Folia Biologica et Oecologica 13: 1–8 (2017)

Acta Universitatis Lodziensis

The characterization of tumor necrosis factor alpha (TNF-α), its role in cancerogenesis and cardiovascular system diseases and possibilities of using this cytokine as a molecular marker

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ABSTRACT

The inflammatory process is directly associated with secretion of cytokines, e.g. tumor necrosis factor alpha (TNF-α). This molecule is one of the 22 proteins which belong to TNF family and is secreted mainly by: macrophages, monocytes, T lymphocyte and mast cells. The biological effects of TNF-α is possible through binding this cytokine to specific receptors – TNFR1 and TNFR2. The large number of reports provides that this cytokine plays extremely important role in cancers and cardiovascular disease – two groups of inflammatory diseases. Unfortunately, these diseases are the main cause of death in spite of advances in medicine and increasing public awareness of prevention.

It is believed that better understanding both molecular potential of this cytokine and the impact in cancerogenesis and others inflammatory diseases may cause using TNF-α as a molecular marker in these diseases and will make it possible to observe the effects of anti-inflammatory therapy. It will be able to cause a drop in the incidence of these diseases and better monitoring of them.

KEY WORDS: cytokine, inflammatory process, cancerogenesis, cardiovascular diseases, marker

Introduction

Tumor necrosis factor alpha (TNF- α) as an example of cytokine

Cytokines are broad and small proteins, molecules and hormone-like proteins (5-20kDa) (Badowska-Kozakiewicz 2013) playing an extremely important role in many cellular processes, such as growth, differentiation, migration, and apoptosis. They also play an important role in immune reactions,

DOI: 10.1515/fobio-2017-0001

inflammatory processes, maintenance of tissue homeostasis. Cytokines can cause pyrogenic effects on energy balance of the body due to the change of appetite, impact both on the structure and functioning of the cardiovascular system or the regulation of activity of the autonomic nervous system. The biological effects of cytokines are possible because they are important mediators of signaling pathways (Chechlińska 2003, Commins *et al.* 2010).

The family of cytokines includes: chemokines, interferons, interleukins, lymphokines and tumor necrosis factors. These molecules are produced by different kinds of cells, for example: active immune cells, keratinocytes, cardiomyocytes, myocytes, fibroblasts, neurons and glial cells. The characteristic feature of the cytokines is the fact that they have pleiotropic, often opposing activity depending on both the type of cell by which they are secreted and acting (Ufnał & Wołynczyk-Gmaj 2003). This fact can cause a problem with classification of cytokines but generally it is carried out on the basis of pro- and anti-inflammatory effects (Bergler-Czop & Brzezińska-Wcisło 2011).

The characterization of tumor necrosis factor alpha (TNF- α)

One of the best characterized cytokine is a tumor necrosis factor alpha (TNF-α) which is known also as a cachectin or differentiation-inducing factor (DIF) and secreted mostly by: monocytes, macrophages, T lymphocytes and mast cells. It is a pro-inflammatory cytokine and one of the 22 proteins which belong to the TNF family (Badowska-Kozakiewicz 2013). The gene encoding this compound is built with 4 exons and is relatively small (3kbp) compared to genes encoding, for example: interleukin 1β (31 kbp) or isoform 1 of cyclooxygenase (22 kbp) and isoform 2 of this enzyme (8.3 kbp) (Korobowicz 2006).

Polymorphisms in the promoter region of the TNF-α gene play an extremely important role because they regulate the transcriptional activity of this cytokine and also have an influence on the biological activity. The best known TNF-α polymorphism is biallelic polymorphism -308G / A. The allele -308A is associated with increasing transcriptional activity of the TNF-α gene in vitro and synthesis of greater amounts in vivo than the allele -308G. Other polymorphisms having the ability to modulate gene expression of TNF-α are: -238G / A, -865C / A, -859G / A, -1032T / C (Kocierz *et al.* 2007).

The role of TNF- α and its receptors in transduction of molecular signals

This proinflammatory cytokine is present in two forms. First is a membrane (precursor) form with a molecular weight of 26 kDa and second is a 17 kDa secretory form after the enzyme modification (Korobowicz 2006, Horiuchi *et al.* 2013).

The result of the translation process is 26 kDa precursor form, called the transmembrane TNF-α (tmTNF-α). It is modified involving metalloproteinase enzyme TACE (TNF-α-converting enzyme, EC3.4.24), resulting in cutting off 76 N-terminal amino acids and making biologically active form of the cytokine - sTNF-α (soluble TNF-α, 17 kDa). Both forms are homotrimers capable to interact with receptors (Juszczyński & Warzocha 2002, Horiuchi *et al.* 2013).

There are evidences that both forms of TNF-α - soluble and precursors, participate in the inflammatory response. They also indicate that tmTNF-α may act as a bipolar molecule transducing the signal, as a ligand by attaching to receptors of TNF-α or as a receptor for transmitting signals to cells producing TNF-α. Transmembrane form of TNF-α is capable of binding to both receptors - TNFR1 and TNFR2, but it seems that the

signaling pathway with the participation of TNF-α anchored in the membrane is initiated by receptor-2 (Horiuchi *et al.* 2013).

The biological changes caused by TNF-α still remain not fully explained, however it is known that these changes occur via two receptors for this cytokine – TNFR1 and TNFR2 and it will help to understand the transduction of the molecular signal. There are two types of this receptors – transmembrane (tmTNFR1 and tmTNFR2) and soluble form (sTNFR1 and sTNFR2) (Wcisło *et al.* 2002, Badowska-Kozakiewicz 2013).TNFR1 is expressed on the surface of most nucleated cells while TNFR2 only on the surface of immune cells.

Transmembrane form of TNFR1 and TNFR2 are built by three domains – ECD (extracellular domain), TMD (transmembrane domain) and ICD (intracellular domain) (Korobowicz 2006). The soluble form is built only by ECD domain and is formed by proteolytic hydrolysis of the extracellular domain of immune cells, particularly monocytes and macrophages. There are evidences that sTNFR1 and sTNFR2 are present in the cerebrospinal fluid – spinal, tissues with difficulty of draining the lymph (Serwin *et al.* 2004). Soluble receptors play an important role in the processes associated with the modulation of the immune response. In addition, they are involved in the binding and inactivation of TNF-α, contributing to the modification of the activation of programmed cell death (Mielczarek *et al.* 2011). Increased expression and elevated plasma concentrations of both forms of the soluble receptors for TNF-α are observed in obesity. However, sTNFR1 has the greatest influence on the development of obesity and responds to insulin resistance, increasing energy expenditure and in consequence reducing the body weight (Olszaniecka-Glianowicz 2005, Goral 2008, Szalecki *et al.* 2008).

The signaling pathways of TNF-α cause two different effects: cell death (mainly by TNFR1 which has death domain associated with ECD) or activating NF-κB signal transduction leading to cells survival (Krzyżowska *et al.* 2009, Szołtysek *et al.* 2011, Skórka & Giannopoulos 2012). It can be observed that signaling pathway of this cytokine is a complex process.

Cancers and cardiovascular disease as a global health problems

The cancers and cardiovascular diseases are two main death causes. The World Health Organization's (WHO) statistical analysis shows that in 2008, 30 percent of all global deaths were associated with cardiovascular disease and this number has been increasing. Data collected by WHO highlights also that „cancer is a leading cause of death worldwide, accounting for 8.2 million deaths in 2012" (www.who.int). According to these data cancer and cardiovascular diseases are very serious global problem despite advances in medicine and increasing public awareness of prevention. Therefore, besides better understanding of the mechanisms associated with the disease, it would be important to find a complementary diagnostic molecular marker, which may be TNF-α. TNF-α is called a „new marker of inflammatory process" (Będowska 2007, Kabłak-Ziemnicka 2010).

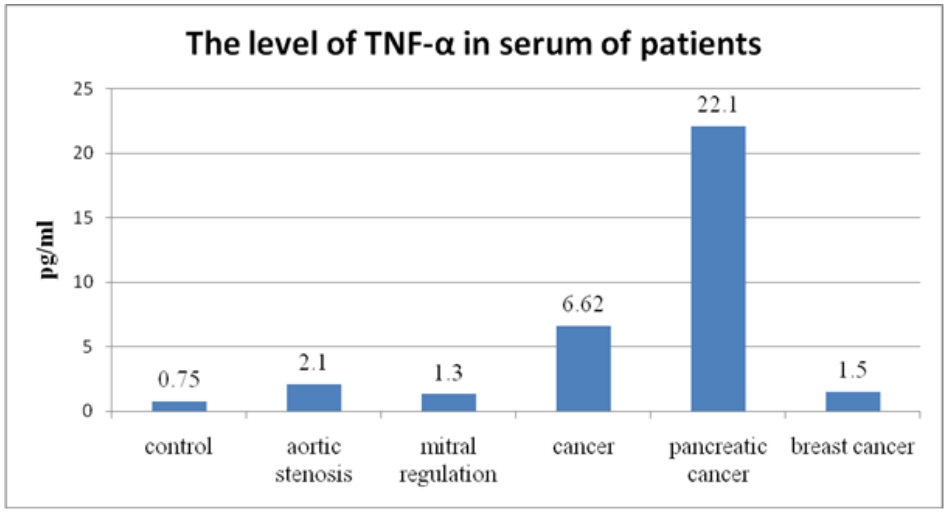
TNF-α as a molecular marker in diseases

Some reports show that TNF-α is useful as a potential marker. Kacperska *et al.* noted that changes in serum concentration of TNF-α may be a potential marker in multiple sclerosis (MS) which is an inflammatory and neurodegenerative disease (Kacperska *et al.* 2014). The possibilities of using this cytokine as a marker were observed in inflammatory bowel disease (IBD)

although some reports show the opposite information (Eder *et al.* 2007). In spite of these discrepancies, Komatsu *et al.* provided a higher concentration of TNF-α in serum of patients with IBD, recommending to analyse the changes using immuno-PCR, which is more sensitive than ELISA method (Komatsu *et al.* 2001). Olczyk-Kwiecień *et al.* observed that patients with rheumatoid arthritis treated aggressively had low levels of TNF in serum what confirmed the role of this cytokine in inflammatory process (Olczyk-Kwiecień *et al.* 2006).

The figure 1 shows the changes in level of TNF-α in serum of patients with cancers and cardiovascular diseases. It can be observed that during these processes this cytokine is secreted with higher amounts compared to control (healthy people). The graph shows the wide variation in specific tumor types (from 1.5 pg/ml in the breast cancer to 22.1 pg/ml in the pancreatic cancer). According to this results it can be observed that cardiovascular diseases and cancers are pro-inflammatory diseases of the substrate, accompanied by increased secretion of inflammatory agents including TNF-α (Scheen-Chen *et al.* 1997, Kapadia *et al.* 2000, Gasiorowska *et al.* 2016).

Figure 1. The level of TNF-α in different cancers and types of cardiovascular diseases and control. This chart was based on data from: Scheen-Chen *et al.* 1997, Kapadia *et al.* 2000, Gasiorowska *et al.* 2016.



TNF- α in cancer and cancerogenesis

TNF-α in carcinogenesis has two opposite ways of action. On the one hand it inhibits the proliferation of tumor cells and increases apoptosis of this kind of cells although it can promote metastasis by influencing the synthesis and activity of matrix metalloproteinases. TNFR1 is responsible for cytotoxicity of tumor necrosis factors against tumor cells. In contrast, TNFR2 is responsible for effects of the acute phase (Wolańska *et al.* 2010).

It was observed that the synthesis of small amounts of TNF-α in the tumor microenvironment, promoting development of tumor growth as well as the surrounding cells, induces apoptosis. However, the higher amounts initiate tumor cell death and stimulate the antitumor response (Tse *et al.* 2012). It is believed that chronic inflammation is one

of the main risk factors for the development of carcinogenesis process, in which TNF-α plays an extremely important role. It is involved in all aspects of the carcinogenesis: transformation, proliferation, angiogenesis and metastasis (Wang & Lin 2008). The antitumor effect of TNF-α is associated with modulation of immune response and leads to instant destruction of tumor stroma by cytotoxic T lymphocyte or activation of dendritic cells.

The reports show the higher level of this pro-inflammatory cytokine in the serum of patients with various types of cancers. Furthermore, the transcriptional activity of TNF-α increases in precancerous stages and is a negative prognostic indicator of tumor development (Wang & Lin 2008).

TNF-α exhibits a devastating effect on tumor vessels, including by changing the properties of endothelial cells from anticoagulant to procoagulant leads to stimulation of tissue factor expression and inhibition of thrombomodulin (Juszczyński & Warzocha 2002). NF-κB stimulated by TNF-α has the opposite effect, anti-tumorigenic in the organ that regenerates itself rapidly (liver) cells and pro- tumorigenic in colon, which regenerates slowly (Wang & Lin 2008).

The data analysis provide ambivalent effect of TNF-α on cancerogenesis, which can be a problem with the use of this cytokine as a marker. Despite this fact, some reports show possibilities of using this agent to observe and diagnose the process associated with cancerogenesis.

The role of TNF-α in cardiovascular diseases

In hypertension, which is one example of cardiovascular disease there is an increase in level of pro-inflammatory cytokines in the blood and tissues of the cardiovascular system (Ufnał & Wołynczyk-Gmaj 2011). The studies have confirmed the higher serum levels of many pro-inflammatory proteins, for example: CRP, IL-6, IL-8, TNF-α in patients with hypertension (Głuszek & Kosicak 2011). It is believed that TNF-α and other cytokines produced in large amounts are the main factors responsible for the progress and development of heart failure. Depending on the concentration, TNF-α exerts protective or harmful effect on the cell function of the heart and myocardium. Low levels of this cytokine is associated with a protective effect (Kurrelmeyer *et al.* 2000), while the higher leads to toxic effect on the myocardium, for example: dysfunction and remodeling of left ventricular, myocardial metabolism disorder, intensification of oxidative stress and endothelial dysfunction. Otherwise activating sphingomyelinase exacerbates the apoptosis of cardiomyocytes (Agnoletti *et al.* 1999).

TNF-α is involved in the production of other pro-inflammatory cytokines, i.e. IL-1, IL-6, which in turn increases metabolic disorders associated with myocardial infarction (Puszkarska & Głuszek 2010, Głuszek & Kosicak 2011). TNF-α is one of the most important cytokine responsible for the endothelial dysfunction, which is characteristic of hypertension (Pacholczyk *et al.* 2008). The mechanism occurring in this process is the activation of NF- κB, which by binding to the promoter sequence of the genes that encode cell adhesion molecules: VCAM-1, ICAM-1, MPC-1, E-selectin in endothelial cells and vascular smooth muscle cells increases their expression (Ouchi *et al.* 1999). TNF-α is also responsible for the damage to the integrity of the endothelial cells by induction of apoptosis of these cells (Hermann *et al.* 2000).

Summary

The large number of reports shows that TNF-α is directly associated with

inflammatory process, cancer and cardiovascular disease. It is extremely important to better understand the mechanisms and signaling pathways of TNF-α to use this cytokine as a molecular marker of pro-inflammatory diseases. This action will be useful in thediagnosis and treatment of cancers and cardiovascular diseases.

The studies and statistical data show how cancer and cardiovascular diseases are a serious problem and highlight the need to find new diagnostic marker. TNF-α can be used as a potential marker, which was confirmed in a large number of reports, however a better understanding of the biological role of this cytokine is absolutely essential.

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Streszczenie

Proces zapalny jest bezpośrednio związany z sekrecją cytokin, np. czynnika martwicy nowotworu alfa (ang. Tumor Necrosis Factor alpha; TNF-α). Ta cząsteczka jest 1 z 22 białek należących do rodziny TNF i wydzielana jest głównie przez: makrofagi,

monocyty, limfocyty T oraz komórki tuczne. Biologiczne efekty działania TNF-α zachodzą dzięki wiązaniu się tej cytokiny ze specyficznymi dla niej receptorami – TNFR1 i TNFR2. Duża liczba prac potwierdza kluczową rolę TNF-α w nowotworzeniu i chorobach układu sercowo-naczyniowego, będących chorobami o podłożu prozapalnym. Niestety, mimo postępu medycyny i wzrostu świadomości społeczeństwa, wymienione choroby stanowią główne przyczyny śmierci na świecie. Lepsze zrozumienie roli tej cytokiny w kancerogenezie i chorobach zapalnych może spowodować wykorzystanie TNF-α jako markera tych chorób oraz do monitorowania przeciwzapalnych efektów terapii.