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DNA BREAKS AND REPAIR IN LYMPHOCYTES AS A DIAGNOSTIC MARKER IN PATIENTS WITH GASTRIC CANCER

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ABSTRACT

Relevance: *Timely detection of foci of DNA double-strand breaks (DSBs) with subsequent initiation of the repair mechanism plays a crucial role in the overall response to DNA damage. Untimely resolution of DNA DSBs and disruptions in the repair pathway constitute a fundamental mechanism in cancer development and progression. A search for biomarkers is needed to identify DNA DSB foci and achieve a better outcome of targeted therapy.*

The study aimed to *identify comparative differences in DNA double-strand breaks and repair activity in γ-H2AX and 53BP1 parameters in apparently healthy individuals and patients with gastric cancer.*

Methods: *Analysis of focal points of γ-H2AX, 53BP1 with lymphocyte parameters using the automated AKLIDES® system in gastric cancer patients (n=30) and apparently healthy individuals (n=30).*

Results: *Statistically significant differences were found between apparently healthy individuals and patients with gastric cancer in γ-H2AX parameters: "Total number of breaks" (p=0.001), "Number of nuclei with break foci" (p=0.015), "Average number of breaks per cell" (p=0.016), "Mean value of all break foci per cell" (p=0.001), and in 53BP1 parameters: "Number of nuclei with repair foci" (p=0.001), "Mean intensity of repair fluorescence in arbitrary units" (p=0.001), "Mean number of repairs per cell" (p=0.001), and "Number of damaged cells with low fluorescence intensity" (p=0.019).*

Conclusion: Biomarkers of DNA DSBs with repair activity (γ-H2AX, 53BP1) have clinical significance, contributing to the development of targeted medicine in oncology.

Keywords: *DNA double-strand break (DSB), γ-H2AX, 53BP1, gastric cancer.*

Introduction: Gastric cancer is the 5th most common malignant disease worldwide and the third leading cause of cancer mortality. In 2020, the incidence of gastric cancer in Kazakhstan was 9.5 per 100,000 population. This pathology ranked 3rd in cancer morbidity (after breast cancer and lung cancer) and 2nd in cancer mortality. In men, gastric cancer ranked 2nd in cancer incidence after lung cancer (12.7% per 100,000 male population) and second in cancer mortality. In women, gastric cancer ranked 4th in incidence (6.6% per 100,000 female population) and 3rd in cancer mortality. Unfortunately, in the Republic of Kazakhstan, 5-year survival with gastric cancer is only 28.2% [1, 2].

More than half of gastric cancer patients are diagnosed at advanced stages and the 5-year survival rate ranges from 20 to 30%. Despite current achievements in treating gastric cancer, the prognosis remains unfavorable. The classification of TNM is the main prognostic tool for the categorization of patients and the choice of treatment. However, its limitations are increasingly recognized. Early relapses can occur at an early stage of the disease, and patients at the same stage may have heterogeneous outcomes [3]. Thus, there is a need to study the relevant prognostic factors for further identification of therapeutic targets.

Carcinogenesis has a complex scheme that involves multiple endogenous and exogenous DNA double-strand breaks (DSB). DNA DSBs are among the most dangerous events that lead to genomic instability and subsequent development of the cancer process. However, DNA damage activates a multiplicate cellular response, which includes detecting the damaged site through a cascade of protein kinases, signal amplification, and activation of several effectors contributing to cell cycle arrest, DNA repair, and apoptosis activation. This combination of complex mechanisms represents the DNA damage response [4]. During oncogenesis, precancerous cells often acquire changes that lead to loss of functionality of DDR genes responsible for repair activity; this accelerates mutagenesis and induces carcinogenesis [5].

Although healthy cells overcome minor damage and take full advantage of DNA repair, malignant cells often possess reduced DNA repair functionality to cope with increased replication stress and endogenous DNA damage [6].

The condition of the terminal structures of DNA DSBs and the cell cycle phase determine the repair path.

In a DNA DSB, the relevant multiple mechanisms coordinate and communicate the cell cycle state to repair sites that involve many genes. In response to a DSB, ATM,

ATR, and DNA-PKc phosphorylate Ser139 of the H2AX histone (γ-H2AX). Within 30 minutes of rupture, many γH2AX molecules are formed in the chromatin around the fracture site. They form a focal point where accumulated proteins are involved in DNA repair and chromatin remodeling [7]. Subsequent recruitment occurs at the 53BP1 protein rupture site. This site, controlled by the γH2AX signaling cascade, plays a role in determining DNA repair [8]. This amplification allows the detection of individual DNA breaks and repair activity with antibodies to γH2AX /53BP1. DSBs indicate genomic instability and can make it possible to assess the effectiveness of anticancer therapy. Monitoring cell rupture by detecting the formation of γH2AX and 53BP1 foci may be a sensitive tool for monitoring cancer progression and treatment [9].

The study aimed to identify comparative differences in DNA double-strand breaks and repair activity in γ-H2AX and 53BP1 parameters in apparently healthy individuals and patients with gastric cancer.

Materials and Methods: This pilot study involved 30 apparently healthy people and 30 patients with a morphologically confirmed diagnosis of 'gastric cancer'. The study was carried out in the Medical Center and the «West Kazakhstan Marat Ospanov Medical University» NCJSC (Aktobe, Kazakhstan). The study protocol was approved by the local bioethics commission (Minutes No. 57, 17.01.2020).

The study material was peripheral venous blood, 10 ml (EDTA tube), containing mononuclear cells. Peripheral blood sampling was performed on a vacutainer with EDTA2 after obtaining informed consent of the study participants.

The γ-H2AX, 53BP1 foci in lymphocytes were analyzed using the γ-H2AX, 53BP1 immunofluorescence staining kit, following the manufacturer's instructions (AKLIDES Nuk Human Lymphocyte Complete, Medipan).

The results were statistically processed in Statistica.10 (Dell Technologies, Round Rock, Texas, USA) using IBM SPSS Statistics 25 software (IBM, NY, USA). The Mann-Whitney frame of reference was used to test two unlinked groups. For the evaluation of diagnostic performance and diagnostic method quality, ROC analysis (MedCalc Software Ltd., Ostend, Belgium) was used to analyze sensitivity and specificity, select the cutoff threshold, and select the model with the best predictive ability. Statistical processing involved the following parameters: measurement of the area under the curve (AUC), calculation of the diagnostic characteristics of the test sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and test accuracy (Accuracy). The results were considered statistically significant at $p<0.05$.

Results: The AKLIDES system determined the ruptures in the lymphocyte nuclei. Patients with gastric cancer demonstrated statistically significant differences in the mean diameter of DNA DSBs ($p=0.001$). However, the nuclei with increased luminescence intensity differed much more in apparently healthy patients ($p=0.001$). The number of nuclei with ruptures also differed significantly ($p=0.015$).

Table 1 assesses DNA DSBs and repair activity in patients with gastric cancer and apparently healthy individuals. The following parameters demonstrated statistically significant differences: the total number of ruptures ($p=0.002$) and the mean value of the intensity of the ruptures in c.u. ($p=0.001$), the mean number of ruptures per cell ($p=0.01$), the average value of all rupture foci in the cell ($p=0.001$), the number of damaged cells ($p=0.001$), the average value of all low foci in a group ($p=0.009$), mean low intensity of all foci in a group ($p=0.009$), and the number of damaged cells with low luminescence intensity ($p=0.01$). No statistically significant differences were found in other cellular parameters.

Table 1 – Comparison of the control group and patients with gastric cancer by the parameters of the AKLIDES system

Parameters of DNA double-strand breaks for the FITS channel using the AKLIDES system (γH2AX histone)	Control	Gastric cancer	*p**
Number of foci counted [n]	861.000	969.000	0.431
The average diameter of nuclei [μm]	617.500	1212.500	0.001
Foci with increased luminescence intensity [AU]	1178.000	652.000	0.001
Number of nuclei with break foci [n]	1078.000	752.000	0.015
Total number of breaks [n]	1122.500	707.500	0.001
Diameter of breaks [μm]	820.000	1010.000	0.163
Mean luminous intensity [AU]	1226.000	604.0000	0.001
Average number of breaks per cell [n]	1134.500	695.5000	0.016
Average number of break foci in a cell [n]	1134.500	695.5000	0.001
Number of damaged cells [%]	1123.500	706.5000	0.0017
The average number of low foci in a cluster [n]	1090.000	740.0000	0.009
Mean low intensity of all foci [n]	1090.000	740.0000	0.009
Number of damaged cells with low luminescence intensity [%]	1082.500	747.500	0.012

Notes: FITS – a marker of DNA DSBs (γH2AX histone); p - Mann-Whitney U-test; Bilateral marked criteria were significant at p<0,05.*

The determination of reparative activity (Table 2) revealed statistically significant differences in both groups by parameters such as 'the number of nuclei with repair foci' ($p=0.001$), 'the mean luminous intensity of repair in c.u.' ($p=0.001$), 'average number of repairs per cell" ($p<0.001$), 'average number of low foci in a group' ($p=0.001$), 'mean low intensity of all foci in a group' ($p=0.031$), and 'the number of damaged cells with low luminescence intensity" ($p=0.019$). No statistically significant differences were found in other cellular parameters.

Table 2 – Comparison of the control group and patients with gastric cancer by the parameters of the AKLIDES system

Parameters of DNA double-strand break reparation for the double-strand DNA break reparation channel (53BP1)	Control	Gastric cancer	*p**
Number of nuclei with reparation foci [AU]	1211.000	619.000	0.001
Total number of reparations [n]	820.000	1010.000	0.163
Diameter of reparation [μm]	810.500	1019.500	0.122
Mean of the reparation luminescence intensity [AU]	1225.000	605.000	0.001
The average number of reparations per cell [n]	777.000	1053.000	0.001
Average number of all foci in the cell [n]	815.500	1014.500	0.142
Number of damaged cells [%]	846.500	983.500	0.313
The average number of low foci in a cluster	703.0000	1127.000	0.001
Mean low intensity of all foci [n]	770.0000	1060.000	0.031
Number of damaged cells with low luminescence intensity [n]	757.0000	1073.000	0.019
Среднее значение всех низких очагов в кластере [n]	1090.000	740.0000	0.009
Среднее значение низкой интенсивности всех очагов [n]	1090.000	740.0000	0.009
Повреждённые клетки с низкой интенсивностью свечения [%]	1082.500	747.500	0.012

Notes: p - Mann-Whitney U-test; bilateral marked criteria were significant at p<0,05.*

The new diagnostic method requires an evaluation of the effectiveness, specificity, and sensitivity of the test (ROC curve). For that purpose, the ROC analysis was performed on the main parameters of DNA DSBs and the reparations of the AKLIDES system for the FITS channel.

At a threshold value of 90, the ROC analysis of the total number of DNA DSBs had a sensitivity of 70%, a specificity of 75%, a PPV of 25.7%, a NPV of 95.3%, and an AUC of 0.72 [95% CI: 0.59-0.83] (p=0.001) (Figure 1).

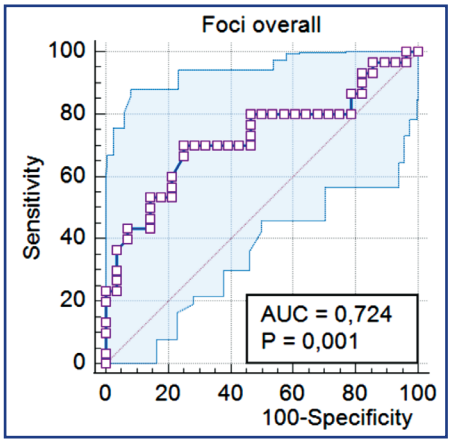

Figure 1 – ROC curve for the "total number of DNA breaks" at values ≤90

The average number of DNA DSB in conventional units (cu): at ≤72.95, the sensitivity was 70%, the specificity was 85.71%, and the AUC was 0.82 [95% CI: 0.70-0.91] (p<0.001) (Figure 2).

The average number of foci with low fluorescence intensity in a cluster of DNA DSB: the sensitivity was 50%, the specificity was 85.71% and the AUC was 0.648 [95%CI: 0.51-0.76] at values ≤1.344 (p = 0.046). The average number of DNA DSBs in a cluster was 66.67%, the specificity was 78.6%, and the AUC was 0.71 [95% CI 0.57-0.81] at values ≤0.804 (p<0.0033). For the number of damaged cells, the sensitivity was 66.67%, the specificity was 78.57%, and the AUC was 0.73 [95% CI 0.59-0.83] at values ≤52.34, p=0.001. For the average number of foci with DNA DSB low luminescence intensity of DNA DSB, the sensitivity was 50%, the specificity was 85.7% and the AUC was 0.65 [95% CI: 0.51-0.76] at values ≤1.344 (p=0.05).

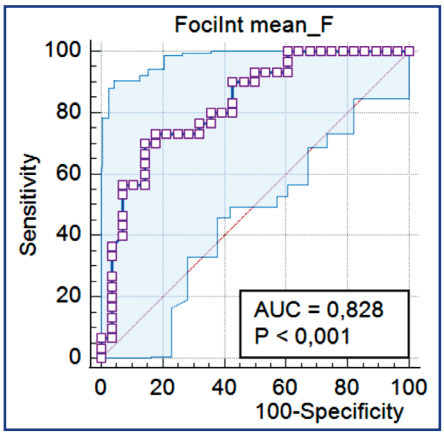

Figure 2 – ROC curve for the 'average number of breaks' at values ≤72.95

The following DNA DSB reparation parameters were obtained for the APC (reparation) channel:

For the 'average number of repairs' of DNA DSBs in c.u., the sensitivity was 73.33%, the specificity was 89.29% and the AUC was 0.83 [95% CI: 0.70-0.91] (p<0.001) (Figure 3).

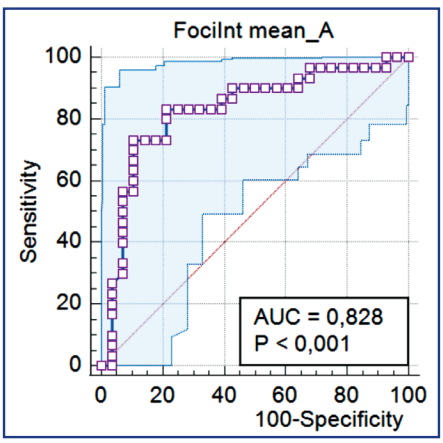

Figure 3 – ROC curve for the "average number of break repairs" at values ≤330.5

For the average number of DNA DSB reparation foci with low fluorescence intensity, the sensitivity was 33%, the specificity was 100% and the AUC was 0.699 [95%CI: 0.56-0.81] at values >5.573 (p=0.0037).

Other parameters of the ROC curve of DSBs and repairs were not statistically significant.

Discussion: Some studies assessed the γH2AX in patients with gastric cancer. According to Chang et al., in the analysis of DNA fragmentation (γH2AX and phospho-53BP1) in histological tissues in 44 patients with gastric ulcer before and after eradication of *H. pylori*, the average γH2AX expression of H2AX was significantly higher in the gastric epithelium infected with *H. pylori* compared to the gastric epithelium with eradicated *H. pylori* (8.8±5.5 vs. 6.2±5.3, p=0.008). The expression of phospho-53BP1 with pre- and post-eradication of *H. pylori* was not statistically different but tended to be higher with *H. pylori* infection. DNA fragmentation was significantly stronger in cell lines exposed to *H. pylori* [10].

In a Korean study by Kim et al., tissue microarrays from 121 patients after gastric cancer surgery and 51 patients after endoscopic gastric adenoma resection were immunohistochemically stained for 53BP1 and gamma-H2AX markers to determine the differences in 53BP1 and gamma-H2AX expression as DNA DSB markers in normal tissues, gastric adenoma and gastric adenocarcinoma. Normal tissues were taken from tissues without histologically confirmed cellular atypia obtained from patients with gastric adenocarcinoma. According to the study results, the expression of 53BP1 and gamma-H2ACh in gastric carcinoma cells was higher than in normal epithelial and gastric adenoma cells (p<0.01). There were no differences in 53BP1 and gamma-H2AX expression in the normal epithelium and gastric adenoma. 53BP1 expression in adenomas with grade II and III atypism was higher than with grade I atypism. 53BP1 and gamma-H2AX expression did not differ significantly in patients with gastric adenocarcinoma with different clinical and pathological parameters [11].

According to Xie et al., the γH2AX overexpression in gastric cancer was correlated with tumor location and differentiation, depth of invasion, stage of TNM, and lymph node metastasis [12].

Conclusion: The statistical differences between apparently healthy individuals and patients with gastric cancer in the results of DNA DSB and DNA repair activity suggest the clinical relevance of studying γH2AX and 53BP1 as diagnostic biomarkers in gastric cancer.

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АҢДАТПА

АСҚАЗАННЫҢ ҚАТЕРЛІ ІСІГІ БАР НАУҚАСТАРДА ДИАГНОСТИКАЛЫҚ МАРКЕР РЕТІНДЕ ЛИМФОЦИТТЕРДІҢ ДНҚ ЫДЫРАУЫ ЖӘНЕ ҚАЛПЫНА КЕЛУІ

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Өзектілігі: *Қостізбекті ДНҚ үзілістері ошақтарының уақытылы анықталуы, содан кейінгі репарация механизмінің басталуы ДНҚ зақымдалуына жалпы жауап беруде маңызды рөл атқарады. Өйткені, қос тізбекті ДНҚ үзілістерін уақытылы жоймау және қалпына келтіру жолын бұзу, ісік дамуының ғана емес, сонымен қатар онкологиялық процестің дамуының негізгі механизмі болып табылады. Мақсатты емдеудің жақсартылған нәтижесіне жету үшін, қостізбекті ДНҚ үзілістерінің ошақтарын анықтауда биомаркерлерді іздеу қажет.*

Зерттеу мақсаты: *Шартты дені сау адамдар мен асқазан обыры бар емделушілер арасындағы γ-H2AX, 53BP1 параметрлеріндегі қос тізбекті үзілістер мен ДНҚ репарация белсенділігінің салыстырмалы айырмашылығын бағалау.*

Әдістері: *Асқазан обыры бар науқастарда (n=30) және шартты сау адамдарда (n=30) автоматтандырылған AKLIDES® жүйесін пайдалана отырып, лимфоциттердегі γ-H2AX, 53BP1 параметрлері бар ошақтарды талдау.*

Нәтижелері: *Дені сау адамдар мен асқазан обыры бар науқастар арасында γ-H2AX параметрлерінде статистикалық маңызды айырмашылықтар анықталды: «Үзілістердің жалпы саны» (p=0,001), «Үзіліс ошақтары бар ядролар саны» (p=0,015), «Бір жасушада-*

гы үзілістердің орташа саны» (p=0,016), «Жасушадағы барлық үзілістердің орташа мәні» (p=0,001), сондай-ақ 53BP1 параметрлерінде: «Репарация ошақтары бар ядролар саны» (p=0,001), «Шартты бірліктерде репарацияның ағару қарқындылығының орташа мәні» (p=0,001), «Бір жасушадағы репарацияның орташа саны» (p=0,001), «Ағару қарқындылығы төмен зақымдалған ұяшықтар» (p=0,019).

Қорытынды: *Қос тізбекті ДНК жіпшелерінің үзіліс пен репарация активтілігін көрсететін биомаркерлер (γ-H2AX, 53BP1) клиникалық тұрғыдан дербестенген диагностикалық әлеуеті анықталды.*

Түйінді сөздер: *ДНҚ қос тізбекті үзілуі, γ-H2AX, 53BP1, асқазан обыры.*

АННОТАЦИЯ

РАЗРЫВЫ И РЕПАРАЦИЯ ДНК В ЛИМФОЦИТАХ КАК ДИАГНОСТИЧЕСКИЙ МАРКЕР У ПАЦИЕНТОВ С РАКОМ ЖЕЛУДКА

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Актуальность: *Своевременное обнаружение очагов двухнитевых разрывов ДНК с последующим запуском механизма репарации занимает важную роль в совокупной реакции при повреждении ДНК. Несвоевременное устранение разрывов двухнитевых ДНК и нарушение пути репарации является основным механизмом не только развития рака, но и прогрессирования онкологического процесса. Для достижения улучшенного результата целенаправленного лечения необходим поиск биомаркеров для выявления очагов двухнитевых разрывов ДНК.*

Цель исследования *– выявить сравнительные различия в показателях двухнитевых разрывов и репарационную активность ДНК в параметрах γ-H2AX, 53BP1 у условно здоровых лиц и пациентов с раком желудка.*

Методы: *Проведен анализ параметров повреждения очагов γ-H2AX, 53BP1 в лимфоцитах на автоматизированной системе AKLIDES® у пациентов с раком желудка (n=30) и условно здоровых лиц (n=30).*

Результаты: *Выявлены статистический значимые различия между условно здоровыми лицами и пациентами с раком желудка в параметрах γ-H2AX: «общее количество разрывов» (p=0,001), «количество ядер с очагами разрывов» (p=0,015), «среднее количество разрывов на клетку» (p=0,016), «среднее значение всех очагов разрывов в клетке» (p=0,001), а также в параметрах 53BP1: «количество ядер с очагами репарации» (p=0,001), «среднее значение интенсивности свечения репарации в у.е.» (p=0,001), «среднее количество репараций на клетку» (p=0,001), «поврежденные клетки с низкой интенсивностью свечения» (p=0,019).*

Заключение: *Биомаркеры двухнитевых разрывов ДНК с репарационной активностью (γ-H2AX, 53BP1) имеют клиническую значимость и потенциал применения в качестве диагностического маркера при персонифицированной медицине.*

Ключевые слова: *двухнитевые разрывы ДНК, γ-H2AX, 53BP1, рак желудка.*

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