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Original Article

Erythropoetin and Erythropoetin Receptor Systems, and Oxidative Status in Patients with Basal Cell Carcinoma

Ergul Belge Kurutas[1], Perihan Ozturk[2]

[1] *Department of Medical Biochemistry, Faculty of Medicine, Sutcu Imam University, Kahramanmaras, Turkey*
[2] *Department of Dermatology, Faculty of Medicine, Sutcu Imam University, Kahramanmaras, Turkey*

Corresponding author: Ergul Belge Kurutas, Department of Medical Biochemistry, Faculty of Medicine, Sutcu Imam University, 46050, Avsar Campus, Kahramanmaras, Turkey; E-mail: ergulkurutas@gmail.com; Tel.: +90 3443003336

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Abstract

Introduction: Erythropoietin (Epo) controls a variety of signal transduction pathways during oxidative stress. The main function of Epo and its receptor (EpoR) is the stimulation of erythropoiesis.

Aim: The role of Epo and EpoR on non-hematopoietic normal and cancerous tissues is still poorly understood. This is the first report in which we aimed to investigate the role of Epo and EpoR systems at oxidative condition in human basal cell carcinoma (BCC), which is the most common tumour in the world.

Materials and methods: Fresh normal and cancerous skin paired tissue was obtained from 63 patients who underwent curative BCC resection in Kahramanmaras, Turkey. Preliminary diagnosis of BCC was made in the dermatology clinic by excision and then the diagnosis was confirmed as histopathologic findings. Oxidative stress biomarkers such as superoxide dismutase (SOD) and catalase (CAT) activities, and malondialdehyde (MDA) levels in biopsy samples were measured spectrophotometrically, and also the levels of Epo and EpoR were measured by ELISA.

Results: While the levels of MDA in cancerous tissue of patients with skin BCC were significantly higher than normal neighbouring skin tissue ($p<0.05$), SOD and CAT activities decreased ($p<0.05$). Furthermore, a remarkable increase was found in the Epo level of patients with skin BCC in comparison with the normal neighbouring skin tissue ($p<0.05$). However, we found that EpoR levels decreased ($p<0.05$).

Conclusions: Results indicate that there is an active oxidative process in BCC biopsies. The levels of increased Epo and decreased EpoR in oxidative condition due to hypoxia may aggravate tumour growth by its angiogenic activity.

Keywords

basal cell carcinoma, Epo, EpoR, oxidative stress

INTRODUCTION

Basal cell carcinoma (BCC) is the most common skin cancer in humans. A variety of different phenotypic presentations of BCC are possible. Although BCCs rarely metastasize, these tumours commonly destroy underlying tissues and should therefore be treated promptly. As vascular formation and angiogenesis are indicators of tumour development and progression, the presence of blood vessels, their morphology and architecture are important mar-

kers in skin lesions, providing critical information towards pathogenesis and diagnosis.[1] Lupu et al. reported that in contrast to normal skin, significant variations of blood vessel densities were found in the peritumoural stroma of different tumour entities, where the highest counts were present in BCCs and significantly lower counts in the peritumoural stroma of benign tumours such as trichofolliculomas, trichoepitheliomas, and trichoblastomas.[2,3]

Human erythropoietin (Epo) is the primary regulator of erythropoiesis, stimulating growth and promoting differentiation of red blood cell progenitors. The primary stimulus for Epo release is decreased oxygen delivery, most often due to anemia or hypoxia.[4] Epo is an acidic glycoprotein hormone that is produced by the kidney and to a much lesser degree (<10%) by the liver. Epo binds to transmembrane Epogen receptors (EpoR), which are expressed primarily by hematopoietic progenitor cells but also by nonhematopoietic cells and tissues such as endothelial cells, cardiomyocytes, and neurons, the liver, uterus, and retina.[5] Epo also shows angiogenic activity in vitro by stimulating vascular endothelial cells to proliferate and migrate.[6] Epo is now also known as a potent anti-apoptotic factor for EpoR presenting cells, particularly neural cells.[7] Epo and EpoR expressions in neoplasia were first reported in clear cell and chromophilic cell renal carcinoma[8] and subsequently functional autocrine and paracrine Epo-EpoR systems were identified in human breast carcinoma, melanoma, prostate cells, and cervical cancer cells[9] suggesting a link to tumour progression. Pascual et al. found that preoperative administration of Epo stimulates tumour recurrence in an animal model of colon cancer, but no evidence of increased angiogenesis or enhanced-cell proliferation as possible mechanisms of Epo-induced recurrence was seen.[10] Significantly, Epo/EpoR levels correlated well with angiogenesis and progression of patients with hepatocellular carcinoma, neuroblastoma, squamous cell carcinoma of the tongue, melanoma, and gastric adenocarcinoma.[11,12]

The recombinant form of human erythropoietin (rHuEPO) has been widely used in clinical practice for the prevention or treatment of anemia associated with cancer and chemoradiation therapy.[13] The expression of Epo and EpoR in tumour tissue is of critical importance in relation to the administration of rHuEPO in the treatment of cancer related anemia. Epo binds to the EpoR on the red cell progenitor surface and activates a Janus kinase 2 (commonly called JAK2) signalling cascade. EpoR expression is found in a number of tissues, such as bone marrow and peripheral/central nervous tissue. In the bloodstream, red cells themselves do not express EpoR, so they are not able to respond to Epo.[14] However, indirect dependence of red cell longevity in the blood on plasma erythropoietin levels has been reported, a process termed neocytolysis.[15] The majority of anemic patients with cancer of the gastrointestinal tract have iron deficiency due to subclinical blood loss; therefore, an iron supplement has been advocated.[16] Results of a study with anemic nude mice engrafted with human glioblastoma tumours indicated that administration of rHuEPO improved tumour radiosensitivity, presumably by correcting anemia and subsequently improving intratumoural oxygenation.[17] On the other hand, in a study, prevention of anemia with rHuEPO partially restored the radiosensitivity of xenografted glioblastomas to fractionated irradiation.[18] Kelleher et al.[19] demonstrated, in a murine model, that tumour growth was not affected by rHuEPO in either anemic or normal animals. Tumour blood flow and oxygenation in the anemic animals were lower than in the normal controls. As a result, research results show that using rHuEPO in the treatment of patients with anemic cancer is controversial.

Oxidative stress significantly impacts multiple cellular pathways that can lead to the initiation and progression of varied disorders throughout the body.[20] So, oxidative status assessment is an initial step in tumour related studies. Epo controls a variety of signal transduction pathways during oxidative stress. The role of Epo and EpoR on nonhematopoietic normal and cancerous tissues is still poorly understood.

AIM

This is the first report in which we aimed to investigate the levels of Epo and EpoR, and also the ratios of Epo/EpoR, and oxidative status in biopsy specimens of BCC patients, which is the most common tumour in the world.

MATERIALS AND METHODS

The study was approved by the local ethical committee of Sutcu Imam University, Medical Faculty, Kahramanmaras, Turkey. Prior to the initiation of the study, each subject was informed about the aim of the study and signed an informed consent form. The data collection of the study was performed from June 2017 to May 2019. A total of sixty-three subjects were included in this study. The preliminary diagnosis of BCC was made in the dermatology clinic by excision and then the diagnosis was confirmed as histopathologic findings. The biopsies specimens were obtained from lesional (as BCC tissue) and non-lesional areas (as normal tissue) in Kahramanmaras Sutcu Imam University Hospital, Turkey.

Biochemical Analysis

Preparation of tissue homogenates

All biopsies specimens were homogenized in two volumes (w/v) of the 1.15% ice-cold KCl solution, using a Heidolph 50110 R2R0 homogenizer (Schwabach, Germany). Biochemical assays were performed on the supernatant preparation in a Sorvall RC-2B (Minneapolis, MN, USA) centrifugation of the homogenate at 39,880 g for 30 min at 4°C.

Measurement of CAT activity

The CAT activity was measured in samples using the method applied by Beutler.[21] The decomposition of the substrate H_2O_2 was monitored spectrophotometrically at 240 nm. Specific activity was determined as micromole substrate decomposed per minute per milligram of protein (i.e. U/mg protein).

Measurement of SOD activity

The SOD activities were estimated for the tissue samples using the method described by Fridovich.[22] SOD estimation was based on the generation of superoxide radicals produced by xanthine and xanthine oxidase, which reacts with 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyl tetrazolium chloride (INT) to form a red formazan dye. The SOD activity was measured at 505 nm by the degree of inhibition of this reaction. SOD activity was expressed as U/mg protein.

Measurement of lipid peroxidation

Lipid peroxidation level in the tissue samples was expressed in MDA. Measurement was based on the method of Ohkawa.[23] The reaction mixture contained 0.1 mL of sample, 0.2 mL of 8.1% sodium dodecyl sulfate, 1.5 mL of 20% acetic acid, and 1.5 mL of 0.8% aqueous solution of thiobarbituric acid (TBA). The mixture pH was adjusted to 3.5 and volume was finally made up to 4.0 mL with distilled water and 5.0 mL of the mixture of n-butanol and pyridine (15:1, vol/vol) were added. The mixture was shaken vigorously. After centrifugation at 4000 rpm for 10 min, the absorbance of the organic layer was measured at 532 nm. MDA levels were expressed as nmol/mL.

Measurement of Epo and EpoR levels

Epo and EpoR levels in the tissue samples were measured in duplicate using commercially available solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) kits (MyBioSource Company, USA) according to the manufacturer's protocol.

Statistical analysis

Statistical analysis was carried out using SPSS 15.0 for Windows. The conformability of the quantitative data to the normal distribution was examined by the Kolmogorov-Smirnov test. The paired Student's ttest was used to compare mean values for all parameters between lesional and nonlesional skin.

RESULTS

Thirty-tree patients were female (52.38%) and 30 patients were male (47.61%). Also, the mean age of patients was 53±12 years (range, 21-58 years). The mean disease duration was 4±1 months (range, 36 months).

In our study, we found that the levels of MDA in lesional areas of patients with BCC were significantly higher than those in non-lesional areas (p<0.05). However, SOD and CAT activities were decreased in lesional areas of patients with BCC compared to non-lesional areas (p<0.05) as shown in **Table 1**.

Table 1. The levels of oxidative stress biomarkers, erythropoietin and erythropoietin receptor in lesional and non-lesional areas of patients with BCC

	Lesional areas (mean ±SD)	Non-lesional areas (mean ± SD)
SOD (U/mg protein)	1.02±0.05*	2.35±0.13
CAT (U/mg protein)	0.29±0.04*	1.02±0.19
MDA (nmol/mg protein)	3.98±1.65*	1.76±0.45
Epo (ng/mg protein)	9.27±3.15 **	4.02±1.27
EpoR (ng/mg protein)	0.59±0.13**	1.43±0.17
Epo/EpoR ratios	15.71±6.74**	2.81±0.95

* Significant differences in the levels of oxidative stress biomarkers such as SOD, CAT and MDA in lesional and non-lesional areas in BCC (p<0.05); ** Significant differences in the levels of Epo and EpoR and ratios of Epo/EpoR in lesional and non-lesional areas in BCC (p<0.05). Epo: erythropoietin; EpoR: erythropoietin receptor; SOD: superoxide dismutase; CAT: catalase; MDA: malondialdehyde; BCC: basal cell carcinoma; SD: standard deviation

A remarkable increase was found in the Epo level in BCC tissues compared with the normal tissues (p<0.05). However, we found that EpoR levels decreased in BCC tissues compared to normal tissues. Also, the ratios of Epo/EpoR were significantly higher in BCC tissues than in normal tissues as shown in **Table 1** (p<0.05).

DISCUSSION

BCC is one of the most common skin cancers in the world mainly due to environmental factors, life style, the increasing chemical pollution, and poor nutrition. This cancer is increasing in the Turkish population. The most important causes of this cancer is the oxidative stress and the abnormal production of free radicals, thus the antioxidant activities of the body are so important.[20,24] In the present study, MDA levels, as an indicator of oxidative stress, increased in the lesional areas of BCC patients; however, the activities of SOD and CAT as antioxidant enzymes showed significant decrease in the lesional areas of BCC patients. We thought that SOD and CAT enzymes were consumed during oxidative stress process in lesional areas of the patients with BCC. Decreased antioxidant enzymes like CAT, SOD in BCC may contribute to multistep carcinogenesis. However, the increase of MDA may show the increasing oxidative condition in lesional areas of BCC. Thus,

MDA may serve as a screening test for malignant diseases at the early stages and for screening of the treatment progress in antioxidant therapy.

Many hypoxia-regulated genes, such as vascular endothelial growth factor, are known to play a key role in carcinogenesis and tumour progression. The best known hypoxia-regulated gene is Epo, a glycoprotein hormone stimulator of erythropoiesis.[25] Epo gene expression is primarily modulated by tissue hypoxia[26] and this regulation occurs mainly at the mRNA level mediated by hypoxia-inducible transcription factor-1 (HIF-1)[27]. During adult life, Epo is normally produced by the kidney and liver.[28] The EpoR belongs to the cytokine receptor type I superfamily.[29] The signalling mechanisms after receptor activation include the Jak/STAT and the Ras/MAP kinase pathways.[30] EpoR stimulation in erythroblasts promotes their proliferation and differentiation, and leads to increased expression of the anti-apoptotic proteins bcl-2 and bcl-XL and inhibition of apoptosis.[31] EpoR mRNA and protein and their expression is enhanced by hypoxia.[32] Furthermore, a number of studies demonstrated that Epo signalling is biologically active and stimulates tyrosine phosphorylation, DNA synthesis, and proliferation in breast cancer cells.[33]

To our knowledge, this is the first study examining the levels of Epo and EpoR in patients with BCC. In the present study, we measured the levels of Epo and EpoR in the biopsy samples by a sensitive and accurate ELISA method. We found that the levels of Epo in lesional areas of patients with BCC were higher than the levels in the non-lesional areas. However, EpoR levels of these patients were decreased in the lesional areas. These changes of Epo and EpoR levels may relate to oxidative status of patients with BCC. Hypoxia may increases the production of Epo in heavy oxidative stress conditions in BCC. Thus, we thought that elevated oxidative stress and Epo response may be associated with the hypoxia in BCC. In addition, the reduction of EpoR levels in our study is possibly due to a compensatory response to the higher levels of Epo. We think that EpoR may act as an Epo "buffer" regulating available circulating Epo concentration. A lower EpoR concentration may increase unbound free plasma Epo and, therefore, its availability for binding EpoR. Evidence suggests that increased Epo and EpoR expressions paralleled with increased serum Epo levels are not merely the consequence of the hypoxic adaptation of the constantly proliferating cancer.[25,27]

In our study, the increased ratios of Epo/EpoR may be due to high Epo levels. Until now, Epo/EpoR ratio has not been reported in patients with BCC. So, we did not compare our results. There is increasing evidence suggesting a wider biological role for Epo/EpoR related to malignant biological behavior of tumour, including tumour angiogenesis.[34] Epo induces endothelial cell proliferation and migration. Tumour cells lining the vasculogenic mimicry networks express multiple endothelial markers, and resemble endothelial cell functions.[35] The expression of EpoR in tumour cell and vascular endothelium imply that Epo/EpoR may affect the tumour microenvironment, perhaps by stimulating tumour angiogenesis and vasculogenic mimicry formation. Our findings indicated that the increased levels of Epo/EpoR ratio may relate to increased blood flow, microvascular density, and faster solute exchange rates in lesional areas compared with a matched control skin site. The increased Epo and EpoR ratios in BCC may suggest the autocrine and paracrine mechanisms leading to tumorigenesis and progression of BCC. Future studies with additional samples may lead to more conclusive answers regarding the potential roles of Epo and EpoR in BCC.

The major limitations of this study include the small sample size and its cross-sectional design. Also, the results obtained with human tissue Epo and EpoR levels may not completely reflect the signal pathways of Epo and EpoR at molecular levels in patients with BCC. Thus, experimental animal studies are required to gain more insight into the signal pathways of Epo and EpoR. Nevertheless, to our knowledge, there is no study in the literature assessing the Epo and EpoR levels in BCC patients, which makes this study the first research on this issue. The outcome of the present study is important in terms of providing data for a treatment approach through target receptors in BCC.

CONCLUSIONS

Our results showed that a dynamic Epo-EpoR signalling system is present in the BCC, and may offer a new therapeutic modality in cases where surgery cannot be performed. Further study of Epo and the EpoR in BCC tissues is warranted to determine the potential therapeutic usefulness of rHuEPO as well as to determine the signalling pathway responsible for its effect in vivo.

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Conflicts of Interest

There are no conflicts of interest.

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Эритропоэтин и рецепторные системы эритропоэтина и окислительный статус у пациентов с базально-клеточной карциномой

Ергюл Белге Куруташ[1], Перихан Озтюрк[2]

[1] *Кафедра медицинской биохимии, Медицинский факультет, Университет имени Кахраманмараша Сютчуйама, Кахраманмараш, Турция*
[2] *Кафедра дерматологии, Медицинский факультет, Университет имени Кахраманмараша Сютчуйама, Кахраманмараш, Турция*

Адрес для корреспонденции: Ергюл Белге Куруташ, Кафедра медицинской биохимии, Медицинский факультет, Университет имени Кахраманмараша Сютчуйама, 46050, Кампус Авсар, Кахраманмараш, Турция; E-mail: ergulkurutas@gmail.com; Тел.: +90 3443003336

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Резюме

Введение: Эритропоэтин (Epo) контролирует различные пути передачи сигнала во время окислительного стресса. Основная функция Epo и его рецептора (EpoR) – стимулировать эритропез.

Цель: Роль Epo и EpoR в негематопатических нормальных и злокачественных тканях еще полностью не изучена. Это первый отчёт, в котором мы стремимся изучить роль систем Epo и EpoR в окислительном состоянии при базально-клеточной карциноме человека (БКК), которая является наиболее распространённой опухолью в мире.

Материалы и методы: Комбинация свежей нормальной и злокачественной кожной ткани была взята у 63 пациентов, перенёсших медицинскую резекцию БКК в Кахраманмараше, Турция. Предварительный диагноз БКК был поставлен в дерматологической клинике путём иссечения, и диагноз был подтверждён гистопатологическими данными. Биомаркеры окислительного стресса, такие как активность супероксиддисмутазы (СОД) и каталазы (КАТ) и уровни малонового диальдегида (МДА) в образцах биопсии, измерялись спектрофотометрически, а уровни Epo и EpoP – с помощью ELISA.

Результаты: В то время как уровни МДА в раковой ткани пациентов с кожным БКК были значительно выше, чем в нормальной прилегающей ткани кожи (p<0.05), активность СОД и КАТ снизилась (p<0.05). Кроме того, у пациентов с кожным БКК было обнаружено заметное увеличение уровней Epo по сравнению с нормальной прилегающей тканью кожи (p<0.05). Однако мы обнаружили, что уровни Epo снизились (p<0.05).

Заключение: Результаты показывают, что в биопсиях БКК наблюдается активный окислительный процесс. Уровни повышенного Epo и пониженного EpoR при окислительном состоянии из-за гипоксии могут нарушать рост опухоли из-за её ангиогенной активности.

Ключевые слова

базально-клеточная карцинома, Epo, EpoR, окислительный стресс