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Neoangiogenesis - forming an effective network of blood vessels as a critical determinant of tumor development

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Abstract

The development of a tumor in the early stages of growth is associated with the delivery of nutrients and oxygen to the tumor cells by diffusion from the surrounding healthy tissue, while in the

later stages, when the tumor size is so large that it begins to lack oxygen and nutrients, comes to neoangiogenesis - the formation of blood vessels in the area of the affected tissue. Tumor vessels are leaky, winding and have a lot of bottlenecks and dead-ends. Abnormalities of blood vessels anatomy determine the deceleration rate and residual blood flow. Tumor vascularization affects its local growth, and in the case of tumors with the potential to distant metastases, the increase vascularity of tumor by increasing the density of the blood vessel network is directly proportional to the risk of distant metastasis. The aim of the study was to summary the role of the formation of tumor blood vessels in the context of the development of tumors.

Keywords: tumour vascularization, neoangiogenesis

1. Introduction

Tumor angiogenesis is a process that involves the creation of new blood vessels and occurs in the course of many cancers. The initial development of cancer cells is dependent on a cellular neighbour, from which it derives vital substances. The increase in the number of tumour cells determines the need for additional demand substances necessary for further development, in this case, tumor tissue induces false signals relative to the circulatory system, as a consequence of the new network is formed blood vessels, while the tumour tissue dependent. Tumor angiogenesis plays an important role in the progression and metastasis [1].

2. Purpose of work

The aim of the study is to determine the role of the formation of tumour blood vessels in the context of the development of tumours.

3. Description of knowledge

The creation of new blood vessels can be carried out on the basis of vasculogenesis and angiogenesis. In the first case, this relates to the formation of blood vessels from hemangioblast that arises in blood islands of the yolk sac of the embryo, the end result of this process is to produce a primary vascular plexus [2-4]. Formation of the blood in the later stages of their formation, followed by vascular endothelium existing and it is related to angiogenesis. The process formation of blood vessels is an important aspect in embryogenesis and plays a key role in the phenomena of physiological and pathophysiological [2,4-6]. The development of a tumour is associated with the process of angiogenesis, which contributes to its growth, and what is important in the clinical aspect allows metastasis.

In the sixties of the twentieth century, research on tumour angiogenesis was highlighted, among other things, Judah Folkman, first hypothesized that a malignant tumour cannot

develop if he could not produce the relevant supply lines, a network of blood vessels. Folkman professional experience as a surgeon allowed to find much evidence of his hypothesis, because all tumours that were operated by him, was characterized by abundant blood supply made possible by the presence of a delicate and twisted blood vessels. Conclusion Folkman was clear that capillary cells to deliver oxygen and nutrients and remove waste products of metabolic processes in cells. A tumour can survive only if when provided with a plurality of capillaries. Under physiological conditions, blood vessels arise when it is necessary to heal all wounds, or after menstruation. The mechanism of angiogenesis is regulated properly and is under the strict control of the body [6]. In the case of cancer cells, they have the ability to take control of the process of angiogenesis, so as to enable tumour growth. Folkman based on his research drew the following conclusions [5-7]:

- micro-tumours to enter the dangerous stage of cancer need to create a new network of blood vessels that provide it nourishment;
- micro-tumours produce angiogenin, a chemical that makes the blood vessels to approach a tumour and produce new branches;
- caused cancer cells that spread throughout the body, or metastasize are dangerous when they cause the creation of new blood vessels;
- Primary tumours are the source of metastases to strengthen its autonomy, angiostatin produces a substance that inhibits the growth of new blood vessels, thus lead to reduce the impact on the body distant colonies.

As mentioned above, in the case of tumour tissue angiogenesis gets out of the controls, and tumour cells in a continuous release growth factors, angiogenic character. Neovascularization of tumour growth increases as a result of perfusion and paracrine actions, the manufacture of growth factors to tumour cells endothelial cells, whereas the same process of neovascularization in the following sequence [8-9]:

- activation of endothelial cells inside the blood vessel and expansion of stem;
- degradation of the basement membrane and extracellular matrix;
- migration of activated endothelial cells from the parent vessel into the factors stimulating angiogenesis;
- the proliferation of endothelial cells;
- formation of light and loop of new vessels;
- forming a basement membrane, incorporation of pericytes and smooth muscle cells (in the case of some blood).

In the case of endothelial cells, the newly formed loops a vascular tumour characterized by [10]:

- abnormal shape;
- wrong size;
- wide intercellular connections;
- irregularity in the course of blood;
- leaky basement membrane.

Compared to normal physiological blood, vessel tumour characterized by incomplete differentiation of arteriovenous and incomplete differentiation of perivascular space, while the blood flow is temporally and spatially variable [11].

The process of neoangiogenesis governed by factors produced by tumour cells and the host, and the origin can be divided into [4-9]:

- endocrine diseases (of the blood flow);
- paracrine (adjacent the tumour stroma, the inflammatory cells or the extracellular matrix);
- autocrine (same with endothelial cells).

One major regulator of angiogenesis and vasculogenesis is vascular endothelial growth factor (VEGF) is the most powerful and specific endothelial cell growth factor but has no activity against other types of cells [15-16].

The results of numerous studies show expression of VEGF in cells of tumours - cancer [17-19]:

- lungs;
- breast;
- gastric cancer;
- kidney;
- bladder;
- ovary;
- stem and cervical cancer;
- hemangiosarcoma cells;
- cells of glioblastoma multiforme.

The most frequently cited endogenous stimulators and inhibitors of angiogenesis are shown in Tables 1 and 2.

Table 1. Selected endogenous stimulators of angiogenesis

Endogenous angiogenesis stimulators	
Vascular endothelial growth factor	VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E
Placental growth factor	PlGF
Fibroblast growth factor	FGF-1, FGF-2, FGF-3, FGF-4, FGF-5
Angiogenin	ANG
Angiopoietin-1	ANGPT-1
Hepatocyte growth factor	HGF
Transforming growth factor-β	TGF-β
Insulin-like growth factor	IGF
Tissue factor	TF
Platelet-derived growth factor	PDGF
Platelet-derived endothelial cell growth factor	PD-ECGF
Interleukin-8	IL-8
Proliferin	PLF
Prostaglandin E-	PG-E

Source: Own calculations based on [8-9,12-14].

Table 2. Selecting endogenous angiogenesis inhibitors

Endogenous inhibitors of angiogenesis	
Angiostatin	AS
Angiopoietin 2	ANGPT-2
Endostatin	ES
Restin	RSN
Vasostatin-1	VS-1
N-terminal platelet factor (4) fragments	PF4
N-terminal fragments prolactin	PRL
Proliferin-related protein	PRP
Antithrombin III fragments	AT III
Thrombospondin 1	TSP-1
Product of digestion of osteopontin	OPN
Interferon alfa	IFN-α
Interferon beta	IFN-β

Source: Own calculations based on [8-9,12-14].

Other studies have demonstrated the presence of the relationship between the degree of tumour vascularity of a tumour and the expression of VEGF, as well as elevated levels of

VEGF in patients in whom cancer (breast, stomach, lung). It is noteworthy that patients who reported a higher concentration of VEGF in worse prognosis with respect to patients with low levels [20-21].

The microcirculation of tumours is essential for the metabolism and specific behaviour of the tumour tissue. When the processes occur in tumour growth, while there is very often necrosis in the central portion thereof. This is due to progressive renal functional and angiogenic tumour vasculature and tumour vascular degeneration. The simultaneous occurrence of both of these processes, typical of a tumour vascular system makes the spatial arrangement of living tissue tumour model reproduces substantially surround the active vasculature. There is no doubt that in the case it is possible to block angiogenesis inhibition of not only the primary tumour but also of metastatic [22-25].

In 1994, as a result of experimental studies in mice, the first angiostatin inhibitor - angiostatin - was diagnosed. This substance confirmed its effectiveness in the treatment of various types of experimental mouse and human tumors [26]. In 1997, Thomas Boehm and his colleagues showed that endostatin, angiostatin, inhibits the formation of blood vessels in three therapies of tumor-forming tumors after implantation under the skin of mice [27] (Figure 1).

In the process of tumour growth, we deal with both the mechanisms that stimulate new blood vessel formation, as well as from processes which for reasons unknown factors leads to the synthesis of anti-angiogenic activity (Figure 2).

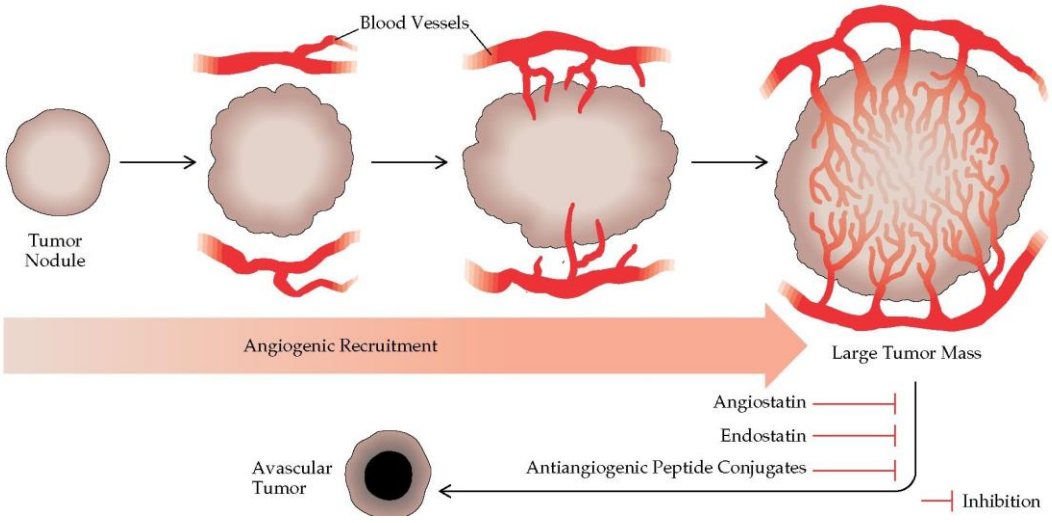

Figure 1. Inhibition of tumour microcirculation [28].

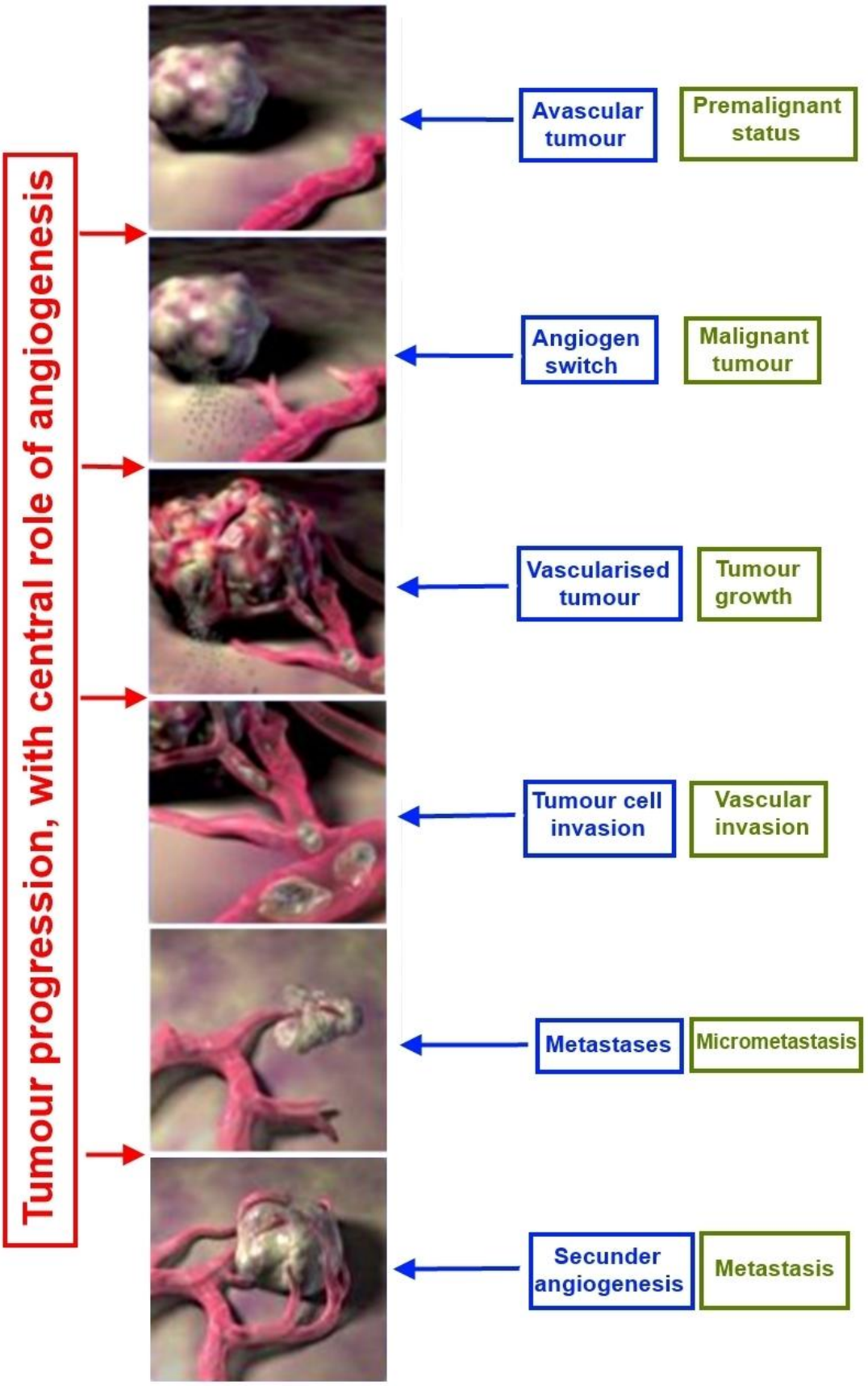

Figure 2. The role of angiogenesis in tumor growth [29].

There are two methods for inhibiting tumour angiogenesis. The first of these is the classic inhibitors of angiogenesis (targeted therapy), which inhibit the proliferation and neovascularization. The second group includes substances that destroy existing vessels, leading to necrosis of a tumour. Drugs inhibiting angiogenesis in a tumour, leading to its death by cutting of life-giving blood. Antiangiogenic agents are used as monotherapy (independently) in situations when it comes to the longest inhibition of tumour growth classified as incurable. There are natural methods, which strongly affect angiogenesis without causing side effects, and which can be combined with conventional therapy [30].

These are:

1. The specific diet rich in foods that inhibit angiogenesis, for example. Certain types of green tea, spices and herbs;

2. Anything that contributes to the elimination of inflammation, which are the direct cause of the development of new blood vessels.

4. Conclusions

In terms of the complex issues of the vascular system resulting from neoangiogenesis on the way, it is necessary to continue further research at the genetic level that will contribute to the mechanism of microcirculation of cancer tissue and will be an invaluable source of information not only in scientific but also clinical and diagnostic.

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