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# Correlation between endothelial growth factors family and development of cancer in metabolic syndrome

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**Abstract:** Vascular endothelial growth factors (VEGF) family is a key to regulation of angiogenesis, lymphangiogenesis or endothelium physiology. These proteins play a crucial role in pathogenesis of cancer, cardiovascular or ocular disorders. Patients suffering from metabolic syndrome (MetS), which is, in brief, compose of obesity, insulin resistant, dyslipidemia, and hypertension, also develop colon, hepatic, cervical and pancreas cancer more often. The aim of this paper is to summarize the knowledge, which connects these two very frequently pathologic statements – cancer and metabolic syndrome in a few aspects. The emphasis was placed on factors, which signaling pathways are downstream via type 2 of a receptor to VEGF. VEGF-A and VEGF-B are the best knows proteins, which are qualified in this group. Few of isoforms of these molecules regulates endothelial functions, like proliferation, migration and forming new vessels from preexisted ones. They are also involved in other processes like regulation of transport of fatty acids. Chronic inflammation and impaired function of vascular endothelium is characteristic of metabolic syndrome and may probably influence on endothelium functioning also in tumors. VEGF pathways are important in the treatment of cancer because many therapies are focused on VEGFs or their receptors. Dysregulation of this signaling pathway via antibodies or kinases inhibitors results in the reduction of pathological angiogenesis in the tumor. A potentially pathological condition of the endothelium can modulate response for these therapies. MetS and tumors are a hot topic in research, due to widespread in the developed countries, but data about the correlation of VEGFs family in cancer in a group of patients with MetS are limited. Further studies in this field can be useful in answer to a question about the role of VEGF in cancer in the MetS.

## 1. Introduction

The vascular endothelial growth factor was first thoroughly characterized in 1986. Initially, it was called the vascular permeability factor (VPF)(Senger, Perruzzi et al., 1986). The VEGF (Vascular Endothelial Growth Factor) proteins family and their associated receptors are key factors regulating angiogenesis or lymphangiogenesis. They are crucial in physiological and pathological conditions, and in embryonic development. Cardiovascular diseases, cancers, or some ophthalmologic pathologies are directly dependent onthe VEGF/VEGFR pathway. The most important elements included in this family are VEGF-A, VEGF-B, VEGF-C, VEGF-D, PLGF (Placenta growth factor), VEGF-E (present in viruses) and VEGF-F (present in snakes). Furthermore, the appropriate function of this pathway is also dependent on VEGFR-1, VEGFR-2 and VEGFR-3 receptors and other co-receptors like neuropilins (Karaman, Leppanen et al., 2018, Peach, Mignone et al., 2018). Genetic and environmental factors causing insulin resistance, abdominal type obesity, lipid metabolism disorders leading to atherosclerotic plaque development, elevated blood pressure, prothrombotic status, and endothelial dysfunction make up the clinical symptoms of metabolic syndrome(MetS) (Kaur, 2014). The association of more frequent occurrences of tumors, mainly of the large intestine, liver in men and the large intestine, endometrium and pancreas in women, suffering from metabolic syndrome is well-proven(Esposito, Chiodini et al., 2012). Moreover, oncological treatment can be an important factor to initiate the development of MetS (Westerink, Nuver et al., 2016).

Due to the important role of the family of vascular endothelial growth factors in the tumor development, which is, for example in regulating the formation of blood vessels in a tumor mass, it was decided to summarize the knowledge on this subject. The aim of the paper was focused the most on VEGFs, the functioning of which is mainly dependent on VEGFR-2. VEGF pathways are important in the treatment of cancer because many therapies are focused on VEGFs or their receptors. Dysregulation of this signaling pathway via antibodies or kinases inhibitors results in reduction of pathological angiogenesis in tumor. Potentially pathological condition of endothelium can modulate response for these therapies. MetS and tumors are hot topic in research, due to widespread in the developed countries, but data describing the cor-

relation of VEGFs family in cancer in a group of patients with MetS is limited. Additionally, an attempt was made to answer the question about the correlation between the development of tumors, VEGF signaling impairment and the metabolic syndrome. The paper was based on data obtained from the PubMed database using key words such as: "VEGF","VEGF-A", "VEGF-B", "angiogenesis", "tumor", "cancer" and "metabolic syndrome". Particular attention has been paid to literature reports from the last five years.

## 2. Vascular endothelial growth factor-A

VEGF-A is produced by many different cells. Its presence was detected in endothelial cells, fibroblasts, smooth myocytes, platelets and peripheral blood mononuclear cells such as neutrophils and macrophages (Uchida, Uchida et al., 1994, Namiki, Brogi et al., 1995). In addition, about 60% of tumors are capable of secretion of vascular endothelial growth factor (Peach, Mignone et al., 2018). VEGF-A secretion is also stimulated by hypoxia and proinflammatory cytokines (Imaizumi, Itaya et al., 2000).

In angiogenesis, the most important role is played by VEGF-A. It is a large protein with a non-globular structure, which in the secondary structure consists of a tightly twisted opposite structure β, which creates two distorted hairpin loops, cysteine knot on one side and a single loop on the other. This protein occurs in the form of homodimers, which are maintained by hydrophobic interactions. Each monomer consists of two α-helixes and seven β-chains. Three of them are slightly in contact with central parts. They are form very irregular structure. This region is a soluble part of β-structure. Moreover, this area features a very twisted structure, with the greatest intensity in the position β4. In this region of the protein is the main concentration of hydrophobic bonds. The dimeric structure is stabilized by the cysteine knot and the middle, hydrophobic protein motif. The cysteine knot is formed by the first two disulfide bonds and the polypeptide backbone joining with the disulfide bonding. The system also includes two other disulfide bonds that bind the monomers together. Structure of the protein is crucial in thermostability and protection against proteolytic enzymes (Muller, Heiring et al., 2002, Iyer and Acharya, 2011).

The alternative splicing of the Vegfa gene, which causes the formation of few functionally different proteins, is significant in the functioning of vascular endothelial growth factor A (Woolard, Bevan et al., 2009). This gene in a human is located in the chromosome 6p21.1. It consists of eight exons and seven introns (Venables, 2006). Due to the alternative splicing, it is possible to modify the pre-mRNA by creating many different proteins from the same gene (Tischer, Mitchell et al., 1991). So far, sixteen VEGF-A isoforms have been described. The most important, however, are six - VEGF-$A_{111}$, VEGF-$A_{121}$, VEGF-$A_{145}$, VEGF-$A_{165}$, VEGF-$A_{189}$, VEGF-$A_{206}$ (Woolard, Bevan et al., 2009, Gu, Li et al., 2013). In addition, differently functioning molecules with the same amount of amino acids have been characterized. The first described VEGF-$A_{165}$a, act in the opposite manner to VEGF-$A_{165}$b (Eswarappa, Potdar et al., 2014). Alternative splicing is regulated by a complex of proteins - spliceosom. It is also regulated by other proteins e.g. SRSF1 (serine / arginine-rich splicing factor 1), which is phosporylated by its kinase - SRPK1 (Guyot, 2015). Dysregulation of SRPK1kinase was observed in tumors for example in colon carcinoma cell line, prostate cancer and melanoma. This was reflected in the attempts to apply a therapy modulating the alternative assembly of VEGF (Oltean, Gammons et al., 2012).

Differences in the presence of specific exons in the protein determine the different properties of VEGF-A isoforms. Furthermore, in tumors are present in high level specific to cancer type isoforms of VEGF-A (Vempati, Popel et al., 2014). The first five exons are of constitutive nature and they are present in each of the isoforms of type A vascular endothelial growth. In this part of the protein there is a signal sequence between the first and second exons , a glycosylation site - Asp74 and a potential site of action for plasmin - Arg110 and Ala111 (Keyt, Berleau et al., 1996). The remaining part of the protein, i.e. exons 3 and 4, is a binding site for VEGFR-1 and VEGFR-2 (Holmes and Zachary, 2008, Woolard, Bevan et al., 2009, Vempati, Popel et al., 2014). The most significant differences in the functioning of the different VEGF isoforms are exons 6a and 7. They are responsible for the interaction between electronegative heparan sulfate in the extracellular matrix (ECM), which determines the bioavailability of certain isoforms of VEGF type A (Krilleke, DeErkenez et al., 2007, Lee, Folkman et al., 2010). The key binding site for neuropilin-1 (NRP-1 - Neuropilin-1) is the product of exon 7 (Soker, Takashima et al., 1998). This domain has ability to create a complex NRP-1/VEGF/ VEGFR2 (Kawamura, Li et al., 2008). Shorter isoforms such as VEGF-$A_{111}$, VEGF-$A_{121}$ are devoid of these exons and they do not bind to the ECM, which makes them diffuse freely (Houck, Leung et al., 1992). Longer isoforms - VEGF-$A_{145}$, VEGF-$A_{189}$, VEGF-$A_{206}$ contain exons 6a and 7 in their structure, thus they can be bound to glycoproteins containing heparan

sulphate (Houck, Ferrara et al., 1991). VEGF-$A_{165}$ is an intermediate form between a completely soluble and bound form (Houck, Leung et al., 1992).

Another domain where there are differences between the isoforms is C - the end of the protein. $VEGF_{xxx}$a isoforms contain exon 8a, and $VEGF_{xxx}$b exon 8b (Bates, Cui et al., 2002). As a result of this modification, the last six amino acids are changed at the C-terminal of the protein. This difference between the CDKPRR sequence in the VEGFxxxa isoforms, and SLTRKD in the VEGFxxxb isoforms results in significant functional implications (Ladomery, Harper et al., 2007). VEGFxxxa isoforms have proangiogenic activity, increase the permeability of blood vessels, increase proliferation, survival, and cell migration (Olsson, Dimberg et al., 2006). In contrast, VEGFxxxb isoforms have a counter-action. By what they become regulators and inhibitors of angiogenesis (Woolard, Wang et al., 2004, Catena, Larzabal et al., 2010). In conditions in which it is not necessary to create new vessels, predominantly there are isoforms having anti-angiogenic properties, whereas in tumor growth a reduction of these inhibitory isoforms is observed (Bates, Cui et al., 2002). The presence of exon 8a is important site of binding to neuropilin-1 (Kawamura, Li et al., 2008). The formation of these two different forms is also regulated by other molecules. Insulin-like growth factor-1 (IGF1) and tumor necrosis factor-α (TNFα) affect the increased synthesis of exon 8a, whereas tumor growth factor-β (TGF-β1) of those with exon 8b (Nowak, Woolard et al., 2008). For regulation of this mechanism are mainly responsible, the SRSF1 protein with which are creating the isoforms $VEGF_{xxx}$a and SRSF6, which contributes to the formation of $VEGF_{xxx}$b isoforms. $VEGF_{xxx}$b isoforms probably do not occur under physiological conditions in human and murine cells (Harris, Craze et al., 2012, Bridgett, Dellett et al., 2017).

Another possibility to increase the diversity of VEGF-A is its proteolytic processing through plasmin (Keyt, Berleau et al., 1996) or metalloproteinases (MMPs), e.g. 1,3,9,7,12,16,19 (Lee, Jilani et al., 2005, Lundkvist, Lee et al., 2007). The proteolysis site is located in exon 5. This process leads to the formation of respectively 13kDa and 16kDa fragments of protein (Lee, Jilani et al., 2005). In this process, domains capable of binding to the receptor are not removed from the protein. Furthermore, the biological activity of VEGF is reduced, because the modified proteins have no possibility of binding to NRP-1 and heparan sulphates (Keyt, Berleau et al., 1996). About 40-80% VEGF undergoes proteolysis under pathological conditions (Lee, Jilani et al., 2005, Lundkvist, Lee et al., 2007, Gutierrez, Konecny et al., 2008). MMPs can also produce a proangiogenic forms of VEGF-A. For example, MMP-9 is responsible for modifications of VEGF, that results in increased angiogenesis in breast, cervical and colon cancer (Vempati, Popel et al., 2014).

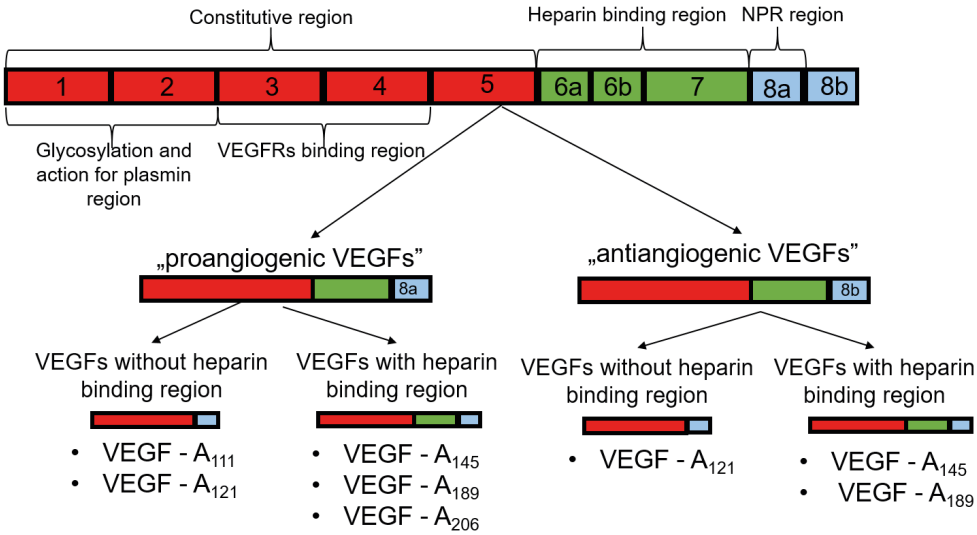


Figure 1. Scheme of VEGF-A isoforms. Formation of each of VEGF-A isoforms is precisely described above. Figure is based on (Ladomery, Harper et al., 2007, Nowak, Woolard et al., 2008, Sargent, Clopton et al., 2016).

## 3. Vascular endothelial growth factor-B

VEGF-B is a growth factor that is encoded by the Vegfb gene, located in the 11q13 chromosome (Olofsson, Pajusola et al., 1996). Two isoforms VEGF-B - VEGF-$B_{167}$ and VEGF-$B_{186}$ are formed as a result of the alternative splicing. They differ in the presence of a domain that has the ability to bind to heparan sulfate. Due to the lack of this fragment of the protein in VEGF-$B_{186}$ it is characterized by a greater ability to diffuse in the intercellular matrix (Grimmond, Lagercrantz et al., 1996, Olofsson, Pajusola et al., 1996). Both isoforms have affinity for the VEGFR-1 receptor and its soluble form, as well as NRP-1. VEGF-$B_{186}$ requires proteolytic treatment to be able to interact with neuropilin-1 (Olofsson, Pajusola et al., 1996, Makinen, Olofsson et al., 1999). In vitro, this protein is able to form heterodimers with VEGF-A, but they have not been observed in vivo (Olofsson, Pajusola et al., 1996).

The expression of VEGF-B is observed in the early stages of embryonic development, in the heart, central nervous system and in brown adipose tissue. Under physiological conditions its production is elevated in cardiomyocytes, skeletal muscle myocytes and in neuronal tissue. The main isoform that occurs in mice is VEGF-$B_{167}$, which is about 80% of the total secreted VEGF-B.(Li, Kumar et al., 2012)

It is believed that the role of this growth factor is to augment the function of VEGF-A (Robciuc, Kivela et al., 2016). VEGF-B is not able to initiate the process of formation of blood vessels - the density or the permeability of blood vessels in the tissue does not change under its influence (Aase, von Euler et al., 2001, Malik, Baldwin et al., 2006, Zhang, Tang et al., 2009). The essential action of this growth factor is also to inhibit apoptosis of endothelial cells and smooth myocytes. In addition, in an environment rich in other factors that stimulate angiogenesis, VEGF-B has antagonistic activity to these molecules (Li, Zhang et al., 2008, Li, Lee et al., 2009). VEGF-B is also associated with the transport of fatty acids to endothelial cells. At its low levels, the decrease of Fatp3 and Fatp4 proteins is also observed, which are involved in this process. The type B endothelial cell growth factor also contributes to the development of insulin resistance (Hagberg, Mehlem et al., 2012).

In cardiac muscle after an ischemic event, VEGF-B expression is reduced (Mehrotra, Wu et al., 2014). In cardiac muscle, VEGF-B activates the Akt/mTORC1 and Erk1/2 MAPK pathways. Activation of the Erk1/2 MAPK pathway results in the phosphorylation of VEGFR-2, thereby increases the effect of VEGF-A (Kivela, Bry et al., 2014).

## 4. Lymphangiogenesis associated endothelial growth factors – VEGF-C and VEGF-D

Part of the VEGF family that is particularly related to lymph vessels is VEGF-C and VEGF-D. Both of these factors play an important role not only in lymphangiogenesis but also in angiogenesis. The “lymphatic” endothelial growth factors undergo proteolysis, which determines the diversity of proteins. This regulation of forming a different isoforms of VEGF-C and VEGF-D is characteristic to “lymphatic” part of family. (Rauniyar, Jha et al., 2018, Stacker and Achen, 2018)

VEGF-C is the main stimulant for the formation of lymphatic vessels. It was characterized in 1996 (Joukov, Pajusola et al., 1996). Like every member of the VEGF family, it contains a domain that is homologous with the rest of the family - VHD (VEGF homology domain. differently to described above VEGF-A and-B, VEGF-C is capable of binding only with NP - 2 (Karpanen, Wirzenius et al., 2006, Xu, Yuan et al., 2010). VEGF-C is produced as a propeptide that needs proteolytic activation. It is this process molecules with different peptide chain lengths are formed, thus diversity of VEGF-C and-D is most related to alternative splicing as “angiogenic” VEGF (Joukov, Sorsa et al., 1997, Stacker, Stenvers et al., 1999). Proteases taking part in this are different in the case of VEGF - C and VEGF - D (Bui, Enis et al., 2016).

VEGF-C has binding properties to VEGFR-2 and VEGFR-3. The strength of this binding depends on the protein proteolytic process. The propeptide has no activity to stimulate the receptor - first it must be processed by furin, ADAMTS3 (a disintegrin and metalloproteinase with thrombospondin motifs 3) or plasmin (McColl, Baldwin et al., 2003, Siegfried, Basak et al., 2003, Jeltsch, Jha et al., 2014). As a result of proteases, two forms of protein are formed that differ in length by in nine amino acids. The longer protein is formed with the participation of ADAMTS3, and shorter by the action of plasmin (McColl, Baldwin et al., 2003, Jeltsch, Jha et al., 2014). The differences between the effects of both forms have not been described so far (Rauniyar, Jha et al., 2018). Nevertheless, pro-VEGF-C only with the participation of NRP-2 can also binds to its receptors. Interaction of immature VEGF-C with NRP-2 and VEGFR-2 or VEGFR-3 results in reduction of activity of the mature proteins (Jeltsch, Jha et al., 2014). Under conditions of inflammation, the level of VEGF-C increases. Its production is mainly stimulated by cytokines secreted from macrophages (Ristimaki, Narko et al., 1998, Krebs,

Tikkanen et al., 2012). Activation of the receptor via VEGF-C leads to stimulation of the MAPK / ERK and AKT pathways, which is associated with the growth, survival and migration of lymphatic endothelial cells (Makinen, Veikkola et al., 2001, Deng, Zhang et al., 2015).

VEGF-D was first described as FIGF (c-fos-induced growth factor) (Orlandini, Marconcini et al., 1996). Like VEGF-C, it has VEGFR-2 and VEGFR-3 receptor-stimulating properties (Ogawa, Oku et al., 1998). The c-FOS transcription factor and factors affecting its activity together with the cadherin - 11 suppress the secretion of VEGF-D (Orlandini, Marconcini et al., 1996, Orlandini and Oliviero, 2001). In addition, β-cadherin increases mRNA stability for VEGF-D (Orlandini, Semboloni et al., 2003). VEGF-D may also exist in the form of a monomer, which is quite unique for VEGF protein family (Stacker, Stenvers et al., 1999).

VEGF-D is produced in the form of a propeptide that undergoes proteolytic treatment, which determines the formation of various forms of the protein. This process occurs in both mice and humans (Stacker, Stenvers et al., 1999, Stacker, Williams et al., 2014).Significantly different proteins with a different polypeptide chain length affect the bioactivity of this growth factor. Pro-VEGF-D also binds to two receptors, thus competing with mature forms to form a negative feedback loop (McColl, Paavonen et al., 2007). Due to the possibility of binding to VEGFR-2 and VEGFR-3, the D-type endothelial cell growth factor may stimulate both angiogenesis and lymphangiogenesis (Achen, Jeltsch et al., 1998, Stacker, Williams et al., 2014). In embryo development, the formation of blood vessels depends on the presence of the transcription factor SOX18, which expression is precisely regulated through VEGF - D (Duong, Koltowska et al., 2014). This growth factor also limits inflammation, which may be an alternative in the treatment of diseases with this background (Huggenberger, Ullmann et al., 2010, Huggenberger, Siddiqui et al., 2011).

## 5. Another proteins from VEGF family - PLGF, VEGF-E and VEGF-F

Another molecule belonging to the VEGF family is PLGF (placenta growth factor). characterized in the early 1990s. This protein forms homodimers. As a result of the alternative splicing, four isoforms are formed - PLGF-1-4, but in the largest number there are only the first and the second isoforms (Maglione, Guerriero et al., 1991, De Falco, 2012). Only the PLGF-2 isoform is found in mice (DiPalma, Tucci et al., 1996). PLGF also has a C-terminal binding domain with heparin. The cooperation between PLGF and heparin is necessary to interaction with NRP-1 and NRP-2. Heparin binding site can be suppressed by proteolysis of the c-terminal fragment of the protein by plasmin. The PLGF-$2_{123 - 144}$ domain also allows interaction with ECM (Migdal, Huppertz et al., 1998, Persico, Vincenti et al., 1999, Hoffmann, Willenborg et al., 2013, Martino, Briquez et al., 2014). This growth factor only binds to the VEGFR-1 receptor and its soluble form – sVEGFR-1, but not to VEGFR-2 (Kendall and Thomas, 1993, Park, Chen et al., 1994). PLGF-2 homodimers via phosphorylation of VEGFR-1 and PLGF-2/VEGF heterodimers via forming a VEGFR-1/VEGFR-2 dimer, are able to stimulate the formation of new blood vessels (Ziche, Maglione et al., 1997, Autiero, Waltenberger et al., 2003). In few cancers is observed overexpression of PLGF-1. This isoform can forms PLGF-1/VEGF heterodimers. This interaction, results in limited activation of VEGFRs. It is a way to regulation of VEGF-A activity (Eriksson, Cao et al., 2002). The placenta growth factor also causes an increase in the synthesis of proangiogenic factors such as VEGF, FGF2 or MMP. By activating VEGFR-1, it influences the interaction of VEGFR-1 with VEGFR-2, which results in increased activation of VEGFR-2 by VEGF-A (Autiero, Waltenberger et al., 2003, Roy, Bhardwaj et al., 2005, Marcellini, De Luca et al., 2006).

In physiological conditions, in most cells high levels of PLGF are not observed, but in pathological conditions there is a significant increase in the level of this protein like in cancers. This growth factor causes growth, survival of vascular endothelial cells. It also stimulates the growth of blood vessels and indirectly through interactions with macrophages contributes to the activation of angiogenesis.(Fischer, Mazzone et al., 2008, Hedlund, Yang et al., 2013)

A molecule that has the ability to bind only to VEGFR-2 and an angiogenic effect similar to VEGF-$A_{165}$ has been characterized in 1998 and named VEGF-E. Initially, it was described in the Orf NZ-7 virus. It also has no ability to bind to heparin due to the lack of a suitable domain. It creates homodimers as most of the VEGF family members(Ogawa, Oku et al., 1998). It is also possible to isolate vascular endothelial growth factors - VEGF-F from the snake venom (Yamazaki, Matsunaga et al., 2009).

## 6. Links between vascular endothelial growth factors and cancer in metabolic syndrome

One of the most significant features of cancer development is a creation of metastasis (Fidler, 2003). As was well described before, VEGF proteins family plays, a crucial role in formation of new vessels. A lot of cancer, such as breast, ovarian, endometrial non-small cell lung, colorectal, head and neck and another cancers (Costache, Ioana et al., 2015). Overexpression of VEGFs in neoplasms result in worsen survivals of patients. This is a reasons of many clinical trials which are focused of inhibition of VEGF signaling, for example with bevacizumab or aflibercept (Ramjiawan, Griffioen et al., 2017). The association of the metabolic syndrome with elevated VEGF-A, -B and -C concentration in the patients' serum is well proven (Zafar, Mills et al., 2018). Despite this, are there any data, which are only focused on difference of expression of VEGF family proteins in the group of metabolic syndrome patients versus without this condition ?

In a small group of patients with colorectal cancer, there were no significant differences between the VEGF concentration in patients with metabolic syndrome as compared to patients without such condition, however above study was performed with limited number of patients, which significantly limits the reliability of results (Liu, Druta et al., 2014). No worse survival was observed in patients with metabolic syndrome and hepatocellular carcinoma treated with sorafenib. Therapy with its results in reduction of pathological angiogenesis, because this medicament is an inhibitor of various tyrosine kinases including VEGFRs (Labenz, Prenosil et al., 2018). Based on this two small studies, probably VEGF expression is not significant upregulated in this cancers in metabolic syndrome patients, but more studies in this field are needed to confirm this observations. Despite this, in MetS condition, there a some genetic background of neoplasm development. Patients with metabolic syndrome and carrying polymorphism (1451C> T or 1725G> A) in the VEGF gene are characterized by a particular predisposition to colorectal cancer (Jeon, Kim et al., 2014).

The data, focused on another then VEGF--A expression in the cancer of MetS patients are indirect. High expression of VEGF-B is observed in metabolically active tissues such as cardiomyocytes and skeletal muscle myocytes. Many mitochondria are present in above tissues and fatty acid transport is intensified, which underlines the important role of this growth factor in regulating the level of fatty acids in cells. Expression of VEGF-B is also noticeable in tumor cells such as adenomas, breast cancer, ovarian cancer, lymphomas, melanomas and sarcomas, which may indicate its significant role in angiogenesis in these tumors (Kivela, Bry et al., 2014, Zafar, Zheng et al., 2017). Metformin, which is a drug used in the treatment of metabolic syndrome, can potentially inhibit VEGF-B signaling, which results in reduced growth of tumors, such as pancreatic cancer (Zhu, Zhang et al., 2016). Moreover, this drug probably reduce the angiogenesis in hepatocellular carcinoma, but this hypothesis must be confirmed in bigger group of patients (Cauchy, Mebarki et al., 2015). Nonphysiological secretion of "lymphatic" endothelial cell growth factors is noticeable in some tumors like acute myeloid leukemia or non-small cell lung cancer. In the solid tumors they are responsible for promotion of metastasis (Chen, Chang et al., 2012). Blocking a VEGF-C and VEGF-D dependent pathways in metabolic syndrome in a one of new strategies in treatment of this MetS (Karaman, Hollmen et al., 2015). So far, limited investigations are described association of inhibition of this pathway in cancer in the group of patients with MetS. Currently, there is little evidence suggesting the importance of these and other members of the VEGF family in the pathogenesis of cancer in patients with metabolic syndrome.

On increased secretion of VEGF in MetS condition impacts upregulated secretion of adipokines in visceral adipose tissue (Lopez-Jaramillo, Gomez-Arbelaez et al., 2014). In the well reported, that leptin, which is highly overexpressed in MetS, stimulated angiogenesis via VEGF signaling especially in mammary cancer (Gonzalez, Cherfils et al., 2006). Furthermore, in some cases, like in chondrosarcoma adiponectin can induce secretion of VEGF-A and VEGF-C (Lee, Lin et al., 2015, Huang, Chang et al., 2016), but another especially hepatocellular carcinoma this adipokine works in opposite way (Man, Ng et al., 2010). Dysregulation of leptin and adiponectin secretion in triple negative breast cancer (TNBC) was propose by Davis and Kaklamani. In their hypothesis angiogenesis in MetS patients with TNBC is regulated by two crucial adipokines. Upregulation of leptin secretion and impaired adiponection expression can results in increased secretion of VEGF, which results in promotion of cancer angiogenesis (Davis and Kaklamani, 2012), but this mechanism is not confirmed in the studies.

Furthermore, to MetS condition characteristic is a chronic low-grade inflammation. Pathologic function of upregulated secretion of cytokines like TNF-α, IL-1, IL-6 and infiltration of immune cells in the tissues are involved in pathogenesis of

endothelial damage, which is observed in MetS (Grandl and Wolfrum, 2018). Moreover, overexpression of this cytokines in the group of MetS patient is significant associated with worsen survivals of patients with prostate cancer (Conteduca, Caffo et al., 2018). Inflammatory cytokines, which are produced by that cells are also induce angiogenesis and VEGF activity (Carmeliet and Jain, 2000). This mechanism can be one of reasons of inappropriate new vessels formation in the MetS related cancers, but there are needed more studies which show it directly.

Interesting that, reduction of body weight by bariatric operation (Ashrafian, Ahmed et al., 2011) or diet (Di Daniele, Noce et al., 2017) limit the many cancers development. Furthermore, it was estimated that in the cohort of women with endometrial cancer bariatric operation improve survivals of patients, which undergoes surgical procedure compare to control group (Neff, Havrilesky et al., 2015). In was reported that after operation levels of VEGF family proteins are downregulated (Farey, Fisher et al., 2017). Despite this, the question of potential benefits of inhibition of VEGF signaling in cancers in the group of MetS patients is unsolved.

## 7. Summary

The family of vascular endothelial growth factor proteins play a key role in many physiological processes and maintaining homeostasis. Not without significance is their participation in the progression of solid tumors, which due to the VEGF activity gain the ability to increase size and appropriate conditions for metastasis. The interactions between endothelial cell growth factor and its receptors are very important in the process of tumor angiogenesis, which justifies the use of VEGF blocking antibodies or inhibitors of tyrosine kinases in targeted therapy, which inhibit the signal transmission from these receptors. Due to characteristic features of the metabolic syndrome, in particular chronic inflammation and vascular endothelial cell dysfunction, it can be assumed that the nature of VEGF activity changes. However, the data presented above indicate that in patients with metabolic syndrome, despite the higher levels of serum endothelial cell growth factor, there are no significant differences VEGF activity. There are many spots in VEGF signaling regulation, that can be targeted in therapy of cancer essentially in the group of MetS. Particular attention should be paid to the limited literature data on this issue, which, firstly, limits the information about the differences in the functioning of these proteins in patients with metabolic syndrome, and secondly encourages further research into this issue, especially in this group of patients. This is potentially important due to the possibility of optimizing targeted cancer therapy aimed at the formation of new blood vessels in solid tumors. Vascular endothelial growth factors family plays an important role in pathogenesis of cancer and metabolic syndrome, so further investigations in this area can show unexpected associations of these widespread pathologic conditions.

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