METABOLIC MICROENVIRONMENT OF TUMOR CELLS: A KEY FACTOR IN MALIGNANT PROGRESSION

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The hostile metabolic microenvironment of solid tumors, which is quite heterogeneous both spatially and temporally (4-D-heterogeneity), can trigger malignant progression. Above all, acute and fluctuating hypoxia elicits multiple cellular response pathways that alter gene expression and phenotype (at moderate hypoxia with oxygen concentrations below 1%). Upon severe hypoxia (oxygen concentrations below 0.1%), genomic instability can lead to cell variants with adaptations favorable to survival. These cell variants have growth advantages in the hostile tumor microenvironment and finally expand through clonal selection thus promoting tumor aggressiveness. In addition to hypoxia, high lactate concentrations (above approximately 8 mM) may promote malignant progression. The interpretation of the role of tumor pH in tumor progression is complicated by the frequently occurring coexistence of tumor hypoxia and acidosis. Key Words: metabolic microenvironment, hypoxia, acidosis, lactate, glucose depletion, malignant progression.

The tumor microenvironment (i.e., the sophisticated «network» of different components, their multiple functions and activities, and complex interactions between cells (tumor, stromal and immune cells), the acellular matrix and soluble factors within malignant tumors) is known to be a key player for modulation of the metabolism, for tumor growth, progression and metastasis to distant sites, the development of acquired treatment resistance, and finally for poor patient prognosis [e.g., 1–6]. Pathophysiological conditions related to the abnormal microvascular network as well as heterogeneous and inadequate blood flow, both spatially and temporally (4-D-heterogeneity), substantially contribute to the development of a hostile microenvironment. Besides the abnormal microvascular network and the heterogeneous, aberrant microcirculation, high vascular permeability, distension of the interstitial fluid space, lack of functional lymphatics and high interstitial fluid pressures are components of the «pathophysiological» microenvironment [3]. In addition, the composition and activity of the stroma (stromal cells and acellular components) and immune cells attracted to tumor cells and factors secreted by cells, together all form the so-called «stromal» and «immunological» microenvironment [7–11].

In this mini-review, the consequences of the irregular structure and function of the tumor microcirculation and the flow-related, self-perpetuating hostile microenvironment (via a vicious circle) will be discussed. The following factors of the so-called «metabolic» microenvironment will be discussed: oxygen supply, tumor hypoxia and hypoxia-response processes, upregulation of glycolysis and lactate accumulation, extracellular acidosis and nutrient deprivation. Other factors of the «metabolic» microenvironment such as energy depletion, adenosine accumulation, the tumor redox state and the role of reactive oxygen species, which can alter the behavior of cancer cells and can also lead to adaptive changes in metabolism, malignant progression and development of acquired treatment resistance [2, 12] will not be discussed here, although they are part of the co-operative network responsible for malignant progression.

Hypoxia and malignant progression. In general, chronic hypoxia (i.e., hypoxia lasting longer than 2 hrs) can limit cell proliferation, tumor growth and tumor progression [4, 13, 14], whereas acute, fluctuating or cyclic hypoxia (shorter than 2 hrs) can promote tumor aggressiveness. This «bipolar» phenomenon is called the «Janus face» of tumor hypoxia [2]. Four possible levels of intervention have been described for hypoxia as a driving force in malignant progression:

1) At the transcriptome level, leading to hypoxia-induced, transient changes in gene expression coordinated/orchestrated by a special set of hypoxia-responsive transcription factors, such as the hypoxia-inducible factors (HIFs), nuclear factor-kappaB, activator protein-1 (AP1), indicating redundancy in biological mechanisms as a hallmark of malignant tumors upon exposure to less than 1% oxygen (7 mmHg). Besides these mechanisms, two additional oxygen-sensitive signaling pathways have also been identified, namely signaling through inhibition of the mammalian target of rapamycin (mTOR) kinase and signaling through activation of the unfolded protein response (UPR) [15–17]. Although these different signaling pathways are activated independently, there is evidence that HIF-1α, mTOR- and UPR-dependent responses to hypoxia act in an integrated way [15].

HIF-independent hypoxia-induced proteins also include osteopontin. The latter is overexpressed during hypoxia and has been demonstrated to be involved in metastasis formation.

2) At the proteome and metabolome level via adaptive gene expression, post-transcriptional and post-translational modifications (below 1% oxygen). Changes in the proteome are facilitating angiogenesis, local inva-
tion, intra- and extravasation of tumor cells, cell survival, proliferation, increased metastasis and resistance to apoptosis. Adaptive alterations of the metabolome can lead, inter alia, to an elevated rate of glycolysis via up-regulation of glucose transporter-1 (GLUT-1) and key glycolytic enzymes. The final result is an accumulation of lactate in hypoxic tumor tissue (see below) [18].

(3) At the genome/epigenome level, hypoxia below 0.1% oxygen (0.7 mmHg) can induce genome and epigenome instability driving malignant progression [18].

(4) At the cell population level, severe hypoxia can promote tumor aggressiveness by clonal selection and clonal expansion according to phenotype fitness [19]. These driving forces not only affect tumor progression but they are also involved in the development of acquired treatment resistance [12, 20].

Lactate and malignant progression. Hypoxia shifts the balance of cellular energy production towards glycolysis with generation and subsequent accumulation of lactate [2]. In cancers of the uterine cervix, lactate concentrations ranged from 4–40 mM with a median of 14 mM. In head and neck cancers, the respective median concentration was 7 mM [21]. In the latter study high tumor lactate concentrations were associated with the subsequent development of nodal and distant metastases due to the possible upregulation of metastasis-associated genes [21]. In general, «high-lactate» tumors (with median concentrations above 8 mM) were associated with both a shorter overall survival and disease-free survival compared to «low-lactate» tumors [22].

In this context, it has to be mentioned that normoxic cancer cells, i.e., cells in the neighborhood of microvessels, can take up the lactate produced by hypoxic cells via the monocarboxylate transporter-1 (MCT-1) and can utilize it for oxidative phosphorylation instead of glucose. Although lactate is generally considered a waste product, it also serves as a prominent substrate that fuels the oxidative metabolism of normoxic cancer cells [23, 24].

Acidosis and malignant progression. Due to the excessive lactate production and subsequent release (via MCT-2 transporters) by hypoxic tumor cells, the extracellular space of tumors is acidic. A pH-gradient exists across the cell membrane (intracellular pH is higher than extracellular pH). This gradient is the reverse of normal tissues where the intracellular pH is lower than the extracellular pH [2, 25].

Cellular lactate production and release, however, cannot explain the full extent of acidosis observed in the extracellular compartment of solid tumors. Other key mechanisms contributing are ATP hydrolysis, glutaminolysis, carbon dioxide production and bicarbonate depletion [2].

In the experimental setting, acidosis has been shown to drive invasiveness, resistance to apoptosis and mutagenesis [26–29]. So far, only scarce data for an acidosis-driven malignant progression in vivo have been reported [27]. In many experiments the coexistence of tumor hypoxia and acidosis complicates the interpretation of the role of tumor pH in malignant progression [28].

Glucose deprivation and malignant progression. Cuver et al. [26] have shown that glucose starvation can increase the experimental metastatic ability of murine sarcoma cells in vitro. Based on these data, they discussed the possibility that tumor progression may be caused by facilitating the invasive step of the metastatic process. In these experiments no glucose was available in the medium. Whether these extreme hostile conditions play a relevant role in the in vivo setting is not known so far. Measured mean glucose concentrations in cancers of the uterine cervix in the clinical setting were rarely below 1 mM (=18 mg/dL). Only approximately 1% of the data assessed were below 0.2 mM [30].

CONCLUSIONS

There is clear evidence that a hostile metabolic microenvironment within tumors can elicit malignant progression Above all, acute/fluctuating hypoxia can trigger multiple cellular response pathways that alter gene expression and phenotype at moderate hypoxia levels (below 1%). Upon severe/extreme hypoxia (below 0.1%), genomic instability can lead to tumor cell variants which can survive the oxygen-depleted microenvironment due to expansion and selection processes. In addition to hypoxia, high lactate levels may trigger malignant progression. So far, the role of tumor acidosis in malignant progression in vivo remains unclear and needs further studies.

ACKNOWLEDGMENTS

The valuable assistance of Dr. Debra K. Kelleher in preparing this manuscript is greatly appreciated. This work has been supported by a grant from the Deutsche Krebshilfe (106758).

REFERENCES