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Review

MORPHOLOGICAL CHARACTERISTICS OF THE STROMA IN MALIGNAT EPITHELIAL NEOPLASMS WITH SHORT REVIEW OF SKIN SQUAMOUS CELL CARCINOMA

Lena Kakasheva-Mazhenkovska[1], Vesna Janevska[2], Gordana Petrushevska[2], Liljana Spasevska[2] and Neli Basheska[3]

[1]Institute of Histology and Embryology, [2]Institute of Pathology, [3]Department of Histopathology and Clinical Cytology, University Clinic of Radiotherapy and Oncology, University "Ss. Cyril and Methodius", Faculty of Medicine, Skopje, Republic of Macedonia

Abstract

The stroma of the neoplasm is a highly complex structure built by: specialized mesenchymal cells typical for each tissue surroundings, cancer associated fibroblast/myofibroblast, congenital or acquired immune cells, vascular network with endothelial cells and pericytes, mastocytes, macrophages, leukocytes and adipocytes, all together incorporated in the extracellular matrix. Each neoplasm produces its own unique microenvironment where the tumor grows and modifies. Although most of the cells of the host in the stroma have compulsory tumor suppressor ability, the stroma is changing during the malignant process and it even promotes growth, invasion and metastasis. Genetic changes that occur during the development of the cancer, which are guided by the malignant cells lead to changes in the stroma of the host that will overtake it and adjust it to their own needs. In the early stages of the tumor development and invasion, the basal membrane is degraded and the stroma becomes active and contains an increased number of fibroblasts, inflammatory infiltrate and newly composed capillaries which come into direct contact with the tumor cells. These changes lead to cancer invasion.

Key words: stromatogenesis, cancer associated fibroblast/ myofibroblast, matrix metalloproteinase, angiogenesis, squamous cell carcinoma

Introduction

The skin is situated between the external and the internal environment and is considered as a structurally complex, multifunctional and sophisticated vital organ, the biggest in the human body, specialized to carry out important functions with coordinated cell molecular appearance.
The external influences, first of all the increased exposure to sun, i.e. the ultraviolet radiation, living in polluted environment, the usage of different chemical substances, alcohol, nicotine, the HPV infection, arsenic poisoning, the process of industrialization in the bigger cities, the bad influence of the industrial oil and tar, the chemical substances such as vinyl chloride, polycyclic aromatic hydrocarbons, the exposure to fuel and gasoline evaporation or similar, are some of the factors that cause skin changes of different type [1,2].
In the last decade we have been witnesses of an increased rate of skin cancer as a result of the ultraviolet radiation. Of all skin cancers, around 95% belong to non-melanoma cancer and the squamous cell carcinoma represents 20% of them. Although this cancer is found in a lower percentage it might cause metastasis and death, and hence it is in the first five causers of cancer death around the world [3].

Squamous cell carcinoma

The squamous cell carcinoma (SCC) is a malignant neoplasm of the epidermal keratinocyte. This type of tumor varies according to the clinical appearance depending on the lesion and on the development. On different locations it shows differences regarding symptomatology, origin of the disease, prognosis and treatment of the disease [4,5].
Apart from the above mentioned causes for the skin changes, the main etiological factors in the squamous cell carcinoma are: ultraviolet B radiation, radiological radiation, previous skin burns, inflammatory lesions and long-term skin ulcerations, HPV infections, arsenic poisoning, tars and industrial carcinogen.
Squamous cell carcinoma can be found more often in people with transplanted organs as a result of immunosuppression. This type of cancer appears mostly on the uncovered body parts that are directly exposed to sun, such as: forehead, face, ears, scalp, neck, arms and lips (vermillion). It is more common in older people, young people that have light tan, blonde hair and light colored eyes are more affected. In the highly developed countries, the annual incidence is 166 cases per 100.000 citizens. The incidence is higher in the countries near the equator where the percentage of the diseased is significantly higher. This cancer rarely appears in the black population. In our country we do not have precise data for this skin cancer

Correspondence to: Lena Kakasheva-Mazhenkovska, Institute of Histology and Embryology, "50 Divizija 6", 1000 Skopje, R. Macedonia; Phone: 075 476 697; E-mail: lena59kate@yahoo.com

[5]. Data from the Institute of Public Health of the Republic of Macedonia cover two categories of malignant skin neoplasm: malignant melanoma of the skin and other malignant neoplasm of the skin that include squamous cell carcinoma, basal-cell carcinoma and malignant neoplasm of the sweat and sebaceous glands.
The external skin changes that can be detected by eye in the squamous cell carcinoma, in the previously mentioned areas are mostly presented as shallow ulcers, often with keratinous crust and elevated, indurated surrounds, or as plaques or nodules [6].
Squamous cell carcinoma consists of nests, sheets and strands of squamous epithelial cells which arise from the epidermis and extend into the dermis for a variable distance. The cells have abundant eosinophilic cytoplasm, a large often vesicular nucleus with prominent nucleolus, some of them are hyperchromatic and show dyskeratosis and numerous mitosis. There is variable central keratinization and horn pearls formation, depending on the differentiation of the tumor. The degree of anaplasia in the tumor nests is used to determine the differentiation of the tumor and the categorization of well differentiated, moderately and poorly differentiated tumor. Squamous cell carcinomas occasionally infiltrate along nerve sheaths, the adventitia of blood vessels, lymphatics and fascial planes. The presence of perineural lymphocytes is a sign of spreading of the cancer in the deeper parts [6]. In the periphery of the neoplasm a variable quantity of inflammatory infiltrate may exist. Rare histological variants of SCC include clear-cell, signet-ring, pigment, basaloid and rhabdoid types. The cells of the squamous cell carcinoma are positive to the epithelial membrane antigen and cytokeratin [6,7].
Skin squamous cell carcinoma mainly show local aggression and can appear in several modalities. It has aggressive course in patients who are infected by HPV. The tumors with deep invasion, poor differentiation, perineural invasion and acantholysis features are more likely to recur or metastasize. The risk of metastasis in skin damaged by sun radiation is low and is around 0.5%, while in cancers in areas unexposed to the sun the risk is higher and is between 2-3%. The risk is even higher if the tumor is located on the lips, vulva, perineum, penis, as well as on the so-called Marjolin′s ulcer, radiation scar or thermal burns. The tumor invasion depth is a prognostic variable. Cancers with invasion depth of the smaller than 2 mm can rarely lead to metastases, tumors between 2 and 5 mm invasion depth have a medium risk of around 5% to lead to metastases, while tumors with invasion depth larger than 5 mm have a high risk to metastasize which is around 20%. Tumors that are bigger than 2 cm in diameter have a higher risk of recurrence and metastasis, compared to the smaller lesions [8].
Skin squamous cell carcinomas have a wide spectrum of different shapes, from indolent tumors with low metastasis potential, to aggressive tumors with high invasion potential. Distinctions of the different shapes of this cancer can only be done with microscopic analyses that can provide the exact diagnosis and determine the further treatment [9].

The tumor stroma

The tumors structurally contain **parenchyma** built of tumor cells, specific for each tumor type and **stroma** structure that originate from the host and is built of connective tissue, blood vessels and inflammatory cells. If there is no stroma the tumor cells cannot survive and grow, because they take from it all that is necessary for their survival, growth and spreading. The stroma is not only a supportive element of the neoplasm, but also a new shaped and modified place by the parenchyma cells, where mutual and continuous interaction between the components of the neoplasm exists [10].
The stroma of the neoplasm is a highly complex structure built of specialized mesenchymal cells typical for each tissue surrounding, cancer associated fibroblasts (CAFs)/ myofibroblasts, congenital and acquired immune cells, vascular network with endothelial cells and pericytes, mastocytes, macrophages, leukocytes and adipocytes, all together incorporated in the extracellular matrix (ECM). The extracellular matrix is built of structural proteins (collagen and elastin), specialized proteins (fibrillin, fibronectin and elastin) and proteoglycans. Each of the neoplasms creates its unique microenvironment where the tumor grows and modifies. Although most of the cells of the host in the stroma have suppression ability, the stroma is changing during the malignant process and it even promotes growth, invasion and metastasis [11]. The genetic changes that occur during the development of the cancer, which are guided by the malignant cells lead to changes in the stroma of the host that will overtake it and adjust to their own needs. In the early stages of the tumor development and invasion, the basal membrane is degraded and the stroma becomes active and contains increased number of fibroblasts, inflammatory infiltrate and newly composed capillaries which come into direct contact with the tumor cells. These changes lead to cancer invasion [12].
Stromatogenesis is the formation of a new, specific type of stroma at sites of active cell tumor cell invasion as an integral part of the invading process. The new stroma is produced and is managed by the invasive tumor cells with absolute tolerance and with participation of the local fibroblasts of the host. Stromatogenesis is not the formation of theusual reactive fibrosis that surrounds benign neoplasms (fibrous capsule) nor is it the formation of avascular connective tissue that fills the gap of a wound (scar tissue) and forms the fibrous floor of a chronic peptic ulcer (zone of cicatrization).
The new stroma is stranger in the structure of the normal tissue, supports the invasion of the tumor cells and the migration of the endothelial cells and is not aimed at maintaining and delaying of the neoplastic process.
Stromatogenesis can be compared to a railway upon which the train slips, and the fast train is the invasive tumor [13].

During the process of carcinogenesis, the tumor cells interact with the nearby tumor surrounding tissues including the ECM growth factors, cytokines, all together being in mutual association with ECM, as well as with the nearby endothelial cells, fibroblasts, macrophages, mastocytes, neutrophils, pericytes and adipocytes. The four features of the cancers (migration, invasion, metastasis and angiogenesis) are dependent on the nearby micro-surrounding. The key players in this process are the matrix metalloproteinases (MMP) because they break the different cell adhesion molecules, modulate the connections between the cells and the connections of the cells with the ECM [14,15].

What happens during the malignant process that leads to the process where the malignant cells break the normal tissue barriers and cause invasion?

It is believed that the following mechanisms are included:

- The mechanic pressure caused by the enormous production of the malignant cells along the tissue levels with lowest resistance;
- The weakening of the tumor cell adhesions-loss of the surface molecules of the cadherins and integrins;
- Increased motility of tumor cells/amoeboid movement through secretion of motogen cytokines with appearance of increased number of receptors for growth factors;
- Degradation of the extracellular matrix through release of more proteolytic enzymes, i.e. metalloproteases, collagenases, plasminogens, cathepsinasis etc.
- The angiogenesis stimulation through secretion of the vascular endothelial growth factors (VEGF) and tymidine phosphorylase (TP), increasing the survival of the malignant cells and their penetration in the circulation.

ECM is a dynamic structure that manages the survival of the cells along with all factors of that ECM. The proteolytic activity of MMP is necessary for the cancer cells to break the physical barriers during the local tumor expansion as well as during intravasation in the nearby blood vessels, coming out of the circulation and further locations. During the invasion, locally MMPs stimulate the production of specialized structures on the surface of the cells, the so-called invadopodia that support the invasion. These structures exist everywhere, where ECM degrades. Through the transmembrane invadopodia-related proteinases on the local place are activating the MMPs such as MMP-2 and MMP-9 and they degrade the different ECM molecules and provide the invasion.

There are several mechanisms which MMP participate in the tumor cell proliferation. In fact they modulate the bioavailability of the growth factors and the functions of the surface cell receptors. The members of the MMP release cell membrane precursors for the insulin-like growth factor (IGF) and the epidermal growth factor (EGF) that support the proliferation. MMP -1,-2,-3,-7,-9,-11 and -19 connect to the IGF connecting protein and regulating the bioavailability of the growth factor. EGF is a mediator of the proliferation and is involved in the cancer progression because exists in 1/3 of the tumors [16].

Many studies have pointed out the interaction between glycose aminoglycans, matrix metalloproteinase and growth factors leads to activation of the pro-matrix metalloproteinase and their proliferation effects. It means that the glycosaminoglycans (GAGs) recruit the matrix metalloproteinase (MMPs) to release the growth factors (GFs) from the cell surface which induces proliferation of the cancer cells. MMP also play a role in the tumor angiogenesis, MMP-2,-9 and MMP-14 being the key players, and MMP-1 and -7 are less important. Production of new blood vessels is necessary for the cancer cells in order to continuously grow and start to migrate. The first step in eliminating the physical barriers in ECM is its degradation and the appearance of pro-angiogenesis factors. MMP-9 is the main initiator in the activation of the angiogenesis process since it increases the bioavailability of the important factors included in this process, such as vascular endothelial growth factor and it is the potent mediator in the tumor vasculature, as well as human basic fibroblast growth factor (bFBGF), by degradation of the extracellular components such as collagen type IV, VIII and perlecan, in the order given. The angiogenesis balance is strongly regulated by the MMPs because they can decrease the formation of the blood vessels through release of tumstatin, endostatin, angiostatin and endorepellin, which are products of the degradation of collagen type 4 and type 17, as well as plasminogen and perlecan. During the carcinogenesis the epithelial cells lose the polarity and they have tendency to take on mesenchymal phenotype and consequently the intracellular interactions reduce and the migration capacity increases. This is done by MMP-2,-3,-9,-13,-14. The communication between the cells is disordered because of the elimination of e-cadherins, thus breaking the cell adhesions and inductions of ECM, and resulting in an increased cell migration [17].

By degradation of the ECM components and the other extracellular molecules appear fragments with new bioactivities appear that can inhibit the angiogenesis. For instance, active endostatin appears during tearing of collagen type XVIII under the influence of MMP -3,-7,-9,-13,-20. Also with tearing of collagen type IVa3 by MMP-9 tumstatin, potent suppressor of the angiogenesis is obtained. This is confirmed with the pathological vascularisation and increased tumor growth in the MMP-9 deficient mices. During the degradation of plasminogen by the MMP-2,-9 and -12, significant amount of angiostatin can be produced, a product with anti-angiogenic function. It means that the MMP can generate angiogenesis inhibition, as well as angiogenesis stimulation. The role of the MMP on lymphangiogenesis has been presented in a small number of cases. It has been reported that the MMPs increase the bioavailability of the vascular endothelial growth factor, especially MMP-9 and this supports the lymphangiogenesis and guides and promotes the spreading of metastasis in the lymph. This

has been shown in experiments done on tridimensional cultures where fragments of ductus thoracicus of mice incorporated in collagen gel have been used, and formation of lymph capillaries in the lumen has been noticed. The increased presence of MMP-1, -2 and MMP-3 is associated with the lymph invasion and metastasis in the lymph nodes. The inhibition of MMP-2,-9 and -14 decreases the angiogenesis, the lymphogenesis and reduces the appearance of the metastasis in the lymph nodes [18,19].

In the stroma of the invasion front in the micro-invasive squamous cell carcinoma expression of MMP-9 was found [20]. The level of MMP-2 can serve as a predictive factor in the appearance of metastasis in the oral squamous cell carcinoma, and the high level of MMP-2 and -9 correlate with the invasion of the squamous cell carcinoma and the shorter general survival of the patients [21,22]. It was confirmed in one research that the MMP-1 can be found in some neoplastic nest of the SCC and in the stroma fibroblasts which surround the neoplastic epithelial cells [23]. It was also confirmed that MMP-9 protein was in correlation with angiogenesis markers and the worse general survival in the squamous cell carcinoma in the head and neck [24]. The increased expression of the MMP-9 and -7 detected in the cancer cells is in correation with deeper tumor invasion [25]. MMP-3 can be found in the stroma cells which surround the tumor [26]. The MMP-7 and MMP-9 are expressed in the cells of the squamous cell carcinoma which are in contact with the stroma [27].

The cooperation between the epithelial and mesenchymal cells plays an essential role in the process of wound healings and tumor progression. It is well known that most of the epithelial tumors are characterized by accumulation of the connective tissue cells and extracellular material on local level. This phenomenon is called a stromal reaction. One of the cell elements of the stromal reaction are the myofibroblasts that are changed fibroblasts with acquired capacity for neo-expression of alpha smooth muscle actin, (a-SMA), isoform typical for the vascular smooth muscle cells which, apart from this feature, are capable of synthesizing a significant amount of collagen and other extracellular components [28]. This type of cells has a clear key role in the connective tissue remodeling that occurs, during wound healing and development of fibrosis. Myofibroblasts are capable of remodeling the connective tissues, but they also react with the epithelial cells and other connective tissue cells, and hence controlling the phenomena such as tumor invasion and angiogenesis. Fibroblasts and myofibroblasts are capable of producing collagen and extracellular proteins, creating desmoplastic reaction and they are key players in the development of the invasion process [29]. Desmoplasia is a process in which host cells respond to the inductive stimulus of the tumor cells. The stroma cells produce collagen, ECM proteins and initiate desmoplastic reaction for mediation in the invasion process of the tumor cells. Therefore, a question is raised whether the stroma around the cancer cells acts as a protective mechanism, or it accelerates the tumor activity. As it has been mentioned above, the stromal matrix degradation of the proteolytic enzymes is essential for cancer invasion and is associated with the inflammatory response. The deposition of stromal collagen by the myofibroblasts during the cancer invasion is associated with

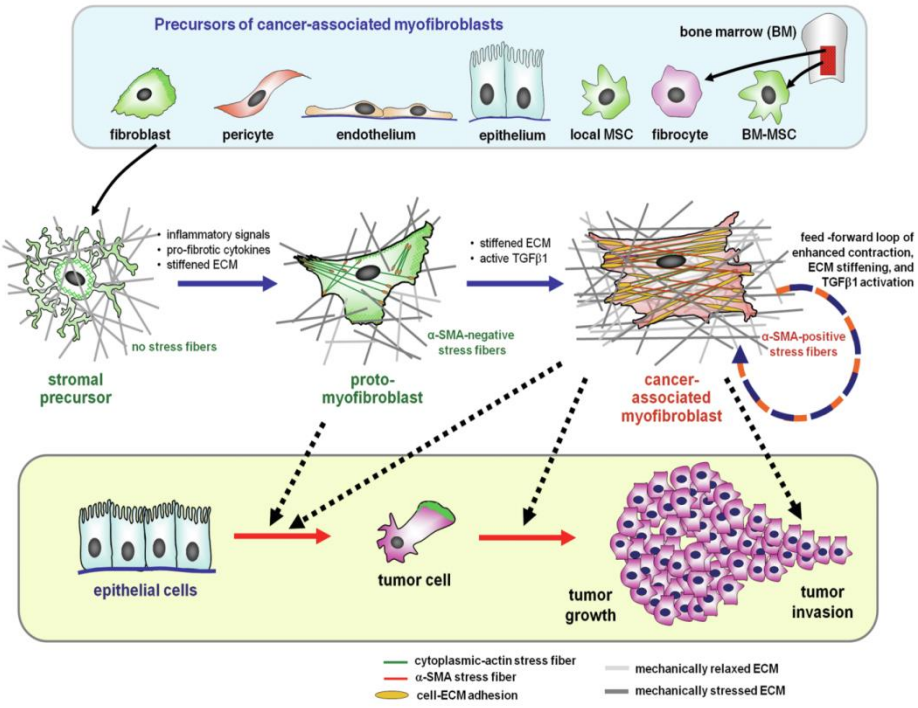

Fig. 1. The myofibroblast in the tumor stroma (from ref. Otranto M *et al*. [30])

desmoplasia. The myofibroblasts produce paracrine motility factor and cytokines such as hepatocyte growth factor (HGF) and fibroblast growth factor (FGF), which also initiate growth of blood vessels and increase the cancer invasion and the metastasis potential [30,31] (Figure 1). In the study that used immunohistochemical staining of myofibroblasts with a-SMA where samples from oral leukoplakia and squamous cancer were analyzed, has been confirmed that there were no myofibroblasts in the normal mucosa and in the oral leukoplakia, but that they existed in different quantity in the squamous cell carcinoma. Stromal myofibroblasts were also significantly more frequently found in the more invasive squamous cell carcinoma compared to those with smaller invasion [32]. The analysis of myofibroblasts marked with alpha smooth muscle actin and CD34 in the non-metastatic and metastatic oral squamous cell carcinoma has shown more a-SMA positive fibroblasts in the metastatic group of carcinomas [33]. It was also confirmed that the myofibroblasts are important component of the stroma in the oral squamous cell carcinoma and that their abundance can be associated with appearance of local recurrence and lower general survival [34], and that they are strong predictors of the invasion and the proliferation of the oral squamous cell carcinoma [35]. Analyzing the myofibroblasts and examining their presence in the stroma in kerato-acantoma and squamous cell carcinoma, it was found that these were significantly more common in the stroma of the squamous cell carcinoma [36].

Angiogenesis

The angiogenesis is a process of formation of new blood vessels from the existing normal capillaries. Tumors with higher angiogenesis activity belong to the category of very aggressive tumors with poor prognosis for the patients [37]. It is believed that the tumors which have more blood vessels than the others are angiogenetic. Tumors also show ability for expression of angiogenesis growth factors such as: VEGF, TP etc [38].
The tumor cells, stromal and tumor-associated macrophages secrete angiogenesis molecules which activate proliferation of endothelial cells, their migration and maturation by forming vascular channels. These activities are mainly achieved by the VEGF and less by TP. There is increased presence of these factors in the tumors with increased vascular density. Also the increased presence of hepatocyte growth factor, the basal fibroblast growth factor and some other interleukins may manifest angiogenesis activities. Weidner *et al*. were the first who used immunochemical staining of the endothelial cells in order to separate malignant tumors into rich angiogenesis and poor angiogenesis tumors. Tumors with increased vascular density may metastasize more often and have worse postoperative prognosis in different human malignomas [39].
Literature data point out that vascular channels are irregularly allocated in the neoplasm. There are areas with many of blood vessels, the so called hot spots on the periphery of the tumor neighboring the normal tissue [40]. This was firstly registered by Thompson *et al*. who described the vascular density in breast adenocarcinoma. They found out that the angiogenesis practically dominates on the invasion front of the tumor and that it can be found even more on the border between the normal tissue and the tumor. This finding helped the authors understand that the tumors get the vascularisation by the blood-vessel joining, and not by the vascular proliferation. Fox *et al*. confirmed the importance of the tumor periphery for the endothelial cell proliferation and suggest that the vascular channels in the internal tumor areas are in correlation with the continuous remodeling.
The analyses of samples from 151 patients with breast cancer and 178 with lung cancer confirmed these data [41]. Thus the vascular density on the hot spots in the tumor periphery was determined, i.e. the area that was appointed as T1 and in two internal zones, T2 (in the middle between the periphery and the center) and T3 (in the center of the tumor). The biggest vascular density was noticed in T1 zone near the normal tissue, and it was decreasing on the way to the internal part of the tumor, with variations depending on the different types of neoplasm. This tendency of the vascular regression from the periphery to the center is has also been confirmed by using antibody for recognition of VEGF and kinase insert domain receptor (KDR) complex that exists on the surface of the vascular endothelium. These blood vessels are numerous in the VEGF expression tumors. VEGF/KDR positive vascular density is bigger in the periphery of the tumor and on places where it touches the normal tissue, and it decreases in the internal tumor areas of VEGF-positive tumors, opposite of the fact that VEGF appears and distributes equally through the tumor stroma. This suggestis that during the tumor angiogenesis, the endothelial activity appears also in the normal tissue near the invasive tumor front [41].
The phenomenon of angiogenesis is seen parallel to the phenomenon of stromatogenesis on the places of active tumor cell invasion. The formed edematous light stroma is convenient for the endothelial cell migration and the proliferation of the tumor cells is facilitated. This fibrovascular proliferation (stromatogenesis/angiogenesis) together with the invasive tumor cells forms well-organized tumor cell area. The formation of new blood vessels and the stromatogenesis happen at the same time with the tumor cell invasion and are closely connected with the tumor metastasis. The conditions in the micro-surrounding of the tumor are not similar everywhere. The hypoxia, acidity, and lack of nutritione products, are dominant specifications in the tumor environment. The question that should be considered is how the tumor exists in the central parties of the neoplasm when the conditions are inappropriate. The explanation would be that the malignant cells and the young blood vessels are tolerant to hypoxia by activation of the glycolytic anarobic path-

ways. The internal circulation tolerates low oxygen concentration through activation of angiogeneis factors (VEGF, VEGF/KDR, TP, bFGF) and inhibitors of endothelial apoptosis (VEGF, bcl-2). VEGF is responsible not only for formation of new blood vessels, but also for inhibition of the endothelial cell apoptosis. By stimulation, endothelial production of nitric oxide (NO) and prostacyclin (PG12) is induced and thus anti-apoptosis is provoked. By the antithrombotic effect VEGF also stops the thrombocytic aggregation, which supports the functional internal tumor vascularisation.

It is obvious that the tumor potential to stand lower vascularisation in the internal part of the tumor depends on the ability for secretion of proteins with anti-apoptosis features. They are produced and secreted from the tumor and the endothelial cells and in this way they determine the tumor feature-vascular survival ability (VSA). On the periphery of the tumor, the invasive malignant cells and newly shaped blood vessels in correlation with the non-malignant tissue are in a privileged position due to the existence of the normal vascular and lymph network. The blood vessels that supply the periphery are typical blood capillaries and the internal part of the tumor has blood vessels with different shape such as: irregularly shaped, dilated, tortuous and can have dead ends. These are not organized in venules, arterioles and capillaries, but rather share chaotic features. The blood vessels of the vascular network formed in the tumors contain wide splots and this is the cause of the bleeding in the surrounding tissues. The perivascular cells often become loosely associated or less abundant. Tumor veassels have cancers cells integrated in to the veassels walls. Blood flows irregularly in the tumor veassels, moving more slowly and sometimes even oscillating. The reason for this different shape is unknown, but it is believed that it is a result of disorder in the appearance and functioning of the angiogenesis factors. The question that needs an answer is related to primary role of the tumor blood vessels is there transport of oxygen and nutrition products to malignat cells or transport of malignant cells from the core of the tumor to the periphery? Maybe the defect walls on the blood vessels enable better proliferation of the malignant cells (Figure 2).

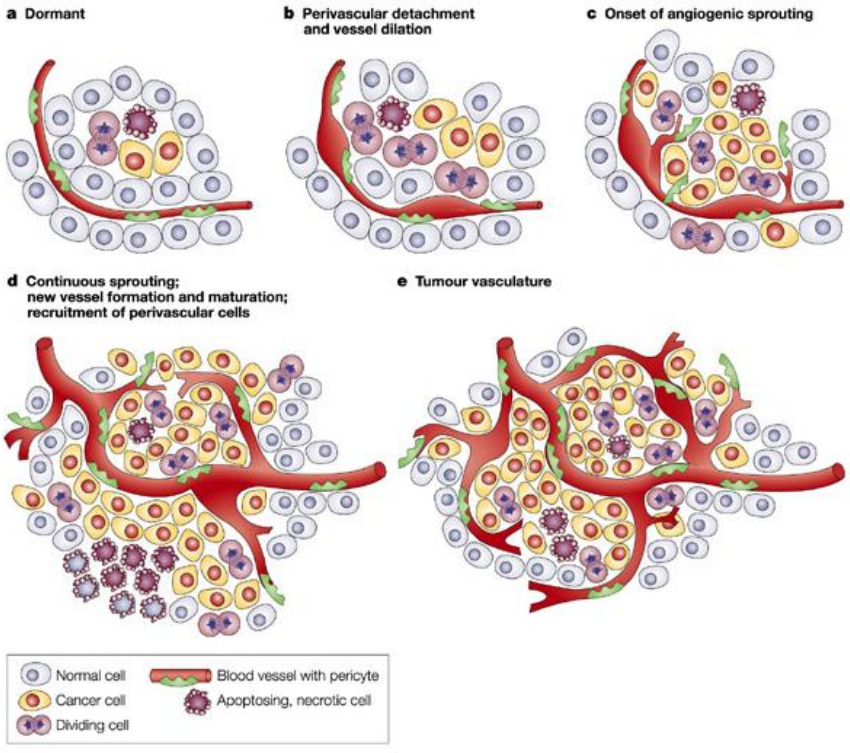

Fig. 2. The classical angiogenic switch (from ref. Bergers G *et al*. [39])

The angiogenesis in the squamous cell carcinoma is analyzed in tumors on more locations, in most of the cases in order to determine its role in the tumor progression or its aggression, and the prognosis of the disease. The analyzes of the angiogenesis in the solar keratosis in the low invasive and in the invasive squamous cell carcinoma, showed significant increase of the micro-vasculature in comparison with the nearby normal skin, indicating that the angiogenesis appears early in the development of the cutaneous squamous cell carcinoma and that the neo-vascularisation is parallel with the tumor progression [42]. The examinations on the density of the micro-vasculature in the squamous cell carcinoma and in the basal cell carcinoma of the skin with immunostaining with CD34 and the determination of the VEGF level showed that the relation between the bigger

micro-vascular density and the higher values of VEGF in the squamous histological type suggest a possible role of the angiogenesis in the determination of more aggressive types of cancer [43]. In the oral squamous carcinoma association between the micro-vascular density and positive lymph node metastasis indicates that the angiogenesis plays essential role in the oral carcinoma [44,45].

Conclusions

The stroma in the neoplasm does not only support the mechanic structures of the tumors, but also metabolic active environment where the cancer cells survive, multiply, provide tumor growth and through the formed vascular pathways enable further guidance to the circulation, so that the four features of the cancers are achieved: migration, invasion, angiogenesis and metastasis. The understanding of the molecular events in the process of stromatogenesis and angiogenesis is essential in the clinical researches where through the anti-angiogenesis or blocking of the enzymes included in the complex cell matrix interactions, relevant information is obtained that can be further included in the treatment protocol of the neoplasm.
The data on the stromal changes in the skin malignant neoplasm presented in the literature are mainly about the malignant melanoma. Compared to the other neoplasms, the data in the literature are relatively poor. The squamous cell carcinoma as a more common type of skin cancer needs further research, taking into consideration that most of the published studies are related to the oral squamous cell carcinoma. The cutaneous squamous cell carcinoma with the mechanisms of its invasion and metastasis, as well as the interactions between the epithelium and the stroma still remain unclear and can be considered as an interesting field of research, not only because of the frequent occurrence of this tumor, but also because of the access to materials for research. The elaboration of the above mentioned mechanisms has not only academic value, but could be considered as a basis for determination of prognosis and treatment modality.

Conflict of interest statement. None declared.

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