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Angiogenesis in Hodgkin's Lymphoma

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ABSTRACT

Angiogenesis is a multistep process controlled by a number of stimulating and inhibiting factors. Aberrant angiogenesis is involved in cancer progression. The best-known elements responsible for regulation of angiogenesis are vascular endothelial growth factor, their membrane-bound receptors, and circulating, soluble receptors. The major objective of the present review is twofold: firstly, it seeks to explore knowledge about angiogenesis in Hodgkin's lymphoma, and secondly it indicates the necessity and relevance of carrying out further research dedicated to this process. Hodgkin's lymphoma is a proliferative disease of the lymphatic system. The process of angiogenesis in Hodgkin's lymphoma has not been studied thoroughly. There is a significant role of paracrine interactions of Hodgkin and Reed-Sternberg cells with reactive cells of the immune system, which makes studying the mechanisms of development of Hodgkin's lymphoma more difficult. It has been proven that several angiogenesis-stimulating proteins are expressed in Hodgkin and Reed-Sternberg cells both *in vitro* and in tumour tissue. Moreover, some of these proteins are produced by the reactive cells. Vascular endothelial growth factor, basic fibroblast growth factor, and hepatic growth factor serum concentrations are elevated in patients with Hodgkin's lymphoma. The role of circulating endothelial progenitor cells in the pathogenesis of Hodgkin's lymphoma has not been thoroughly explained. Similarly, there are no satisfying data on the modulation of the angiogenic potential of the blood caused by vascular endothelial growth factor soluble receptors in patients with Hodgkin's lymphoma. Processes controlling angiogenesis in Hodgkin's lymphoma merit more comprehensive investigation.

Key words: angiogenesis, Hodgkin's lymphoma, vascular endothelial growth factor

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Introduction

The process of angiogenesis, that is to say the formation of new blood vessels on the substrate of the already existing blood vessels, occurs both under physiological conditions and as a part of the pathophysiology of certain diseases. It is strictly regulated by a system of stimulating and inhibiting factors [1, 2]. Factors involved in this regulation usually remain in the state of equilibrium or slight advantage of inhibition. Angiogenesis starts in the case of the predominant influence stimulation. Under the physiologic conditions, the process can be observed during foetal development, and in the post-natal period in the process of wound healing and the cyclical changes accompanying ovulation and menstruation [2]. There are two processes involved in angiogenesis: neoangiogenesis, which is the formation of a blood vessel on the basis of existing ones in tumour tissue, and vasculogenesis, which is the *de novo* formation of blood vessels. Until recently, vasculogenesis was believed to occur solely in the foetus. However, evidence exists that it also takes

place during the process of tumour development when endothelial progenitor cells derived from bone marrow are involved in the formation of the vascular system of the tumour. A suitable stimulation initiates a sequence of events in the process of angiogenesis. During the process, endothelial cells are separated from each other. Vascular permeability increases and the matrix metalloproteinases are involved in the breakdown of the basement membrane and surrounding structures. This facilitates the migration of cells towards angiogenesis stimulus, accompanied by endothelial proliferation. Subsequently, the prepared cell cord produces lumen and the new structure takes the function of a blood vessel [2]. Aberrant angiogenesis, which occurs in some chronic inflammatory diseases, diabetic retinopathy, and ischaemic diseases of the cardiovascular system, plays an important role in the development of cancer.

For some time, the progression of cancer remains independent of the formation of new blood vessels. In the initial phase, the tumour is made up of approximately 1 million cells, which have a volume of 1–2 mm³. At this stage oxygen, nutrients, and growth factors reach

the cells through diffusion [1]. In the subsequent phase, insufficient supply of oxygen instigates necrosis of the central zones of the tumour, whose growth would not be possible without an additional provision of blood, or as a consequence of a process referred to as an angiogenic switch, wherein cells undergo permanent genetic modifications leading to the uncontrolled production of angiogenic factors. In this perspective, angiogenesis allows progression of cancer. In addition to providing supplies of tumour tissue with oxygen and nutrients, this process paves the way for the spread of cancer cells in the body.

The role of angiogenesis in cancer progression: development of the concepts

The first theories indicating that development of cancer is angiogenesis-dependent date back to the 1970s and more precisely the pioneering study of Folkman [3]. The article presented observations on induced neovascularisation and proliferation of endothelial cells, which is required for tumour growth and underscores the importance of stimulating the growth of blood vessels by tumour cells, which enables further proliferation and tumour growth. This concept marked the beginning of intensive work dedicated to the understanding of the molecules regulating angiogenesis, as well as attempts to describe this process on the example of various cancer types. The authors anticipated that the research on angiogenic substances may be relevant for the development of potential anticancer therapies. In this way, the formation of new blood vessels in tumours could be a therapeutic target. Subsequent research confirmed the existence of soluble substances that inhibit angiogenesis [4].

Aim of the review on angiogenesis in HL

Data on the process of angiogenesis in Hodgkin's lymphoma (HL) are scarce, and the results of studies are often contradictory. The objective of the present review is to explore knowledge about angiogenesis in HL and to indicate the necessity of carrying out further research dedicated to this process.

Search strategy

Electronic searches were performed in PubMed/Medline and Google Scholar databases without time limitations and were completed on 17th April 2017. The main search strategy used a combination of words "Hodgkin lymphoma" or "Hodgkin's lymphoma" and "angiogenesis" OR "angiogenic" OR "proangiogenic" OR "anti-angiogenic" OR "vasculogenesis" OR "vascu-

lature" OR "micro-vessels" OR "lymphangiogenesis" OR "VEGF" OR "VEGFR" OR "sVEGFR" OR "HIF-1" OR "angiogenic" OR "angiopoietin" OR "FGF" OR "SDF-1" OR "HGF" OR "PDGF" OR "PIGF" OR "TGF" OR "TNF". Searched results including references were then studied manually for additional information. No language restrictions were applied. Searches were collated, checked for duplicates, and sorted by the first author. Results were discussed and selected for this review by the first author and co-authors.

Angiogenesis regulating factors

Presently there are many known factors involved in the regulation of angiogenesis, and the list is constantly expanding [1]. The list of proangiogenic and antiangiogenic factors is shown in Table 1.

Role of the vascular endothelial growth factor and its receptors

Vascular endothelial growth factor (VEGF) and its receptors (VEGFR) are the best-known elements that stimulate angiogenesis. VEGF exists in several isoforms resulting from alternative splicing. VEGF stimulates the migration and mitosis of vascular endothelial cells and increases the capillary permeability. In this way, it controls at least some steps of the process that initiates "sprouting" of the new blood vessels. Adhesion of individual endothelial cells with each other is reduced by the action of VEGFR via cadherin phosphorylation and internalisation. VEGF gene expression is regulated by the HIF transcription factor (hypoxia-induced factor) and the tumour suppressor gene von Hippel-Lindau in response to the insufficient level of oxygen supply [5]. VEGF-A binds to the membrane-bound receptors VEGFR-1 and VEGFR-2 localised on the surface of vascular endothelial cells. VEGFR-2 mediates almost all known cellular responses to VEGF. The activation of tyrosine kinase in these receptors starts a cascade of intracellular signalling, which eventually affects the above-mentioned effects of VEGF. The vascular endothelial growth factor can further mobilise bone marrow endothelial progenitor cells and other cells of the myeloid lineage to settle in vasculogenesis [2, 6]. VEGF-C and VEGF-D are primarily associated with lymphangiogenesis by interaction with the endothelial receptors VEGFR-3 and VEGFR-2 [7].

Methods used in studies concerning cancer angiogenesis

There are several methods described, whose major objective is to expand the knowledge about angiogenesis, including measuring the concentration of regulating

Table 1. Factors involved in angiogenesis [1]

Proangiogenic factors	Antiangiogenic factors
aFGF (acidic fibroblast growth factor)	Angiostatin
Angiogenin	α 2-makroglobulin
Ang-1 (angiopoietin 1)	Platelet factor 4
Ang-2 (angiopoietin 2)	Endostatin
b-FGF (basic fibroblast growth factor)	Interferon α
Chemokine SDF-1	Interferon β
Eph A (ephrin-A)	Interferon γ
Eph B (ephrin-B)	Interleukin 12
Fibrin-derived peptide beta 15–42	N-terminal prolactin fragment
G-CSF (granulocyte colony stimulating factor)	Tissue inhibitors of metalloproteinases
GM-CSF (granulocyte-macrophage colony stimulating factor)	Thrombospondin-1
HGF (hepatocyte growth factor)	Troponin-1
IL-6 (interleukin 6)	
IL-8 (interleukin 8)	
NO (nitrogen oxide)	
PDGF (platelet-derived growth factor)	
PGE1 (prostaglandin E1)	
PGE2 (prostaglandin E2)	
PIGF (placental growth factor)	
PLF (proliferin)	
TGF- β (transforming growth factor beta)	
TNF- α (transforming growth factor alpha)	
VEGF (vascular endothelial growth factor)	

substances in the serum and their expressions in the tumour tissue, determining the number, density, and morphology of tumour vessels, but also counting the number of vascular endothelial progenitor cells in the blood. Initially, research concentrated on carrying out microscopic examinations of the cancerous tissue; subsequently, histochemical evaluation of the microvessel density (MVD) and factors regulating the expression of angiogenesis in the neoplastic tissues was performed. For reasons of easy access, and quick and reproducible results, enzyme-linked immunoassay (ELISA) is often used as a reliable method for measuring concentrations of proangiogenic and anti-angiogenic cytokines in blood serum. In addition, expression of genes responsible for the production of angiogenic tumour cells may be examined by RT-PCR (reverse transcription polymerase chain reaction). Growing availability of flow cytometry permits quantification of vascular endothelial

progenitor cells in the blood. Circulating vascular endothelial progenitor cells (CEPC) are precursor cells derived from bone marrow, which shows proliferative potential. These cells are involved in the process of postnatal vasculogenesis. They form the base for the development of new vessels as a building material, but also stimulating adjacent cells by the paracrine effect. It is suspected that the endothelial progenitor cells play a role in the formation of blood vessels in tumours too. A summary of the methods used in the studies on angiogenesis is shown in Table 2.

Hodgkin's lymphoma overview

Hodgkin's lymphoma (HL) is a neoplastic disease of the lymphatic system characterised by the presence of polynuclear Reed-Sternberg and Hodgkin cells (HRS). These cells induce proliferation of lymphocytes, monocytes, macrophages, and histiocytes. There are two main types of HL: classical HL (95%) and nodular lymphocyte predominant HL (5%). The morbidity due to HL in developed countries is about 2–3 per 100,000/year. In 2010, in Poland, more than 700 new cases were diagnosed with HL, representing approximately 0.5% of malignant tumours. Most cases of HL are diagnosed in people aged between 15 and 40 years [8]. There are no clearly defined risk factors, although it has been suggested that genetic predisposition, viral infections (EBV), and immunosuppression can increase individual chances of developing this disease [9]. The elements of a routine evaluation are staging and assessing prognostic factors [10, 11].

Treatment of HL

Treatment includes radiation therapy, chemotherapy, or sequence of both methods. The first-line treatment regimens used in adult patients are ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone). The majority of patients can be cured as a result of such treatment. The cure rate reaches 80% [9]. Anti-angiogenic drugs are not routinely used in the treatment of this disease, but studies using animal models of HL indicate that some drugs may act synergistically involving the inhibition of angiogenesis [12].

Prognostic factors in HL

One of the directions of research on HL is studying substances with the potential to be new prognostic factors. In the future, this could lead to the identification

Table 2. Methods used in studies concerning angiogenesis

Morphological studies	Studies on the expression of proangiogenic and antiangiogenic factors	Studies on the serum levels of proangiogenic and antiangiogenic factors	Studies on the levels of circulating vascular endothelial progenitor cells (CEPC)
Tumour vasculature characteristics based on classical HE staining and immunostaining: <ul style="list-style-type: none"> • number of the vessels • vascular density • morphology of the vessels 	Immunohistochemical studies of the neoplastic tissue	Concentrations of VEGF, PDGF, HGF, sVEGFR1, sVEGFR2, etc.	Amount of CEPC in the blood using the panel of antibodies against specific cell antigens
Microvessel density and microvessel density to total vascular area ratio (MVD/TVA)	Molecular biology techniques (reverse transcription polymerase chain reaction (RT-PCR))		

of groups of patients who should be considered for reduction of treatment intensity in order to avoid the side effects associated with oncological treatment, or the use of a more aggressive therapeutic approach in patients at high risk of relapse. The observation that high levels of VEGF in the blood serum HL are associated with a poor prognosis suggests that VEGF may be a new prognostic factor [13, 14].

Role of the characteristics of microcirculation in tumour tissue

Studies on vascular morphology HL showed increased vessel diameter with increasing stage of the disease, but microvascular density (MVD) was found to be reduced with more advanced stage. It is speculated that this is due to the predominant effect of factors stimulating the differentiation of blood vessels, such as angiopoietin-1 and 2 and metalloproteinases, over the factors promoting the formation of new blood vessels such as VEGF, bFGF (basic fibroblast growth factor), and HGF (hepatic growth factor) [15]. In addition, it has been shown that the severity of angiogenesis examined on the basis of MVD/TVA (total vascular area) adversely affects the prognosis [16].

Role of expression of proangiogenic factors

Studies using immunohistochemistry have demonstrated the expression of several factors influencing angiogenesis. These include VEGF, FGF1 (fibroblast growth factor 1), FGF2 (fibroblast growth factor 2; basic fibroblast growth factor), FGFR2 (type 2 receptor for fibroblast growth factor), FGFR3 receptor (type 3 for fibroblast growth factor), PDGFR α (receptor for platelet-derived growth factor), HIF-1 α (hypoxia inducible factor 1), matrix metalloproteinases (MMP2 and

MMP9), as well as tissue inhibitor of metalloproteinase (TIMP) [15, 17–19]. In another study, the expression of VEGF was demonstrated, while expression of PDGF increased with disease progression as MVD [20]. Studies of receptor expression for pro-angiogenic factors on HRS cells are few but indicate a high percentage of VEGFR-1 and VEGFR-2 in HRS cells, lymphocytes, and histiocytes [21, 22].

Data on the process of angiogenesis in HL are scarce, and the results of studies are often contradictory. The potential of HRS cells to stimulate angiogenesis was shown in *in vitro* studies [17, 23]. HRS cells not only produce but also have the ability to secrete VEGF [17]. Another study found over-expression of FGF-2 in these cells, and this was confirmed by the study of RT-PCR [23].

Role of the microenvironment

The enumerated substances are known to stimulate angiogenesis factors and are secreted by HRS tumour cells. However, these cells constitute only about 1% of the tumour. The majority of the cells constitute reactive lymphocytes, eosinophils, macrophages, mast cells, plasma cells, fibroblasts, and others. Perhaps the effect on angiogenesis in this disease is not only the consequence of the direct stimulation of the process by cancer cells but also an indirect result of the interaction of the cells with the HRS microenvironment. The survival and proliferation of HRS cells depend not only on the genetic changes but also on the interaction of these cells with the microenvironment. This type of dependency is mediated by the secretion of inflammatory cytokines and chemokines by the cells of the HL, as well as by the protection of the tumour cells from elimination by the immune system. Animal studies suggest that mast cells of the microenvironment HL promote neovascularisation and fibrosis, which can be inhibited by bortezomib [21].

Infiltration of the inflammatory cells in HL can support tumour growth and neovascularisation. Macro-

phage infiltration appears to be particularly interesting. A significant correlation between the expression of CD163 (a marker of monocytes and macrophages) and MVD is documented, suggesting that tumour-associated macrophages can enhance angiogenesis and deteriorate the prognosis [24]. Another study showed that there is no effect of mast cell infiltrations on the number of microvessels [25]. Some of the known factors that promote angiogenesis, like HGF, can be expressed in the cell microenvironment and directly stimulate cell growth HRS [26]. Factors associated with angiogenesis may be linked with the generation of a protective immunological environment for neoplastic cells. For example, TGF- β inhibits cytotoxic T-lymphocytes, and PGE-2 reduces T-cell activation [26].

Serum concentrations of proangiogenic substances

The concentration of certain angiogenic substances, such as VEGF, bFGF, and HGF, is significantly elevated in patients with HL [27–31]. Augmented levels of VEGF and bFGF were reduced due to effective treatment, but both pre- and post-treatment high levels affect the survival of the patients [27]. High levels of VEGF were associated with a higher stage of the disease [28]. The persistently elevated level of VEGF in patients with HL even after achieving a complete remission compared to the levels in healthy subjects is an interesting observation [29]. VEGF levels may be different for different subtypes of HL; higher values were observed in classical HL compared to patients with nodular lymphocyte-predominant HL [30]. In another study, it was shown that VEGF-C was significantly higher compared to the levels in healthy subjects, indicating that this isoform participates in the stimulation of angiogenesis in HL [31].

Circulating vascular endothelial progenitor cells

The correlation between the number of circulating vascular endothelial progenitor cells (CEPC) and the degree of advancement in non-Hodgkin's lymphoma has been demonstrated; however, the data referring to HL in this respect are still non-existent [32]. The role of this cell population in the process of angiogenesis and progression of HL still remain unidentified.

Inhibition of angiogenesis as a therapeutic target in HL

Clinical trials using inhibitors of angiogenesis in cancer are focused on the pharmacological modi-

fication of this process at many different steps. The main groups of antiangiogenic drugs used in cancer treatment include antagonists of the angiogenic factors (anti-VEGF monoclonal antibodies, soluble receptors for VEGF), blockers of receptor signalling (for VEGFR2 or PDGFR), endogenous angiogenesis inhibitors (angiostatin, endostatin), metalloproteinase inhibitors, and anti-inflammatory drugs [33]. Antibodies to VEGF are a typical example of anti-angiogenic therapy but are not routinely used in the treatment of HL. Drugs such as thalidomide, lenalidomide, bortezomib, and histone deacetylase inhibitors may also have their effects by inhibition of angiogenesis. These drugs have been studied in patients with relapsed HL with moderate activity [32].

Concluding remarks

An overview of the research points to the importance of angiogenesis in the pathogenesis of HL. Activation of the VEGF-VEGFR axis may affect both the survival and proliferation of lymphoma cells. Recent studies indicate an important role of the circulating receptors VEGF-A or sVEGFR1 and sVEGFR2 as natural inhibitors of angiogenesis involved in the control of the angiogenic potential of the blood of patients with cancer. The analysis of the literature indicates that there are no data concerning the levels of sVEGFR1 and sVEGFR2 in the blood of patients with HL. Details of the effect of the lymphangiogenesis phenomenon on the biology of the HL are still unknown.

Elements of the angiogenesis regulating system are of interest as potential prognostic factors, and the identification of these factors may in the future have an impact on the decisions to intensify or reduce the intensity of treatment in individual cases. The presented review of studies on the angiogenesis suggests that the balance between proangiogenic and anti-angiogenic factors in the HL can be moved toward the growth of new blood vessels. The information provided in this article suggests that further research is needed to evaluate the mechanisms regulating angiogenesis in this disease.

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