Available online at www.sciencedirect.com
SCIENCE DIRECT®
Transfusion Clinique et Biologique 12 (2005) 5–10
TRANSFUSION CLINIQUE ET BIOLOGIQUE
http://france.elsevier.com/direct/TRACLI/

Original article

Hypoxia and anemia: effects on tumor biology and treatment resistance

L'hypoxie et l'anémie : effet sur la biologie des tumeurs et la résistance au traitement

Peter Vaupel *, Arnulf Mayer

Institute of Physiology and Pathophysiology, University of Mainz, Duesbergweg 6, 55099 Mainz, Germany

Abstract

In locally advanced solid tumors, oxygen (O_2) delivery is frequently reduced or even abolished. This is due to abnormalities of the tumor microvasculature, adverse diffusion geometries, and tumor-associated and/or therapy-induced anemia. Up to 50–60% of locally advanced solid tumors may exhibit hypoxic and/or anoxic tissue areas that are heterogeneously distributed within the tumor mass. In approximately 30% of pretreatment patients, a decreased O_2 transport capacity of the blood as a result of tumor-associated anemia can greatly contribute to the development of tumor hypoxia. While normal tissues can compensate for this O_2 deficiency status by a rise in blood flow rate, locally advanced tumors (or at least larger tumor areas) cannot adequately counteract the restriction in O_2 supply and thus the development of hypoxia. Hypoxia-induced alteration in gene expression and thus in the proteome (<1% O_2, or <7 mmHg), and/or genome changes (<0.1% O_2, or <0.7 mmHg) may promote tumor progression via mechanisms enabling cells to overcome nutritive deprivation, to escape from the hostile metabolic microenvironment and to favor unrestricted growth. Sustained hypoxia may thus lead to cellular changes resulting in a more clinically aggressive phenotype. In addition, hypoxia is known to directly or indirectly confer resistance to X- and γ-radiation, and some chemotherapies leading to treatment failures. Whereas strong evidence has accumulated that hypoxia plays a pivotal role in tumor progression and acquired treatment resistance, the mechanism(s) by which treatment efficacy and survival may be compromised by anemia (independent of hypoxia) are not fully understood.

Résumé

L'approvisionnement en oxygène est souvent réduit ou nul au niveau des tumeurs solides. Cette anomalie est secondaire à des troubles de la microcirculation et à la géométrie de la tumeur mais aussi à l'anémie liée à la maladie et/ou au traitement. De 50 à 60 % des tumeurs solides constituées sont le siège d'une hypoxie ou d'une anoxie. Environ 30 % des patients avant traitement ont une capacité réduite du transport de l'oxygène. Alors que les tissus sains peuvent s'adapter par une vasorégulation, ce n'est pas le cas des vaisseaux tumoraux. L'hypoxie induit l'expression de gènes codant pour des protéines favorisant la croissance. De plus l'hypoxie limite l'action de l'irradiation X ou gamma et de certaines chimiothérapies. Le rôle central de l'hypoxie dans la progression tumorale et la résistance au traitement se confirme comme c'est le cas de l'anémie même si tous les mécanismes ne sont pas encore élucidés.

Keywords: Hypoxia; Anemia; Malignant progression; Gene expression; Proteome changes; Hypoxia-inducible factor; Genomic instability; Clonal selection; Treatment resistance; Aggressive phenotype

Mots clés : hypoxie ; anémie ; facteurs inductibles par l'hypoxie ; résistance aux traitements anticancéreux

* Corresponding author.
E-mail address: vaupel@uni-mainz.de (P. Vaupel).

1246-7820/$ - see front matter © 2004 Elsevier SAS. All rights reserved.
doi:10.1016/j.tracli.2004.11.005

1. The Janus face of tumor hypoxia

1.1. Inhibition of cell proliferation

Cells exposed to hypoxic conditions respond by *reducing their overall protein synthesis* by approximately 50% [16]. There is abundant evidence suggesting that hypoxia (i.e. the state of oxygen deficiency) can slow down or even completely *inhibit* (*tumor*) *cell proliferation* in vitro [8]. Furthermore, sustained hypoxia can change the cell cycle distribution and the relative number of quiescent cells which in turn can lead to alterations in the response to radiation and many chemotherapeutic agents. The degree of inhibition depends on the severity and duration of hypoxia, on the co-existence of other microenvironmental inadequacies (e.g. acidosis, glucose depletion) and on the cell line investigated. The response of cells exposed to hypoxia in terms of cell cycle, is in most cases a G_1/S-phase arrest [18]. Hypoxia levels necessary to induce a disproportionate lengthening of G_1 or an accumulation of cells in this cycle phase are in the range of 0.2–1 mmHg [2]. Above this "hypoxic threshold" the environmental O_2 status appears to have only negligible effects on the proliferation rate. Under anoxia, most cells undergo immediate arrest in whichever phase of the cell cycle they are in.

In addition to hypoxia-mediated changes in tumor cell proliferation, hypoxia can induce programmed cell death (*apoptosis*) both in normal and in neoplastic cells. p53 accumulates in cells under hypoxic conditions and induces apoptosis involving Apaf-1 and caspase-9 as important downstream effectors [28]. However, hypoxia also initiates p53-independent apoptosis pathways including those involving genes of the BCL-2 family [27] and others (for a review see [34]). Below a critical energy state, hypoxia/anoxia may result in *necrotic cell death*, a phenomenon seen in many human tumors and experimental tumor models. Hypoxia-induced proteome changes leading to cell cycle arrest, differentiation, apoptosis, and necrosis, may explain delayed recurrences, dormant micrometastases, and growth retardation in large tumor masses [12].

1.2. Hypoxia-driven malignant progression

In contrast, hypoxia-induced proteome and/or genome changes in the tumor and/or stromal cells may promote tumor progression via mechanisms enabling cells to overcome nutritive deprivation, to escape from the "hostile" environment and to favor unrestricted growth.

Sustained hypoxia in a growing tumor may also lead to cellular changes that can result in a more clinically aggressive phenotype. During the process of hypoxia-driven malignant progression, tumors may develop an increased potential for local invasive growth, perifocal tumor cell spreading, and regional and distant tumor cell metastasis [12]. Likewise, an intrinsic resistance to radiation and other cancer treatments may be enhanced, resulting in a poor prognosis [33].

In this article, current information from experimental and clinical studies is presented, which illustrates the interaction between tissue hypoxia and the phenomenon of malignant progression. Since more and more evidence concerning the fundamental biologic and clinical importance of tumor hypoxia is emerging, the data described here should be considered partially selective and therefore can only represent a "snapshot" of currently available data.

2. Evidence and characterization of tumor hypoxia

Clinical investigations carried out over the last 15 years have clearly demonstrated that the prevalence of hypoxic tissue areas [i.e. areas with O_2 tensions (pO_2 values) ≤2.5 mmHg] is a characteristic pathophysiological property of locally advanced solid tumors and that such areas have been found in a wide range of human malignancies: cancers of the breast, uterine cervix, head and neck, rectum and pancreas, brain tumors, soft tissue sarcomas, and malignant melanomas [3,12,32].

Evidence has accumulated showing that up to 50–60% of locally advanced solid tumors may exhibit hypoxic and/or anoxic tissue areas that are heterogeneously distributed within the tumor mass. The pretherapeutic oxygenation status assessed in cancers of the breast, uterine cervix and head and neck is poorer than that in the respective normal tissues and is independent of clinical size, stage, histology, grade, nodal status and a series of other tumor characteristics or patient demographics. The data do not suggest a topological distribution of the pO_2 values within a tumor. Tumor-to-tumor variability in oxygenation is greater than intra-tumor variability. Local recurrences have a higher hypoxic fraction than the respective primary tumors. There is no clear-cut difference between primary and metastatic malignancies [12].

3. Pathogenesis of tumor hypoxia

Hypoxic (or anoxic) areas arise as a result of an imbalance between the supply and consumption of oxygen [32]. Whereas in normal tissues or organs the O_2 supply matches the metabolic requirements, in locally advanced solid tumors, the O_2 consumption rate of neoplastic as well as stromal cells may outweigh an insufficient oxygen supply and result in the development of tissue areas with very low O_2 levels.

Major pathogenetic mechanisms involved in the emergence of hypoxia in solid tumors are (a) severe structural and functional abnormalities of the tumor microvessels (*perfusion-limited O_2 delivery*), (b) a deterioration of the diffusion geometry (*diffusion-limited O_2 delivery*), and (c) tumor-associated and/or therapy-induced anemia leading to a reduced O_2 transport capacity of the blood (*anemic hypoxia*). There is abundant evidence for the existence of substantial heterogeneity in the tissue oxygenation status, predominantly due to the former two mechanisms.

Perfusion-limited O_2 delivery leads to *ischemic hypoxia* which is often transient. For this reason, this type of hypoxia