REVIEW

EXPERIMENTAL ONCOLOGY

Tumor microenvironment
is not just a silent bystander,
but rather an active promoter
of cancer progression
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EFFECT OF HYPOXIA ON MICROENVIRONMENT FACTORS OF GASTRIC CANCER AND RELATIONSHIP WITH CLINICAL OUTCOME

The tumor microenvironment (TME) plays a critical role in tumor survival, progression, and metastasis. Hypoxia level, as an integral parameter of TME, occupies a central place in the regulation and control of all events occurring in TME. The review focuses on the findings obtained by the authors during the study of the hypoxia impact on the processes related to some microenvironmental factors in order to identify its prognostic significance regarding the course of the disease. It was shown that most microenvironmental factors are largely associated with hypoxia and involved in the processes of the tumor response to therapy. Their significance in the development of minimal residual disease and in the processes that can be affected by adipose tissue is also discussed. Therapeutic strategies based on the tumor's distinctive properties should be more highly selective in relation to the tumor, allowing the highest possible therapeutic gain for a more favorable prognosis of the disease outcome and overall survival of patients with gastric cancer. The literature data on the subject are also discussed.

Keywords: gastric cancer, tumor hypoxia, factors of TME, cancer-associated adipocytes, minimal residual disease.

Gastric cancer (GC) continues to be a malignant neoplasm difficult to treat. Despite a decrease in GC incidence and the development of novel biologic agents and combined therapeutic strategies, the prognosis of GC remains poor. In this regard, an urgent task is to find effective diagnostic biomarkers and therapeutic targets for GC [1, 2].

In the last few decades, many studies have renewed a hope that the components in the tumor microenvironment (TME), as the targets, may provide a promising strategy for early cancer diagnosis and can be leveraged to improve survival of cancer patients and reduce toxicity of chemotherapy [3, 4].

Such approaches, including the availability of sophisticated vaccines, novel antibody technologies, targeting components (including fibroblasts, macrophages, cytokines or chemokines, T-cells, etc.), and novel immune checkpoint inhibitors, supported by improved tissue- and blood-based diagnostic assays, seem promising [5].

However, there is a noticeable difference between the number of markers used in clinical practice and

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the number of reports on new tumor markers. In general, the subsequent publications often provide conflicting or inconclusive results [6].

Special attention has been paid to TME with a particular focus on the innovative therapies targeting the hypoxic TME itself, which hold great potential and point to the importance of understanding the indispensability of oncology research based on pathophysiological principles [7—9]. Numerous attempts have been made to identify the microenvironmental conditions within tumors [10—15].

The pathophysiological characteristics of TME are very different from those conditions found in normal tissues. TME plays a fundamental role in the behavior of cancer and, due to its heterogeneity in composition, with infiltrating and resident host cells, secreted factors, and extracellular matrix, TME represents a milieu that enables tumor cells to acquire the hallmarks of cancer [16, 17].

Currently, the problem of tumor microphysiology is considered from the standpoint of the molecular-physiological relationships between the tumor and the host [18]. The emerging TME, which is mainly a derivative of the microphysiology of the tumor, as well as the organ or tissue where this tumor has formed, reflects the physiological environment for the existence of neoplastic cells, which has a strong influence on tumor development. TME fractures cellular and matrix architecture normality through biochemical and mechanical means, abetting tumorigenesis and treatment resistance [16, 19]. In many respects, TME can be considered abnormal and hostile. TME cells are important elements in tumor tissue, which is composed of cellular and non-cellular components that exist within and around the tumor mass. A hostile TME develops within the tumor and basically reflects conditions of poor perfusion, oxygen deprivation, nutrient deficiency, severe acidity, and elevated interstitial fluid pressure. Hypoxia is now known to be a characteristic feature of TME that plays a critical role in various cellular and physiologic events. As an integral consequence of unregulated growth, hypoxia promotes local invasion, extravasation of tumor cells, and, ultimately, metastatic spread to distant organs [16, 20].

Hypoxia is considered a characteristic feature of most solid animal tumor models [21] and numerous human cancers [11, 22] as the only factor of importance.

From a clinical point of view, hypoxia in the tumor can be used to guide clinicians in providing personalized treatment more appropriately and can determine groups of patients at risk of developing metastases [23].

Forming a peculiar molecular profile of the neoplasm, tumor hypoxia and hypoxia-regulated factors are responsible for the development of tumor resistance to antitumor agents, greatly hindering the efficacy of conventional cancer treatments such as chemotherapy [24] and radiotherapy [25], and promoting genome instability [26] and immune evasion [27]. Future knowledge of the level of the tumor hypoxia also includes biomarker-driven trials of hypoxia-targeted therapies.

Numerous methods have been developed to try to identify hypoxia in human tumors. Hypoxia can be assessed at the level of the whole organ, tissue, or cell, using both invasive and non-invasive methods, and by a range of immunohistochemical, biochemical, or imaging techniques. Currently, the most recommended imaging techniques (MRI (e.g., BOLD), PET, or SPECT detection of radiolabeled tracers) make it possible to noninvasively determine the location and volume of tumor, to monitor the levels of hypoxia, as well as important metabolites, and to evaluate the effectiveness of the introduced therapy based on the changes in their levels predicting the severity of the disease in each patient, which might be an important factor for choosing the optimal treatment [28—31].

Despite intensive research on the characteristics of hypoxia in malignant growth, there is still no unified view regarding its role in determining the degree of GC malignancy. In this regard, there was an urgent need to intensify the study of the molecular mechanisms of the formation of peculiar TME, both metabolic and cellular. Such studies would also reveal new diagnostic, predictive, and prognostic factors. Therapy based on the distinctive properties of the tumor may be highly selective in relation to the neoplasm, allowing to achieve the highest possible therapeutic gain [32]. Considering this, in the present work, we analyzed the data from the literature and our long-term studies focused on the significance of hypoxia as a key component of TME in shaping tumor progression.

Tumor hypoxia and clinical outcome

According to the data of ^{31}P NMR spectroscopy, GC is not a deeply hypoxic tumor, but the presence of hypoxia in GC is a poor prognostic sign. GC is characterized by three levels of hypoxia: severe, moderate, and satisfactory oxygenation: 44% of gastric tumors are hypoxic and 56% «oxygenated» ones [31]. In 88% of patients with GC who died, the primary tumors were severely hypoxic.

Clinically, tumor hypoxia in GC did not correlate with T, N, or M categories, or with the stages of the tumor process, which is consistent with the known conclusion regarding the certain independence of hypoxia from the tumor size, histological structure, differentiation grade, volume of necrosis, and stage of the disease.

As it was found, gastric mucosa, which is disposed beyond the obligatory operative resection of gastric tumor and uninvolved in tumor process (before morphological alterations), is characterized by hypoxia in 52% of GC patients. Severe hypoxia in the tumor was accompanied by severe hypoxia in the mucosa in almost 40% of cases. It may be suggested that the biochemical alterations in tissue surrounding the tumor node and uninvolved in the malignant process may precede morphological changes and may be assessed as neoplastic transformation [33].

Hypoxia in GC provides a negative effect on the efficacy of various methods of treatment such as surgical intervention alone or neoadjuvant or adjuvant chemotherapy.

Neoadjuvant chemotherapy implies that chemotherapeutic drugs would provide an effect on tumor metabolism, leading to a certain correction of the hypoxic state. Nevertheless, neoadjuvant chemotherapy does not provide a positive result, just as it was expected in comparison with surgery alone or adjuvant chemotherapy, especially in the case of hypoxic tumors. In the analysis of the prognostic significance of hypoxia levels in patients who received neoadjuvant chemotherapy, we established that 61.1% of patients with highly hypoxic tumors died, compared to 53.3% of those with oxygenated neoplasms. So, hypoxia negatively affects the tumor response to cytostatic agents.

The greatest effectiveness of chemotherapy was observed in patients with adequately oxygenated tumors who underwent adjuvant chemotherapy. However, the survival of patients with satisfactory oxygenated tumors was better after operation alone.

In patients treated with surgery alone, the survival rates were worse in those with hypoxic tumors compared to patients with satisfactory tumor oxygenation: the risk of unfavorable outcomes increased more than two-fold. This finding indicates the rationale for administering adjuvant chemotherapy in such patients, possibly even at early disease stages and regardless of a negative lymph node (LN) status [34].

It was found that the negative impact of regional metastases (N_1) is enhanced by tumor hypoxia, and even in patients with category N_0 under hypoxia, the risk of an unfavorable outcome also increases. The immunohistochemical method allows us to detect tumor cells in patients with a negative LNs status, and it turned out that 24% of patients with GC of pN_0 category had micrometastases (pancytokeratin-positive cells).

Specifically, the survival rates of patients with panCK-positive cells in the regional LN who underwent surgery alone were worse compared to those who underwent surgery followed by adjuvant chemotherapy. Surgical intervention proved to be more effective for patients with well-oxygenated tumors and negative LN status. Our findings highlight the necessity of monitoring the status of the regional LN using immunohistochemistry to detect occult tumor cells, thereby enabling individualized treatment planning [35].

Thereby, hypoxia as a factor of TME decreases the efficacy of treatment and should be considered to elucidate the way for more effective personalized treatment options.

Factors of the tumor TME associated with intratumoral hypoxia and their clinical significance in GC

Hypoxia and HIF-1α. Hypoxia-inducible factor (HIF-1α) is a transcription factor that ensures the adaptation of tumor cells to hypoxia and initiates various pathways that support the growth of the tumor and its progression. It was established that the HIF-1α expression was observed in 100% of tumors. In normal mucosa, taken beyond the obligatory operative tumor resection margins, this protein was not detected. GC is not characterized by a high level of HIF-1α expression and is not a deeply hypoxic tumor. The expression of HIF-1α in GC is not associated with clinicopathological character-

istics, although there is a correlation with the tumor differentiation grade [36]. A correlation was found between the expression of HIF-1α in the tissue of LN and the expression of HIF-1α in tumor tissue. It was somewhat unexpected that the level of HIF-1α expression inversely correlated with the survival of GC patients may be due to the peculiarities of interaction of hypoxia-regulated pathways in GC, in contrast to most other tumors [36].

Hypoxia and microvessel density. Hypervascularized tumors are likely to be low- and undifferentiated, and hypovascularized tumors are highly and moderately differentiated. Microvessel density (MVD) was not correlated with the level of hypoxia as well as with the expression of VEGF [37]. The presence of micrometastases in LN was detected more often in patients with hypervascularized than hypovascularized tumors (in 90% of patients). A high level of tumor neovascularization is a risk factor for the presence of micrometastases in LN of GC patients and an unfavorable prognosis of the disease outcome. The life span of patients with tumors of categories T_1–T_3 was longer in patients with hypovascular tumors compared to hypervascular ones. That is why MVD as a prognostic factor in GC patients can be informative only in patients with categories T_1—T_3 [37].

Hypoxia and vascular endothelial growth factor (VEGF). Intratumoral hypoxia is a powerful stimulus for angiogenesis, and VEGF is strongly induced by hypoxia in TME. HIF-1α plays a central role in the hypoxic regulation of VEGF. VEGF-positive tumors were observed in 73% of patients [38]. There was a direct correlation between the level of hypoxia and VEGF expression in the tumor. The high levels of VEGF expression in tumors are associated with distant metastases as well as the availability of metastasis in regional LN that increases the risk of an unfavorable disease outcome. This risk turned out to be more significant when the patient received post-surgical chemotherapy.

The VEGF level in the blood serum of GC patients was 5 times higher than in healthy donors. Its increase for a long time after the surgery in relation to the postoperative level indicates a relapse of disease and/or the beginning of the formation of metastases, and can be used as a factor for monitoring the tumor process. A high level of VEGF in serum before surgery may indicate an unfavorable outcome of the disease [39, 40].

Hypoxia and VEGFR1 receptor (Flt-1). Flt-1-positive cells were observed both in bone marrow (BM) and tumor, in 58.5% and 79% of patients, respectively. The correlation between the number of Flt-1-positive tumors and Flt-1-positive BM was not observed. There were no significant correlations between the number of Flt-1-positive cells in the tumor and clinical-pathological characteristics. The probability of the presence of Flt-1-positive cells in BM increased significantly in tumors with severe and moderate hypoxia. The presence of an inverse correlation between the number of Flt-1-positive cells and the MVD suggests that Flt-1 is not a key factor in neovascularization. A large number of Flt-1 positive cells in the tumor indicate the aggressive nature of tumor growth. The life span of patients whose tumors were characterized by a large number of Flt-1-positive cells was significantly shorter compared to those with an insignificant number of such cells [40].

Hypoxia and tumor-associated macrophages. In our study, 100% of tumors in patients with GC were characterized by CD68-positive cells, identified as tumor-associated macrophages (TAMs) [37]. There were significant associations between TAM count and III—IV stage of the disease, low differentiation grade, and distant metastasis (80% of patients). The count of TAMs was much higher in patients with severe hypoxia in the tumor, which confirmed the stimulating influence of hypoxia on the recruitment of macrophages into the hypoxic regions of neoplasia. In the group of patients whose tumors were severely or moderately hypoxic with a high number of TAMs, the risk of lethal outcome doubled, and the survival rate was significantly lower than in those with low TAM counts. In contrast, TAM count does not influence the risk of death under a mildly hypoxic tumor status [37, 40].

Hypoxia and MMP (matrix metalloproteinases). A correlation was established between the MMP-2 activity and the disease stages: the activity of the enzyme increased with the stage. A higher activity of both MMP-2 and MMP-9 was found in the tumors of patients in stage IV without distant metastases. It may be explained by the fact that early metastasis requires an increase in the activity of MMPs, while with formed metastases, proteinases are no longer a decisive factor in the metastatic process. The increase in TAM count was ac-

companied by an increase in MMP-2 activity. MMPs may be produced by TAMs that infiltrate tumor tissue. The multivariate analysis has established that TAMs and MMP-2 activity are independent prognostic factors in GC. There is a distinct correlation between intratumoral hypoxia and MMP activity. The overall survival of patients with strong tumor hypoxia and high levels of TAMs and MMP activities was significantly lower than that of patients without the mentioned tumor characteristics [37, 40].

Transcription factor C-MYC and hypoxia. Expression of C-MYC is detected in GC cells in both nucleus and cytoplasm [41]; among the tumors with cells positive for C-MYC, both by nuclear and cytoplasmic staining, adenocarcinomas and tumors with G3 differentiation grade dominate. In patients with stage III and category T_3, cytoplasmic staining of C-MYC prevails. In tumors that were characterized by high levels of hypoxia, the number of C-MYC-positive cells decreased. There was a direct correlation between the number of C-MYC-positive cells with cytoplasmic staining and MMP-9 activity in the tumor. OS of patients with C-MYC positive tumors with nuclear staining and weak hypoxia (satisfactory oxygenation) was significantly shorter than that of patients with C-MYC negative tumors [41].

Hypoxia and chemokine receptor CXCR4. The CXCL12/CXCR4 axis is a key factor in the crosstalk between tumor cells and their TME [42]. CXCR4 is expressed in 78.5% of GC cases. There was found no strong association of CXCR4 expression in the tumor with clinicopathological characteristics. The expression of CXCR4 plays an important role in the migration of tumor cells from the primary tumor and homing in the distant organs, regulated by hypoxia. The number of CXCR4-positive cells was much higher in tumors characterized by severe and moderate hypoxia and positively correlated with the number of VEGF-positive cells. Tumors with high levels of MVD were characterized by a high number of CXCR4-positive cells, but this association was insignificant. The number of CXCR4-positive cells in the tumor positively correlated with the gelatinase activity in tumor tissue, in particular with the content of the active forms of MMP-2 [40, 43]. The rationale for investigating the expression of CXCR4 in tumors as a prognostic factor for the unfavorable disease outcomes is supported by our analysis of the survival of GC patients. OS of patients with CXCR4-positive tumors was poorer than that of patients with CXCR4-negative tumors. In all patients with CXCR4-positive tumors, the risk of unfavorable outcome increased by almost a factor of 3. 99% of patients with a high number of CXCR4-positive cells in the tumor died in the group treated with surgery alone, and 71.4% in the group treated with adjuvant chemotherapy. CXCR4-positive cells in the BM were found in 46% of all patients and in 62.1% of patients with CXCR4-positive tumors. OS was longer in all patients with BM characterized by CXCR4-negative status, as compared to patients with CXCR4-positive BM [44].

Hypoxia and tumor-infiltrating lymphocytes. According to our data [45], the availability of tumor-infiltrating lymphocytes (TILs) in the tumor was not associated with clinicopathological characteristics. Nevertheless, there are associations between the number of TILs and the level of hypoxia in GC tissue: the probability of a low number of intratumoral $CD8^+$-TILs increased 5-fold when severe or moderate intratumoral hypoxia was detected, but no relationship between the presence of $CD45RO^+$-TILs and the level of hypoxia in the tumor was found. MMP-2 activity in GC inversely correlated with the number of intratumoral $CD8^+$- and $CD45RO^+$-T cells. CD8- and CD45RO-positive status is not an independent prognostic factor of OS for all patients. A prognostic value of tumor infiltration by $CD8^+$- and $CD45RO^+$-TILs was found only in patients with the M_0 category. In patients with tumors of the M_0 category with a small number of TILs, who received adjuvant chemotherapy, the risk of an unfavorable disease outcome increases by a factor of 3.

OS was significantly better in patients whose tumors were characterized by a large number of TILs compared to patients whose tumors had low TIL counts, suggesting that TILs might control tumor growth. Our results indicate that the potential clinical significance of considering the number of TILs as prognostic factors for patients with category M_0 is possibly more important than for patients with category M_1 [40].

Hypoxia and $CD8^+$ and $CD45RO^+$* cells in *BM. In our study [46], 80.5% and 81.3% of patients with GC had $CD8^+$- and $CD45RO^+$-lymphocytes in BM, respectively. No correlation was found be-

tween the presence of $CD8^+$- or $CD45RO^+$-T cells in BM and clinicopathological characteristics. The association between the presence of $CD8^+$ and $CD45RO^+$ T cells in BM and the hypoxia level in GC tissue was not detected and probably did not influence their activities. GC patients with the presence of $CD8^+$ and $CD45RO^+$ T cells in BM demonstrated better OS than those without them. However, the association between the presence of $CD8^-$ and $CD45RO^+$ T cells in BM and OS in patients who had been treated with surgery alone or adjuvant chemotherapy was insignificant [40, 46].

Hypoxia and minimal residual disease. Metastatic disease is the leading cause of cancer-related death and involves critical interactions between tumor cells and TME. Cytokeratin-positive cells (disseminated tumor cells, DTCs) in the BM belong to the category of so-called minimal residual disease. Hypoxia is a potent microenvironmental factor promoting metastatic progression. The hostile conditions of TME, in particular hypoxia, are among the reasons for the exit of tumor cells from the primary node, being a factor of unfavorable prognosis in patients with GC, in particular due to stimulation of hidden metastasis in BM within a long period before the formation of metastases in distant sites.

These findings are supported by our data showing that tumor cells in BM are found in 51.4% of patients with GC of category M_0. There was no association between DTCs in BM and clinicopathological characteristics. There is a significant correlation between the level of tumor hypoxia and the frequency of DTCs in BM. The probability of the appearance of tumor cells in the BM of patients with category M_0 increased by a factor of 11.4 when tumors were characterized by severe and moderate hypoxia [47].

Many of the factors mentioned above stipulate the process of tumor cell dissemination and ultimately affect the disease outcome. We demonstrated that there was a direct correlation between the VEGF-positive cell number in the tumor and DTCs in BM. The tendency was assessed only for the correlation between CK-positive BM and the number of $CD68^+$ cells, as well as MVD in the primary tumor. The inverse correlation was shown between C-MYC expression in the tumor and CK^+-cells in BM. There was also a significant direct correlation between CK-positivity of BM and MMP-2 activity in the tumor. An increased activity of both gelatinases in BM was associated with the presence of DTCs in the BM of patients with M_0, which allows suggesting that gelatinases may play a significant role in the formation of a premetastatic niche, in particular in the reorganization of cellular TME in BM. There is a direct connection between the presence of DTCs in BM and CXCR4 expression in the primary tumor, which is a potential trigger for metastasis into distant organs. When tumors were characterized by positivity for CXCR4 cells, the probability of the appearance of DTCs in the BM of patients is increased by a factor of 4.0. The risk of unfavorable outcome increased significantly in M_0 category patients, both with CXCR4-positive BM and DTCs in BM.

The presence of DTCs in BM was accompanied by Flt-1 positivity of BM. The simultaneous presence of tumor cells and Flt-1-positive cells in BM is clinically relevant for metastasis. It was also evaluated that the OS of patients with category M_0, both with CK^+ cells and Flt-1^+ cells in the BM, was significantly shorter than that of patients without DTCs in BM but with Flt-1-positive BM (these patients were treated with adjuvant chemotherapy).

The OS of patients with DTCs in BM and with $CD8^+$ T cells in BM was significantly longer than that of patients with CD8-negative BM. It may be suggested that tumor cells in BM are controlled in a dormant state by T cells in BM, in particular by the $CD8^+$ T cells. Under strong or moderate tumor hypoxia, the probability of the appearance of DTCs in BM increases by a factor of 3 when the tumors were characterized by a reduced number of TILs.

The OS of patients with M_0 with DTCs in BM who were treated by surgery only was significantly shorter than that of patients without DTCs; they have risk of unfavorable outcome increased by a factor of 2, indicating the necessity of adjuvant chemotherapy [40, 47].

Before making a decision on further treatment, it is necessary to consider the detection of CK-positive cells in BM as an obligatory procedure, in particular, in patients with category M_0. The detection of DTCs in BM is a relevant indicator for personalized cancer therapy, in particular for the choice of treatment tactic in GC patients, especially with category M_0.

Hypoxia and cancer-associated adipocytes. Adipose tissue is appreciated as a major regulator of

metabolic physiology and endocrine homeostasis. Different molecules involved in the dialogue between tumor cells and cancer-associated adipocytes (CAAs) represent promising therapeutic targets in cancer patients. It is suggested that hypoxia has a pervasive effect on the adipocyte metabolism and overall adipose tissue function, underpinning the inflammatory response in the tissue [48].

In hypoxic TME, during interaction with cancer cells, adipocytes dedifferentiate into pre-adipocytes or are reprogrammed into CAAs. They modulate TME by promoting angiogenesis, affecting immune cells, and altering metabolism to support the growth and survival of metastatic cancer cells [48—50].

According to our data, adipocytes are the major component of the TME of GC: 51.6% of patients with GC have a high density of CAAs, among them 89.5% have obesity. No significant correlation between CAAs in the tumor and the clinicopathological characteristics or the hypoxia level was found, but the presence of high-density CAAs is mainly observed at the advanced stage of the disease, and the hypoxic state of the primary tumor essentially determines an excessive amount of CAAs [51].

There is an association between the CAA density in the tumor and the presence of DTCs in BM. Hypoxia in the primary tumor under the high density of CAAs leads to a 4-fold increase in the probability of the appearance of DTCs in BM, which was detected in more than 80% of patients [52]. The OS of patients with GC is influenced mainly by the CAAs density in tumors, and such influence depends essentially on the body mass index. Only 8.3% of patients with a deficiency of body weight of various degrees and a low density of CAAs in the tumor have DTCs in BM, but when tumors are characterized by a high CAA density, the number of such patients increases up to 81.3%. Under a high density of CAAs, the probability of DTCs availability in BM increased significantly (especially in category M_0) in patients with normal weight compared to obese patients. The OS of such patients is shorter with a high risk of mortality. In patients with obesity, the incidence of DTCs availability in BM significantly decreased, despite a low density of TILs and increased level of CXCR4 expression in the tumor. They demonstrated longer OS than the patients with normal weight [53]. Probably, the peculiarities of adipose tissue under obesity stipulate altered conditions within the TME to prevent cells' escaping from the primary lesion. Understanding the pathophysiological mechanisms of metabolic symbiosis between cancer cells and adipocytes in GC patients with normal weight might have clinical relevance and warrants further investigation.

Conclusion

In recent years, the study of TME has been achieving remarkable advances. Understanding of TME is of great potential for new opportunities in personalized therapy to improve clinical treatment and predict the disease outcome. Hypoxia level, as an integral parameter of TME, regulates and controls most microenvironmental factors. Available literature and findings of our extensive research emphasize the clinical relevance of evaluating the potential biomarkers regulated by hypoxia that could be incorporated into strategies aimed at preventing and treating metastatic disease. We suppose that such therapy based on the understanding of distinctive properties of the tumor will be highly selective, allowing the highest possible therapeutic gain for a more favorable prognosis of the disease outcome and OS of patients with GC.

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ВПЛИВ ГІПОКСІЇ НА ФАКТОРИ МІКРОСЕРЕДОВИЩА РАКУ ШЛУНКА. ЗВ'ЯЗОК ІЗ КЛІНІЧНИМ РЕЗУЛЬТАТОМ

Мікрооточення пухлини (ТМЕ) відіграє вирішальну роль у її прогресуванні та метастазуванні. Рівень гіпоксії, як інтегральний параметр ТМЕ, займає ключове місце в регуляції та контролі всіх подій, що відбуваються в ТМЕ. Огляд досліджень зосереджено на висновках, отриманих авторами під час вивчення впливу гіпоксії на процеси, пов'язані з факторами мікрооточення, з метою виявлення його прогностичного значення щодо перебігу захворювання. Було встановлено, що значною мірою більшість факторів мікрооточення, асоційованих з гіпоксією, залучені в процеси відповіді пухлини на терапію, їх значення в розвитку мінімальної залишкової хвороби, а також у процесах, на які впливає жирова тканина. Огляд аналізує результати досліджень процесів, пов'язаних з факторами мікрооточення, а також їх комбінацій, які можуть бути клінічно корисними щодо терапевтичних стратегій з максимально можливим високоселективним терапевтичним ефектом на перебіг захворювання і виживаність хворих на рак шлунка.

Ключові слова: рак шлунка, гіпоксія пухлини, фактори ТМЕ, пухлино-асоційовані адипоцити, мінімальна залишкова хвороба.