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The role of erythropoietin and erythropoietin receptors in gastrointestinal cancers

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Anemia is an independent negative prognostic factor for survival in patients with malignant diseases. Pathophysiology of anemia in patients with malignant disease is multifactorial and anemia has effects on tumor hypoxia and is enhancing resistance to antitumor therapy .

Erythropoietin (Epo) is a glycoprotein hormone that binds to cells with erythropoietin receptor, thus leading to its activation and stimulation of erythropoiesis.The mature form of Erythropoietin receptor (EpoR) is transferred to the surface of the cells where it becomes available to Epo that binds to it. Epo signaling is initiated by binding of Epo molecule to EpoR that forms a homodimer resulting in activation of two Janus kinase 2 (JAK2), (tyrosine kinase molecules). Epo is pleiotropic hormone with angiogenic and neurotrophic functions and thus EpoR can act not only on erythroid progenitors but even in endothelial cells, epicardium and pericardium, kidney, pancreas, placenta, and in certain regions of the brain. Tissue hypoxia is the main stimulus of Epo production . Regulation of Epo expression is controlled by several DNA sequences. In a smaller part Epo is excreted through the kidneys and liver.

Cancer cells and vascular endothelial cells express EpoR. EpoR is activated by Epo in the systemic circulation, which may be endogenous or synthetic origin. Synthetic forms of Epo are often used in clinical practice in patients with malignant diseases, with the aim of increasing the level of hemoglobin, decreasing the frequency of red blood cell transfusions and improving the quality of life (QoL). There are concerns about possibility that Epo can stimulate the proliferation of tumor cells in vitro but recombinant Epo administered in "in vitro" conditions in different tumor cell lines did not lead to growth stimulation, even in cases where the cell lines expressed EpoR. Additional concerns arise that Epo can act as an angiogenic and, in general, as a cell growth factor. Synthetic forms of Epo can stimulate physiological or pathological angiogenesis and can stimulate EpoR expression in tumor and vascular endothelial cells leading to tumor growth and angiogenesis.In colorectal cancer Epo and EpoR expressions are statistically higher in adenocarcinomas versus mucinous carcinomas and in moderately (G2) versus poorly differentiated (G3)tumors . Overexpression of HIF-1α (Hypoxia Induced Factor) was an independent risk factor for recurrence after curative resection of metastatic CRC. In gastric carcinoma angiogenic potential of Epo is similar to that of VEGF and also, microvessel density in tumor tissue was significantly higher in patients with high Epo or EpoR expression, compared to the patients with low EPO or EpoR expression. The most interesting finding (with no explanation) was that the expression of EpoR was age dependent - it was increased in older age. Hepatocellular carcinoma (HCC) promotes erythrocytosis and is associated with increased levels of Epo. Poorly differentiated HCC has a higher degree of vascularity compared to well-differentiated HCC and tumor progression in HCC is associated with angiogenesis and increase in microvascular density is followed by worse prognosis.Pancreatic Ductal Adenocarcinoma (PDAC) is extremely aggressive tumor and is associated with a high rate of malignancy. Ectopic non-malignant sources of Epo (hepatocytes and capillaries) are potential sources of additional secretion of Epo and high levels of endogenous Epo is an independent negative prognostic factor for survival in patients with PDAC .Several randomized trials of ESAs in patients who have cancer have recently reported inferior outcomes in tumor progression or survival, raising appropriate concerns about the safety of these agents in oncology. Although the preponderance of the data suggests that EPO/EpoR alter survival large well-controlled trials addressing this issue are still needed.

Biography

Working as Head of Medical Oncology dpt in Clinic for Radiotherapy and Oncology, Clinical Hospital Centre Rijeka and Professor of Internal Medicine on School of Medicine, University of Rijeka, Croatia.Master of science acchieved in 1987, Specialist of Internal medicine 1995, PhD 1999, Assistant Professor 2003, Medical Oncologist subspecialization 2005 and Professor 2009. During education and careear development participated in numerous international courses, including Zagreb, Boston, Miami, New York, Chicago. In the same time participated as international speaker on Postgraduate courses related to oncology, chemotherapy and pain management in Moscow, Hong Kong, Athens, Tokyo, Rovingno and as International Invited speaker in Vienna, Chicago, Moscow, Bucharest, Philadelphia, Athenes, Sarajevo, Bangkok, Fuzhou, Seoul. All together more than 50 participations that covered various aspects of research and management of oncologic patients. Results of work presented in over 50 international publications and 10 books and books chapters. Involved in several projects sponsored by Croatian Ministry of Health. Member of numerous International and National organizations, including IASGO, MASCC, ASCO, ESMO, EACR. Member of Croatian Medical Oncology Society Executive Committee and Vicepresident of Croatian Oncology Foundation.

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