple myeloma, and it is suggested that Tβ4 can activate the proliferation of tumor cells in myeloma development (Caers et al., 2010).

Another function of Tβ4 refers to apoptosis as it was shown that it reduces apoptosis and induces survival genes which in turn leads to reduced apoptosis. For example, Tβ4 has been shown to inhibit endothelial apoptosis by activating the phosphoinositide/Akt cell survival signaling pathway in cardiomyocytes. It helps in cardiac regeneration by inhibiting myocardial and endothelial cell death after infarction and by inducing vessel growth and myocardial progenitor mobilization (Hinkel et al., 2008).

Tβ4 is the only known molecule to initiate organ wide activation of the embryonic coronary development program in adult mammalian hearts (Bock-Marquette et al., 2004; Hinkel et al., 2008). In a cardiac-specific Tβ4 knock-down mouse model, Tβ4 was shown to promote coronary vessel development and collateral growth not only during embryonic development but also in the adult epicardium by stimulating epicardial vascular progenitors, which migrate and differentiate into smooth muscle and endothelial cells (Smart et al., 2007).

The information about the thymosin function and their expression in the ovary in domestic animal is scarce. Uzumcu and Lin (1994) have found that the thymic factor, fraction V, containing α and β thymosins can modulate basal and gonadotrophin-induced steroidogenesis in rat granulosa cells. They showed that thymosins may have a direct effect on ovarian function. In the rat ovary, prothymosin α (proT) protein was detected in the growing oocyte, granulosa cells and theca cells throughout folliculogenesis and maturation; however, no effect of proT on the first meiosis was demonstrated (Roson et al., 1993). Both β-thymosins β4 and β10 are expressed in rat ovary, with decreased expression of thymosin β10 associated with luteinization and increased thymosin β4 levels during this process (Hall et al., 1991 b). The expression of thymosin β10 is significantly stimulated in immature rat ovaries following the administration of pregnant mare's serum gonadotropin (PMSG) and also it has been described in hen ovarian follicles (Hall et al., 1991 a; Yang et al., 2008). Thymosin β4 has been found to stimulate the release of luteinizing hormone releasing hormone (LHRH) and LH (Hall et al., 1992). In bovine and porcine, blood concentrations of thymosin α and β change throughout the estrous cycle and appear to be

regulated by gonadotrophins through changes in the secretion of ovarian steroids (Ford et al., 1990; Wise and Maurer, 1991). Salhab et al. (2010) demonstrated that both thymosin β4 and β10 occur in the cytosol and nucleus of bovine cumulus cells. They also showed for the first time that the β-thymosins (β4 and β10) are expressed in follicular cells and in the bovine oocyte, and are upregulated in cumulus cells during meiotic maturation *in vitro* and *in vivo*. They also suggested that expression of thymosin β10 was associated with the oocyte maturation, cumulus expansion and progesterone secretion and was negatively correlated with apoptotic rate in cumulus cells during IVM. Labas et al. (2017) show that thymosin β4 and β10 could be used as markers of maturation of bovine cumulus-oocyte complex.

Conclusion

As we can see in many researches Tβ4 takes part in many various biological functions in different pathological stages and physiological processes. Especially, Tβ4 has been associated with healing of diabetic ulcers, bedsores, damaged corneas, and heart muscle injured during heart attacks (Marx, 2007; Wei et al., 2012). Tβ4 inhibits the inflammation (Sosne et al., 2001, 2002) as well as T-cell maturation, proliferation of cell and differentiation (Low et al., 1990).

In many papers we can observe numerous activities of Tβ4. That peptide will be used in the treatment of myocardial infarction, chronic heart failure, diabetes, lupus, stroke, multiple sclerosis, pressure ulcers, burns, dry eye, viral infections and septic shock (Goldstein et al., 2012). Goldstein et al. (2012) also imply that Tβ4 in early clinical tests was safe, well tolerated and effective in dermal and eye wound healing. The use of this peptide in clinical trials as a drug for heart disease is expected to receive hopeful results.

Due to the mentioned broad spectrum of beneficial properties of thymosin β4, we would like to attempt for the first time to use this protein for the *in vitro* maturation of bovine oocytes. The optimum concentration of thymosin β4 in IVM medium has to be determined. To evaluate the effect of thymosin β-4 on meiotic maturity and oocyte quality, the TUNEL method is being applied. Only in the case of the positive influence of the analyzed protein on the maturity and quality of the bovine oocytes they will be used for *in vitro* fertilization. The research undertaken by the Department of Animal Reproduction Biotechnology in the National Research Institute of Animal Production is expected to improve embryo quality and increase the effectiveness of the bovine *in vitro* embryo production.

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THYMOSIN β4 STRUCTURE – MULTIPLE BIOLOGICAL FUNCTIONS AND POTENTIAL THERAPEUTIC APPLICATIONS

Summary

Tβ4 is engaged in many various biological functions in different pathological stages and physiological processes like migration of epidermal cell, formation of blood-vessel in both wound healing and the induction of angiogenesis. Tβ4 inhibits the inflammation, T-cell maturation, as well as cells' proliferation and differentiation. Due to above mentioned activities Tβ4 may be used in the treatment of myocardial infarction, chronic heart failure, diabetes, lupus, stroke, multiple sclerosis, pressure ulcers, burns, dry eye, viral infections and septic shock. Varied attractive Tβ4 activities from embryological point of view encouraged us to test its application in bovine oocytes in *in vitro* maturation and to consider its application in MSC differentiation. This review provides basic information on the family of thymosin β with the special emphasis on thymosin β4.

Key words: thymosin β4, biological functions, therapeutic applications

STRUKTURA TYMOZYNY β4 – WIELOŚĆ FUNKCJI BIOLOGICZNYCH ORAZ POTENCJALNE ZASTOSOWANIA TERAPEUTYCZNE

Streszczenie

Tymozyna β4 to polipeptyd zaangażowany w wiele procesów biologicznych, patologicznych czy fizjologicznych występujących w organizmie, takich jak: migracja komórek naskórka, tworzenie naczyń krwionośnych w procesie gojenia się ran, jak również w angiogenezie. Tβ4 hamuje zapalenie, dojrzewanie komórek T, a także proliferację i różnicowanie komórek. Ze względu na tak szeroki zakres działania Tβ4 może być stosowana w leczeniu zawału mięśnia sercowego, przewlekłej niewydolności serca, cukrzycy, udaru mózgu, stwardnienia rozsianego, wrzodów, oparzeń, infekcji wirusowych czy wstrząsu septycznego. Tak zróżnicowane spectrum aktywności zachęciło nas do przeanalizowania wpływu Tβ4 na dojrzewanie *in vitro* oocytów bydlęcych, jak również jej oddziaływanie na proces różnicowania komórek MSC. Niniejszy artykuł zawiera podstawowe informacje dotyczące rodziny tymozyny β, ze szczególnym uwzględnieniem tymozyny β4.

Słowa kluczowe: tymozyna β4, funkcje biologiczne, zastosowania terapeutyczne

Fot. B. Borys