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Hypoxia-Induced Expression of miR-424, miR-155, *CD47*, and *PD-L1* in a Gastric Cancer Cell Line (MKN-45)

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ABSTRACT

Background: Hypoxia (pO_2 < 5-10 mmHg) is a critical feature of the tumor environment that causes genetic and epigenetic changes. This study aimed to evaluate the effect of hypoxia on the expression of immune checkpoint genes (*CD39, CD47*, and *PD-L1*) and their regulatory microRNAs (miRNAs; miR-155, miR-424, miR-133, miR-142) in the gastric cancer cell line MKN-45.
Methods: MKN-45 cells were cultured under standard conditions and treated with 25 µM of $CoCl_2$ for 24 hours to induce hypoxia. In the next step, the mRNA expression levels of *CD39*, *CD47*, *PD-L1*, miR-155, miR-424, miR-133, and miR-142 were analyzed in the MKN-45 cells under hypoxia versus normoxia. Also, the protein levels of PD-L1 were assessed using Western blot analysis.
Results: Hypoxia was confirmed by increased hypoxia-inducible factor 1α expression in MKN-45 cells treated with $CoCl_2$. Under hypoxic conditions, *CD47* and *PD-L1*, as well as miR-424 and miR-155, showed significantly higher expression levels in hypoxia compared to normoxia. Also, Western blot analysis corroborated the increased PD-L1 expression in hypoxia. However, *CD39*, miR-133, and miR-142 did not show statistical differences between the two conditions.
Conclusion: Our in vitro findings indicate that *CD47* expression under hypoxic conditions may be influenced by other miRNAs (miR-424) or the duration of hypoxia. Also, the relationship between *PD-L1* and miR-155 expression suggests that PD-L1 can be regulated by other miRNAs and that hypoxia enhances its expression. These outcomes indicate that targeting hypoxia in the tumor microenvironment may improve cancer immunotherapy strategies. ***DOI: 10.22034/IBJ.30.4.234***

Keywords: Hypoxia, Gene Expression, MicroRNAs, Neoplasms

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1. INTRODUCTION

Gastric cancer (GC) is the fifth most frequent cancer and the third main cause of cancer death globally[1]. The incidence of GC increases with age, and its prevalence is two to three times higher in men than in women[2]. Environmental factors and lifestyles play a major role in

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disease etiology, and the most important risk factor for this disease is *Helicobacter pylori* infection. However, the contribution of other factors such as dietary factors, cigarette smoking, obesity, alcohol consumption, medications, genetics, and Epstein-Barr virus is also effective in the incidence of gastric cancer[3].

One of the molecular mechanisms for cancer progression is the expression of specific ligands for inhibitory checkpoints in infiltrating immune cells and subsequent immune responses. Immune system checkpoints are regulators of the immune system and play an important role in inhibiting the anti-tumor response and subsequently in the tumor escaping from the immune system[4]. Some of the most important immune checkpoints are PD1/PD-L1, CD47/SIRP1a (signal regulatory protein alpha), VISTA, and CD39[5,6].

Among the suppressor molecules of the immune system, CD39 is an ectoenzyme that, along with CD73, facilitates the conversion of adenosine triphosphate into adenosine diphosphate and cyclic adenosine monophosphate, resulting in the release of an immunosuppressive form of adenosine within the tumor microenvironment (TME)[7]. CD47, a cell surface protein expressed in various cell types such as cancer cells, is a crucial regulator of the TME. The interaction between CD47 on tumor cells and SIRPα on myeloid cells creates a signal that inhibits immune detection and phagocytosis of the tumor cells, facilitating their evasion of immune response and uncontrolled proliferation[8]. PD-L1 in combination with PD-1 also prevents the proliferation of PD-1-positive cells, inhibiting cytokine secretion, inducing apoptosis, and attenuating anti-tumor immunity[9].

MicroRNAs (miRNAs) are a group of non-coding RNAs that play a crucial role in the regulation of gene expression and are involved in various cellular processes, leading to different pathological conditions, including various types of cancer[10]. Many studies have investigated miRNA expression across different types of cancer and discovered that miRNA profiles varied between healthy and malignant cells or tissues. Therefore, it is speculated that each type of tumor has a specific expression pattern of miRNAs, and heterogeneous miRNA expression is significantly related to tumor stage, lymph node metastasis, poor prognosis, and response to different treatments[11].

Recent studies have highlighted correlations between the hypoxia pathway and abnormal miRNA expression, as both are involved in cancer cell metastasis, proliferation, signaling pathways, and differentiation. Further research has documented that the hypoxia pathway impacts miRNA expression profiles and, more attractively, miRNAs affect the hypoxia pathway[10]. miRNAs directly or indirectly control immune checkpoint proteins in numerous cancers, such as glioma, colorectal cancer, melanoma, and acute myeloid leukemia, to impede the anti-cancer capacity of immune cells[14-19].

This study aimed to investigate the effect of hypoxia on the expression of *CD39*, *CD47*, and *PD-L1* genes, along with the miRNAs that control their expression in the MKN-45 GC cell line. Overall, the present study offers novel research on how hypoxia conditions affect the expression of the genes *CD39*, *CD47*, and *PD-L1*, as well as the miRNAs that regulate these genes in the GC cell line MKN-45. While prior research has examined the significance of hypoxia in tumor biology, few studies have examined the coordinated regulation of these immune-related genes and their regulating miRNAs in GC under low-oxygen conditions. Our study offers novel insight into the molecular processes underlying immune evasion and tumor growth in GC by integrating gene and miRNA expression studies under hypoxia, which may identify new targets for therapeutic intervention.

2. MATERIALS AND METHODS

2.1. Cell culture

The human GC cell line MKN-45 was obtained from the National Cell Bank of Iran (the Pasteur Institute of Iran, Tehran, Iran). The cells were cultured in complete Roswell Park Memorial Institute 1640 medium (Gibco, El Paso, TX, USA) supplemented with 10% fetal bovine serum (Gibco), 100 U/ml of penicillin, and 100 U/ml of streptomycin. These cells were kept in a 95% humidified incubator in 5% CO_2 at 37°C for 48 hours.

2.2. Cell treatment

To evaluate the effect of hypoxia on the expression of immune checkpoint genes (*CD39, CD47*, and *PD-L1*) and their regulatory miRNAs (miR-155 and miR-424 for PD-L1, miR-133 for CD47, and miR-142 for CD39), we divided the GC cell line MKN-45 into two groups: one group was treated with 25 μM $CoCl_2$ for 24 hours to induce hypoxic condition, and the other group remained untreated and served as the control. The induction of hypoxia was validated using the MTT assay at different concentrations of $CoCl_2$, as established in our previous studies in the same laboratory (unpublished data).

2.3. Total RNA isolation

Total RNA was isolated from the cells using RiboEX reagent (GeneAll Biotechnology, Seoul, South Korea) according to the manufacturer's protocol. The RNA concentration was determined using a NanoDrop spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA) and then stored at -80°C until expression assessment.

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2.4. Complementary DNA (cDNA) synthesis

cDNA was synthesized by Bio-Tech (Seoul, South Korea) using a Bio-Rad T100 Thermal cycler for mRNA expression analysis. Also, cDNA for miRNA expression was synthesized with the Bio-Tech cDNA Synthesis Kit based on the manufacturer's protocol.

2.5. Primer design

Specific primers were designed using Primer Express 3.0 (Applied Biosystems, Foster City, CA, USA), and their specificity was confirmed by running a BLAST search in the nucleotide database. The final primer sequences are provided in Tables S1 and S2.

2.6. Quantitative real-time PCR (qRT-PCR)

For the assessment of the expression levels of mRNAs and miRNAs, qRT-PCR was performed using SYBR Green master mix on a LightCycler 96 system (Roche Diagnostics, Mannheim, Germany). The expression patterns of mRNAs for target genes were normalized and examined using *GAPDH* as a housekeeping gene. Also, to normalize the miRNAs, we employed U6 as an endogenous control.

2.7. Western blot analysis

To examine the PD-L1 protein expression level, we harvested MKN-45 cells under both normal and hypoxic conditions and lysed them with a lysis buffer (500 µl Tris [pH 8.0], 0.003 g EDTA, 0.08 g NaCl, 1% NP-40, 0.025 g sodium deoxycholate, and one tablet of protease inhibitor cocktail). Equal amounts of protein (30-40 µg) were loaded onto the gel. For Western blotting, anti-PD-L1 or anti-β-actin (both from Santa Cruz Biotechnology, USA) antibodies (2.5 µg/ml) were added and incubated for 16-18 hours. The blots were then washed, and a species-matched peroxidase-conjugated secondary antibody (1:1000) was added. Labeled bands on the washed blots were detected by enhanced chemiluminescence (Amersham, USA). However, the assessment of the CD39 and CD47 proteins was not performed due to the unavailability of monoclonal antibodies for both markers.

2.8. Statistical analysis

SPSS version 25.0 (Chicago, IL, USA) was used for all statistical analyses. All graphs were drawn by GraphPad Prism 6.0.1 software. The normality of variables was checked by the Kolmogorov-Smirnov test. Continuous variables are defined as the mean ± standard deviation (SD). The comparison of data between two groups was determined by a t-test, and the comparison among more than two groups was determined by Kruskal-Wallis and One-Way ANOVA tests. *P* values less than 0.05 were considered significant.

3. RESULTS

3.1. Confirmation of hypoxia

Hypoxia-inducible factor (HIF)-1α is a transcription factor that regulates the expression of dozens of genes involved in oxygen homeostasis within cells. The expression of *HIF-1α* was measured by real-time PCR under normoxic and hypoxic conditions to confirm the development of hypoxia using $COCL_2$ in the cultured cells. The results of *HIF-1α* expression changes are shown in Figure 1.

3.2. Expression levels of *CD39*, *CD47*, and *PD-L1* genes

We observed significantly increased expression levels of both *CD47* and *PD-L1* in hypoxia compared to the normoxic condition ($p \leq 0.05$ and $p \leq 0.01$, respectively). In addition, the expression level of *CD39* increased in hypoxia compared to normoxia (Fig. 2).

3.3. Expression levels of miR-424, miR-155, miR-133, and miR-142

The significantly increased expression of miR-424 and miR-155 was found in hypoxic conditions compared to normoxic conditions. However, miR-133 and miR-142 did not show statistically significant differences between the two conditions (Fig. 3).

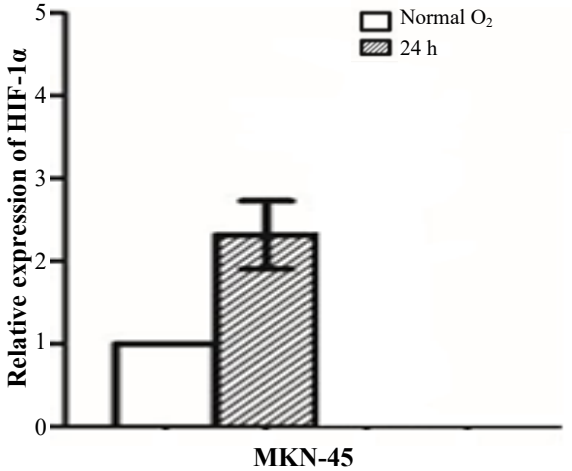

Fig. 1. *HIF-1α* gene expression in hypoxia versus normoxia. Data are presented as mean ± SD from two biological samples, with two technical replicates per sample within 24 hours (p = 0.04).

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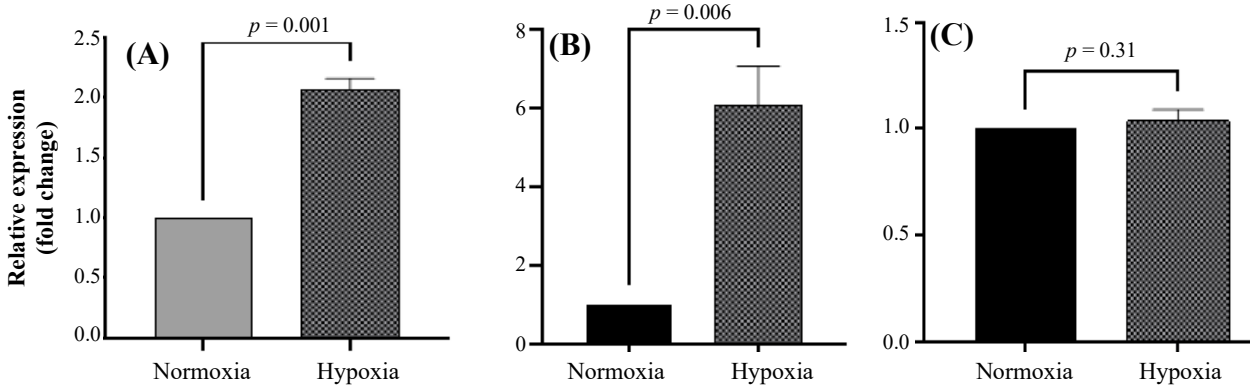

Fig. 2. The expression analysis of (A) *CD47*, (B) *PD-L1*, and (C) *CD39* genes in the MKN-45 cell line in hypoxia condition compared to normoxia. Data are presented as relative gene expression levels normalized to GAPDH and represent the mean of three technical replicates. The numbers above the bars indicate the corresponding *p* values.

3.4. PD-L1 protein expression analysis

Western blot analysis confirmed increased expression of PD-L1 in the hypoxic compared to the normoxic condition in the MKN-45 cell line. Furthermore, β-actin was used as a control. Densitometry was performed using ImageJ software, and the intensity of each band was normalized to β-actin. The results are shown as the relative expression level compared to the control group, which was set to 1.0. As shown in Figure 4, hypoxia significantly increased PD-L1 expression.

4. DISCUSSION

Research has shown that hypoxia occurs in most tumors by reducing normal tissue oxygen levels[12]. In addition, hypoxia frequently changes the metabolism of tumor cells by inducing cell inactivity, as well as altering the transport and/or distribution of chemotherapy, immunotherapy, and radiotherapy, resulting in resistance to these therapies[13]. Depending on its severity, hypoxia can stimulate adaptive responses that affect apoptosis, cell survival, and tumor growth[14,15]. As a regulatory mechanism for gene expression, miRNAs are involved in many cellular processes, including cell division, cell differentiation, angiogenesis, migration, apoptosis, and oncogenesis. The expression patterns of these small non-coding regulatory RNAs (e.g., miR-21 and miR-106a) can change the response to chemotherapeutic agents or other anticancer treatments[16,17].

In the present study, an increased expression of CD47 mRNA and a non-significantly decreased expression of miR-133 were found under hypoxic compared to normoxic conditions. An earlier study has shown a relationship between the increased expression of miR-133 and the inhibition of cell proliferation and migration, as well as the induction of apoptosis, by targeting the CD47 molecule[18]. Suzuki et al. have demonstrated that high expression levels of CD47 are associated with lymph node metastasis, and that miR-133 expression is significantly lower in cancerous tissues compared to adjacent non-cancerous tissues. They also showed that miR-133 is a direct regulator of CD47 that significantly inhibits tumorigenesis and

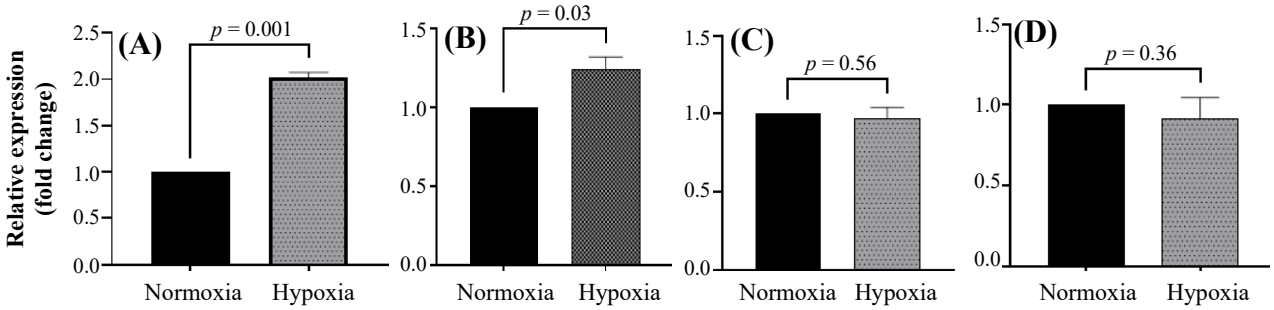

Fig. 3. The expression levels of specific mRNAs. (A) *miR-424*, (B) *miR-155*, (C) *miR-133*, and (D) *miR-142* in the MKN-45 cell line under hypoxia compared to normoxia. Data are presented as relative gene expression levels normalized to GAPDH and represent the mean of three technical replicates. The numbers above the bars indicate the corresponding *p* values.

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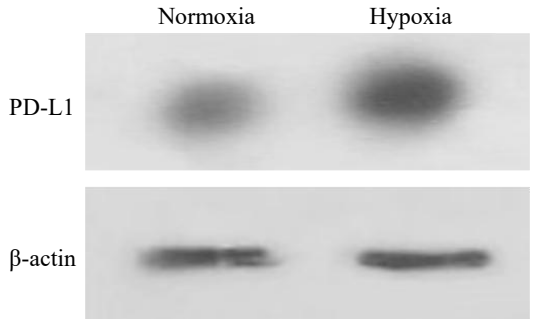

Fig. 4. PD-L1 protein expression analysis by Western blotting. Increased expression of PD-L1 protein under hypoxic versus normoxic conditions in MKN-45 cancer cells.

tumor growth in vivo[19]. Furthermore, Yan et al. have demonstrated that CD47 is upregulated, and miR-133a is downregulated in triple-negative breast cancer, identifying CD47 as a direct target of miR-133a for the first time[20]. The decreased level of miR-133 expression observed in our in vitro study might be due to its long-term exposure to hypoxia. Moreover, an increased expression of CD47 under hypoxic conditions could be consistent with the studies showing the higher expression level of CD47 in metastatic tumors compared to primary tumors. However, these in vitro findings should be interpreted with caution in comparison to similar preclinical or clinical studies. Increased expression of CD47 under hypoxic conditions promotes disease progression by enabling tumor escape from phagocytosis. We observed a significant increase in *PD-L1* gene expression in hypoxic compared to normoxic conditions.

Various studies have shown the role of PD-L1 as a biomarker in immune evasion and metastasis of tumor cells[9]. Studies have also indicated that hypoxia and the PD-L1 molecule are two important factors in the progression and metastasis of various cancers. Zhou et al. have demonstrated that PD-L1 expression is significantly increased under hypoxia and correlates with clinical characteristics of follicular thyroid cancer, such as tumor size, metastasis, and disease stage[21]. Xu et al. have shown that miR-424 expression inversely correlates with PD-L1 expression level in ovarian cancer. They have also found that hypoxia suppresses the PDCD4 protein, a tumor suppressor involved in apoptosis, by inducing miR-424 expression in various cancer cells. In contrast, inhibition of miR-424 enhances apoptosis and increases the sensitivity of cancer cells to chemotherapy[22]. Moreover, Wei et al. have indicated that the upregulation of miR-424 may cause the growth of GC cells[23]. In our study, the increased expression of miR-424 under hypoxic conditions could be indicative of the predominant effect of hypoxia on MKN-45 GC cells. In light of this observation, the level of miR-424 expression may serve as a potential biomarker for the stage and prognosis of this cancer. Of note, other miRNAs, such as miR-146 and miR-155, may upregulate the expression of the *PD-L1* gene[9]. In our study, the expression of miR-155 significantly increased in hypoxic conditions compared to normoxic conditions. Bayraktar et al. have found that miR-155 acts as an onco-miRNA due to its overexpression in various malignant tumors, as well as making them resistant to chemo- and radio-therapy[24]. Furthermore, Babar et al. have demonstrated that hypoxia induces miR-155 expression in lung cancer cells[25]. Golovina et al. have confirmed the combined impact of hypoxia and the deletion of miR-155 on the proliferation rate of MEC-1 cells, where the deletion of miR-155 strongly suppresses cell growth in normoxic and hypoxic conditions[26]. The results from our study indicate that the increased expression of miR-155 may relate to increased PD-L1 expression, which, in turn, can cause the downregulation of anti-tumor immune responses and the apoptosis of activated T cells in favor of disease progression. According to these in vitro findings and related studies, PD-L1 and miR-155 could serve as therapeutic targets in the treatment of GC, although further studies are needed to clarify this relationship.

CD39 is a molecule involved in immune checkpoint regulation and facilitates tumor escape from the immune system. In an acutely hypoxic TME, cell death releases ATP, which is then metabolized to adenosine by the ectonucleotidases CD39 and CD73. This process suppresses T-cell functions in the extracellular matrix[27,28]. Theodoraki et al. have found that patients with advanced cervical cancer exhibit high levels of CD39 expression[29]. Zhao et al. have also demonstrated that the increased expression of CD39 occurs in Treg cells by decreasing the expression of miR-142[30].

In the present study, the expression of the *CD39* gene did not significantly increase under hypoxic compared to normoxic conditions. Likewise, the expression of miR-142 did not decrease significantly in hypoxic compared to normoxic conditions. Cao et al. have shown that the high expression of miR-142 inhibits the growth and development of cancer cells, while its lower expression levels increase the number of cancer cells[31]. Notably, our in vitro findings indicate that longer incubation with CoCl2, an inducer of hypoxia, could change the expression levels of *CD39* and *miR-142*, though it needs to be examined by further studies.

5. CONCLUSION

The present study investigates the effects of hypoxia on the expression levels of immunosuppressive genes (*CD39*, *CD47*, and *PD-L1*) and the miRNAs (*miR-155, miR-424, miR-133, and miR-142*) that regulate these genes. Our in vitro findings indicate that the expression

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of *CD47* under hypoxic conditions may be influenced by other miRNAs or the duration of hypoxia, potentially enabling tumor survival by evading phagocytosis. This observation suggests a potential target for therapeutic intervention. Additionally, the simultaneous increase in the expression of *PD-L1* and miR-155 implies that *PD-L1* might be regulated by different miRNAs, and that hypoxia could enhance its expression. Variability in the expression level of miR-424 in MKN-45 cells and across disease stages exhibits its potential as a diagnostic indicator. Although *CD39* showed an association with miR-142 during hypoxia, the changes were not significant compared to normoxic conditions, suggesting a need for further investigation. Overall, targeting hypoxia in tumors has the potential to improve cancer immunotherapy approaches.

DECLARATION

Acknowledgments

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Generative AI and AI-assisted technologies

During the preparation of this work, we used AI Summerizer to edit and paraphrase some sentences. The authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

Ethical approval

All the experimental procedures in this study were conducted in accordance with the principles of the Helsinki Declaration and approved by the Research Ethics Committee of Hamadan University of Medical Sciences, IRAN (ethical code: IR.UMSHA.REC. 1399.524).

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Authors' contributions

SS and NO: data curation and writing-original draft. TK and GS: conceptualization, methodology, software, supervision, validation, and writing-review and editing.

Data availability

All relevant data can be found within the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Supplementary information

The online version contains supplementary material.

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