BOOK REVIEW

TUMOR HYPOXIA: PATHOPHYSIOLOGY, CLINICAL SIGNIFICANCE AND THERAPEUTIC PERSPECTIVES

P. Vaupel, D. Kelleher, eds. Mainz (Germany): Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 1999, 134 p., illus., ISBN 3-8047-1733-0

The physiology of solid tumors differs from that of normal tissues in a number of important parameters, one of them is a level of oxygenation. It is well known that malignant tumors contain a significant region of low oxygen (hypoxia). Tumor hypoxia is not only a major problem for radiation therapy but also leads to resistance to most anticancer drugs, and, importantly, appears to accelerate malignant progression and increase metastasis. Hence, it is very actually both to clarify our knowledge about tumor hypoxia and design the means for its overcoming. Many laboratories try to solve this problem resulting in the appearance of new and new data that allow us to understand the biological basis of tumor hypoxia and its place in the creation of modern therapeutic strategy.

Tumor Hypoxia is a new multiauthored book that is devoted to covering our current knowledge of tumor oxygenation and its significance for therapy. The authors, mostly from the European universities and oncological centers are recognized experts in this field. The text is focused, well organized, and extremely well concentrated.

The book consists of 15 chapters that can be subdivided in accordance with their scientific profiles into four groups (the names of senior authors are indicated in the parenthesis):

1. Oxygenation status of human tumors, in particular breast cancer, head and neck tumors, soft tissue sarcoma, cervix carcinoma, malignant melanoma. (P. Vaupel, Mainz University, Germany; S. Runkel, Freie Universitat Berlin, Germany; M. Nordsmark, Aarhus University Hospital, Denmark; D.M. Brizel, Duke University, Durham, NC, USA; E. Lartigau, Centre Oscar Lambret, Lille, France; M. Molls, Klinik for Radiation Therapy, Munich, Germany). Some of them demonstrate the relationship between tumor pO_2 and radiation response.

2. Anemia (hemoglobin) and oxygenation status of tumors, modulation of tumor oxygenation by erythropoietin (K. Groebe, Mainz University, Germany; J. Dunst, Martin–Luether University, Halle, Germany; D.B. Kelleher, Mainz University, Germany; M. Henke, University Radiation Klinik, Freiburg, Germany; R.S. Lavey, University of Southern California, Los Angeles, CA, USA).

3. Tumor hypoxia and malignant progression (M. Hockel, University of Leipzig, Germany; A.J. Giaccia, Stanford University, CA, USA).

4. Hypoxia–mediated gene expression (I.J. Stratford, Manchester University, UK; D. Marme, Institute of Molecular Medicine, Freiburg, Germany).

The first group of chapters does an outstanding experience in clinical investigation of tumor hypoxia and covers the areas of oxygen concentration measurement in some human tumors. It is not out of place to mention here that these investigations were not feasible until the advent of computerized pO_2 histography technique that is used now in many clinical studies. It was shown that tumor oxygenation was inadequate and heterogeneous as compared to the normal breast and breast with fibrocystic disease. Nearly 40% of the breast cancers investigated exhibited pO_2 values between 0 and 2.5 mm Hg. It is remarkably that the degree of hypoxia rises with increasing tumor size. The determination of pO_2 in breast cancer could prove to be an important step in predicting clinical outcome, as reported in cervical cancer, as well as the response of tumors to adjuvant cytotoxic and radiation therapy. It was demonstrated that hypoxia in human squamous cell carcinoma of the head and neck is associated with poor locoregional tumor control after primary radiation therapy. The results obtained also gave rise to a new hypothesis, namely that hypoxia in soft tissue sarcomas is determinative of poor response not only for radiation therapy, but for treatment in general.

It was shown that the use of low dose hyperthermia in conjunction with radiotherapy might lead to overall improvements in tumor oxygenation. The clinical experience has allowed for Dr. D.M. Brizel to propose that tumor oxygenation assessment may represent the addition of a "biologic'' parameter to the staging process as well as patients with poorly oxygenated tumors could be selected for more aggressive therapeutic strategies targeted against hypoxia.

Some results confirmed the hypothesis that patients with high pretreatment tumor hypoxic fraction had lower loco–regional tumor control probability as compared to the well–oxygenated group. It is also important to note the data allowing us to suggest that hypoxia stimulates up–regulation of the receptor of urokinase–type plasminogen activator (uPAR) expression on the cell surface, thus possibly promoting tumor invasion and metastasis.

The second group of chapters presents the data is devoted to the problem of anemia and oxygenation status of tumors. A significant correlation between hemoglobin concentration and tumor oxygenation was found in both head and neck and cervical cancer. It was declared that hemoglobin content seemed to have an impact on tumor oxygenation. It was interesting that higher levels of the angiogenic cytokine VEGF (vascular endothelial growth factor) were found in patients with low hemoglobin levels. Anemia seems to have an important impact on tumor oxygenation and thereby may not only influence tumor response to radiotherapy. Human malignancies are frequently accompanied by anemia, which may impair tumor oxygenation. It was shown that modeling anemia–induced changes in tumor pO_2 distributions qualitatively confirms experimental observations according to which the tumor oxygenation status deteriorates as hematocrit falls. Vice versa, the oxygenation recovers as a normal hemoglobin concentration is restored.

It was shown in the experiment that administration of recombinant human erythropoietin (rhEPO) might prevent tumor–associated and chemotherapy–induced anemia. Results obtained suggest that rhEPO treatment can improve tumor oxygenation by increasing O_2 availability to tumor tissue. rhEPO treatment was also shown to result in a significant increase in tumor radiosensitivity. The clinical trials have confirmed these experimental results. A reduced radiocurability of patients with decreased blood hemoglobin content has been clearly demonstrated. rhEPO administration could also result in a rapid increase in hemoglobin content. A randomized trial of radiation therapy with or without rhEPO for primary pelvic malignancies found locoregional control to be statistically significantly higher in the rhEPO group. rhEPO seems to play a potentially large role in the therapeutic management of cancer patients.

The third group of chapters discusses the influence of tumor hypoxia on malignant progression. A strong association between tumor hypoxia and malignant progression has been suggested as a biological phenomenon in cervical cancer. Other investigators have found similar results in various other solid human malignancies and this statement appears to be generally valid. Several important experimental studies provide the clues suggesting that tumor hypoxia is inherently involved in malignant progression. Moreover, the clinical results were recently obtained which strongly support the concept of the hypoxia–mediated selection of apoptosis–incompetent tumor cells as an important mechanism of malignant progression.

Dr. A.J. Giaccia with co–workers have proposed a model for the evaluation of aggressive tumors where hypoxia provides a physiological selective pressure in a tumor for the expansion of transformed cell variants that have lost their apoptotic potential. Therefore, changes in tumor oxygenation may not only cause transient phenotypic changes resulting in resistance to such anticancer modalities as radiotherapy but they may also result in the alterations in the genotypic make–up of cancer cells towards increasing malignant progression.

The fourth group of chapters presents the intriguing data about changes in gene expression in solid tumors that are characterized by hypoxia. Hypoxia–mediated changes include upregulation of VEGF and other genes encoding angiogenic factors. All these hypoxia–regulated genes share common enhancer sequences called HREs (hypoxia responsive elements). The importance of hypoxia–mediated gene expression in tumor biology is demonstrated by cells lacking HIF–1 function growing more slowly as tumors than the same isogeneic cells that are HIF–1 proficient.

The preliminary positive results of the gene therapy based on the manipulation with hypoxia–mediated genes have been demonstrated *in vivo*. Authors suggested that the utilization of HREs to drive therapeutic gene expression gives a novel approach based upon abnormal tumor physiology rather than abnormal tissue genetics and thus provides a degree of tumor selectivity not previously available in other gene therapy approaches.

Elevated levels of serum VEGF are present in metastatic disease in breast and ovarian cancer. Both primary and metastatic tumors contribute to serum levels of the mitogen. It would appear that the VEGF signaling system is an appropriate target for the efforts to interrupt disease progression and metastasis. Inhibition of VEGF receptor tyrosine kinases is under investigation as a therapeutic approach.

The book should stimulate further research in this area, which may in future create new therapeutic prospects for cancer treatment. Several data presented in the book stimulate to discuss the methodological basis of pO_2 measurement in human tumor with a needle electrode. Dr. M. Nordsmark and Dr. J. Overggard have noticed that the pO_2 histography is a reliable assay for assessment of tumor oxygenation but it is limited by being invasive and lesions have to be accessible. They discussed that this assay is not easy to implement in the daily clinical routine. I would like here also to mention that the insertion of electrode into tumor may stimulate the metastasizing due to the mechanical damage of tumor with separation of cells that may get into blood–stream (such manipulation is especially dangerous in the case of malignant melanoma). Methodical remark was also made by Dr. Molls with co–workers who noted that pO_2 measurement with a needle electrode did not distinguish between viable hypoxic tumor tissue and necrosis.

In conclusion it may be summarized that "Tumor Hypoxia: Pathophysiology, Clinical Significance and Therapeutic Perspectives'' is an outstanding reference for both basic and clinic oncologists studying tumor pathophysiology and trying to create a new effective approach to selective cancer therapy. Basic scientists who work in molecular oncology will also find it to be a useful reference, especially to introduce the tumor microphysiology that is not taken into account in studies *in vitro*. In short, the text provides an accurate and comprehensive overview of tumor hypoxia.

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