Formation of new microvessels on the basis of existing ones, or neoangiogenesis, is a requisite for tumor growth [1]. Abundance of microvessels in a tumor favors its rapid proliferation due to continuous nutrition and oxygen supply and elimination of toxic metabolic products. In recent years, more than 40 antiangiogenic drugs have passed phase II and III of clinical trials, and some proved to be efficient when combined with chemotherapeutics [2]. Nevertheless, most tumors do not respond to antiangiogenic therapy [3]. In addition to a series of rational explanations, heterogeneity of tumor vessels may be a key factor: classical angiogenesis in a tumor occurs in parallel with formation of mosaic vessels, and vessel co-option is also observed, providing tumor growth along vessels existing in a tissue [4].

It was found recently that cells of highly aggressive metastatic melanomas can form highly structured vascular channels bounded by basal membrane in the absence of endothelial cells (ECs) and fibroblasts [5]. Formation of vascular channels by aggressive tumor cells (TCs) was named vasculogenic mimicry (VM), which emphasizes formation of these channels de novo, without implication of ECs, i.e. independently of angiogenesis. Vascular channel formation is a unique feature of highly aggressive phenotype; poorly aggressive TCs cannot form such structures [6]. Formation of a channel network within the tumor is expected to maintain homeostasis and prevent premature necrosis within the tumor. Strong statistical correlation between VM and metastatic rate supports this hypothesis.

Vasculogenic mimicry is observed in various aggressive tumors, such as cancer of breast, prostate, ovary, lung, kidney, and soft tissue sarcoma [7], suggesting that it is a novel characteristic of aggressive tumor. VM has no physiological analogs in either adults or children, so it can be regarded as tumor-specific. The only exception is formation of placental vascular channels by cytotrophoblasts during embryogenesis. This fact opens novel possibilities for blocking tumor growth with minimal effect on normal physiological processes.

The basis of cancer disease is blockage of cell differentiation. Tumor cells undergo some dedifferentiation during tumor progression. First, they lose differentiation proteins whose absence gives a selective advantage for “proliferation self-sufficiency”. Moreover, a tumor with repressed function of programmed cell death, being monoclonal in its nature, acquires growing cellular polymorphism. DNA microchip analysis of gene expression profile has shown that highly aggressive melanoma cells compared with poorly aggressive ones express genes characteristic of endothelial, epithelial, hematopoietic, connective, muscular, and stem cells, suggesting partial genetic reversion of aggressive TCs into polypotent embryo-like
phenotype [8]. Highly aggressive TCs that can form VM channels also express genes implicated in angiogenesis. Despite high expression of VEGF, VEGFR1, VEGFR2, bFGF, bFGFR, COX-2, von Willebrand factor, VE-cadherin, and laminin-5γ2 in these cells, VM does not depend on angiogenesis in the tumor [9]. These cells also express matrix metalloproteinases MMP-1, -2, -9, and -14 modifying the extracellular matrix, which is necessary for classical angiogenesis [10]. Thus, highly aggressive TCs can imitate the behavior of ECs and initiate formation of vascular channels.

This review focuses on the molecular characteristics of VM, signaling pathways involved in VM, and clinical significance of VM in diagnosis of tumors and prognosis of cancer disease outcome.

FUNCTIONAL IMPORTANCE OF VM

Numerous recent studies have shown that the presence of VM channels in tumor material of patients correlates with rapid progression of the tumor, elevation of metastatic, and, as a consequence, short survival of patients [11]. Seftor et al. demonstrated high expression of blood clotting proteins in aggressive melanoma of the eye [12]. It is known that blood coagulation is initiated by tissue factor (TF). Deposition of fibrin in tumor vessels and thrombosis are prevented by TFPI-1 (tissue factor inhibitor 1) and TFPI-2 [13]. Both inhibitors are actively expressed in aggressive melanoma of the eye and are negligible in lowly aggressive melanoma. It is worth noting that in tumor material from patients both TFPI-1 and TFPI-2 are localized along the VM channels. The fact that VM-positive tumor, like ECs, supplies itself with an anticoagulation mechanism implies that VM channels are functionally active and can provide blood circulation within the tumor, particularly in zones of deep hypoxia. Involvement of tumor VM in blood microcirculation was demonstrated on a model of ischemic limbs [14]. Five days after injection of fluorescently labeled metastasizing melanoma cells into the mouse ischemic limb, a formation of “mosaic” vessels composed of ECs and TCs, as well as vascular channels formed by TCs was observed. This study has significantly altered our understanding of the role of VM.

Using dynamic resonance angiography and histological and immunohistochemical analysis of experimental breast tumor, a Japanese research group has shown that the vasculogenic component is predominantly localized in the central area, whereas neoangiogenesis predominantly occurs on the periphery [15]. Moreover, blood flow exists between neoangiogenic and VM loci, because a contrasting fluorescence dye stained both peripheral and central tumor areas. The dye did not accumulate in the central area of tumors lacking VM. Thus, in tumors VM is involved in the integrated system of blood circulation.

MOLECULAR DETERMINANTS OF VM

Ability to form a unique vascular network, which was first found in histological material of patients with uveal melanoma, was later confirmed in vitro on so-called 3D-cultures in gel matrixes (Matrigel and collagen gel) [16, 17]. A test for formation of capillary-like structures (CLS) in 3D-culture was developed initially for in vitro identification of angiogenesis inhibitors and activators [18]. ECs attached to the gel imitating the extracellular matrix and formed CLS. The cells of metastatic tumor were also capable of forming these structures (Fig. 1a). CLS formation in 3D-cultures is presently regarded as an in vitro model of VM [19].

**Fig. 1.** Formation of vascular channels in vitro. a) CLS; b) tubular structures.