THEORETICAL MEDICINE

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 617.735-007.281:616.379-008.64-06:577.21:616-091.8 Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
DOI: https://doi.org/10.32345/2664-4738.2.2026.06 Received: 17.01.2026 Revised: 03.05.2026 Accepted: 28.05.2026 Published: 30.06.2026

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Expression of PMS2 and p53 proteins in retinal tissues in experimental diabetic retinopathy and the effects of insulin and cellular protein kinase inhibition

Abstract

Relevance. The relevance of the study lies in the need to clarify the role of DNA repair mechanisms and genomic stress in the pathogenesis of diabetic retinopathy for the search for new therapeutic targets.

Aim. To determine the expression of PMS2 and p53 proteins in the retinal tissues of rats with experimental diabetic retinopathy (DR) and to assess the effects of insulin and the cellular protein kinase blocker sorafenib.

Materials and methods. The study was performed on 50 male Wistar rats. Diabetes mellitus was modelled by a single intraperitoneal injection of streptozotocin (50 mg/kg). After 7 days, animals with persistent hyperglycaemia were randomised into groups: no treatment, insulin treatment, and combined treatment with insulin and sorafenib. Animals were withdrawn from the experiment after 7 days, 28 days, and 3 months. Immunohistochemical examination was performed using antibodies against PMS2 and p53. The proportion of immunopositive cells was determined per 100 cells in 5 fields of view.

Results. In intact animals, PMS2 and p53 immunoreactivity was minimal. During the development of experimental DR, the number of positively stained cells progressively increased. PMS2-positive cells were localised mainly in the ganglion cell layer and plexiform layers of the retina, whereas p53-positive cells were more strongly associated with the vascular bed. Treatment with insulin and sorafenib was accompanied by increased expression of both markers, with the most pronounced effect after combined administration of the drugs. After 3 months, combined therapy increased the proportion of PMS2-positive cells 2.5-fold and p53-positive cells 3.5-fold compared with the control group ($p < 0.05$).

Conclusions. The development of experimental DR is accompanied by activation of the PMS2- and p53-associated cellular response to DNA damage in retinal tissues. Increased PMS2 expression during treatment with insulin and sorafenib may reflect activation of MMR-associated reparative and adaptive mechanisms. The results support considering PMS2 as a promising marker of genomic stress in diabetic retinopathy.

Keywords: DNA repair; genomic stress; immunohistochemistry; sorafenib; replication.

Suggested Citation:
Usenko K, Ziablitsev S, Diadyk O. Expression of PMS2 and p53 proteins in retinal tissues in experimental diabetic retinopathy and the effects of insulin and cellular protein kinase inhibition. Med Sci Ukr. 2026;22(2): 48–55. DOI: https://doi.org/10.32345/2664-4738.2.2026.06

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INTRODUCTION

Since the early 2000s, the attention of researchers in biology and medicine has focused on DNA repair mechanisms. J.A. Awosika *et al*. [1] demonstrated that mismatch repair (MMR) improves the accuracy of DNA replication by several orders of magnitude, whereas loss of MMR leads to a mutator phenotype that predisposes to cancer. M.G. Marinus [2] noted that mismatch repair is a highly conserved mechanism found in all kingdoms of life. Overall, the role of mismatch repair is to preserve the DNA sequence by removing mismatched base pairs created during replication or homologous recombination. In higher organisms, it is also necessary for successful meiosis, mitosis, and immunoglobulin diversity. In humans, defective mismatch repair is associated with sporadic and hereditary cancers, especially non-polyposis colorectal cancer. U. Chakraborty & E. Alani [3] presented the role of key repair proteins. One of the key components of MMR is the PMS2 protein, encoded by the gene of the same name. As Y. He *et al*. [4] indicated, PMS2 is part of the MutLalpha heterodimeric complex (MLH1/PMS2), which ensures recognition and correction of DNA replication errors, including nucleotide mismatches and insertions/deletions that arise during cell division. The PMS2 protein is characterised by endonuclease activity and participates in the initiation of repair by cleaving the damaged DNA region. Disruption of its expression leads to defects in the MMR system, accumulation of mutations, and development of microsatellite instability, which is associated with an increased risk of neoplastic processes [3-4]. According to Y. He *et al*. [4] and V. Lee *et al*. [5], PMS2 expression is assessed immunohistochemically in clinical practice: the absence of nuclear staining in tumour cells in the presence of internal control staining (stroma) is considered a sign of MMR deficiency. Thus, PMS2 is regarded as a marker of impaired genomic stability.

However, data on PMS2 expression in retinal tissues, particularly in diabetic retinopathy (DR), are practically absent. Current understanding of DR pathogenesis, presented by A.K. Morya *et al*. [6], Y. Yudistira *et al*. [7], and A. Callan *et al*. [8], focuses mainly on the roles of oxidative stress, chronic inflammation, neurodegeneration, reactive gliosis, angiogenesis, including the involvement of vascular endothelial growth factor (VEGF), and endothelial dysfunction. According to M. Zhang *et al*. [9] and Y. Long *et al*. [10], excessive generation of reactive oxygen species during hyperglycaemia can directly damage DNA by inducing double-strand breaks and replication errors. Under these conditions, activation of the cellular DNA damage response system can be expected, including p53 protein, poly(ADP-ribose) polymerase (PARP), and components of the MMR system (MLH1, PMS2, MSH2, and MSH6) [5, 11]. In this context, PMS2 and p53 may potentially serve as markers of genomic stress and activation of reparative processes in retinal cells during DR. The aim of the present study was to determine the expression of PMS2 and p53 proteins in the retinal tissues of rats with experimental diabetic retinopathy and to assess the effects of treatment with insulin and the cellular protein kinase blocker sorafenib.

MATERIALS AND METHODS

An experimental study was conducted in a rat model of streptozotocin-induced diabetes mellitus, with randomised allocation of animals to treatment groups. The study included 50 three-month-old male Wistar rats weighing 140-160 g. Type 1 diabetes mellitus was modelled by a single intraperitoneal injection of streptozotocin (50 mg/kg; Sigma-Aldrich, Co, China) dissolved in cold 0.1 M citrate buffer (pH 4.5). Glycaemia was monitored every three days using a glucometer and disposable test strips (ACCU-Chek Instant, Roche, Mannheim, Germany) in fasting blood collected from the tail vein. Three days after injection, blood glucose in the animals was no less than 15 mmol/L. During the experiment, marked polydipsia, polyuria, ketonuria, and glucosuria were observed; the animals lost substantial weight, which provided grounds for considering the used model of insulin-dependent diabetes mellitus with ketosis in rats adequate. In this study, the animals were observed for 3 months. Five intact animals were used to determine baseline data. After 7 days, animals with persistent hyperglycaemia were divided by blind randomisation into 3 groups of 15 animals each. In group 1 (control), hyperglycaemia was not treated. In group 2, short-acting insulin (Actrapid HM Penfill, Novo Nordisk A/S, Bagsvaerd, Denmark) was administered intraperitoneally every other day at a dose of 30 units. Animals in group 3 received insulin according to the group 2 regimen and were also given an aqueous solution of sorafenib (Sorafenib 200 mg; Cipla, India) orally every day at a dose of 50 mg/kg.

Animals were withdrawn from the experiment after 7 days, 28 days, and 3 months, 5 animals at each time point, by lethal thiopental injection (75 mg/kg). For morphological studies, the eyes were immersed in 10% neutral formalin solution and embedded in paraffin. Serial histological sections 2-3 micrometres thick were prepared from paraffin blocks on an HM 325 rotary microtome (Thermo Shandon, England). Immunohistochemical examination was performed using monoclonal antibodies against PMS2 protein (mouse monoclonal anti-PMS2 antibodies; clone A16-4; dilution 1:100; Biocare Medical, USA) and p53 protein (mouse monoclonal anti-p53 antibodies; clone DO-7; dilution 1:100; Abcam, Great Britain). The Master Polymer Plus Detection system (Master Diagnostica, Spain) was used. Antigen retrieval was performed by heat treatment of sections in citrate buffer (pH 6.0) at 95-98°C for 20 min. The sections were counterstained with haematoxylin. Microscopic examination and photographic archiving

were performed using ZEISS light-optical microscopes with the Axio Imager. A2 result-processing system (Germany). For each animal, 5 independent fields of view were analysed, after which the mean proportion of immunopositive cells was calculated. Group results were expressed as percentages and, after normality testing (Shapiro-Wilk test), calculated as medians and interquartile ranges (Me; QI-QIII). Statistical analysis was performed using Statistica 10 software (StatSoft, Inc., USA). Values were compared using the Kruskal-Wallis test, and intergroup comparisons were performed using the Dunn test; differences were considered significant at $p < 0.05$. The study was conducted in accordance with the standards and principles of Directive 2010/63/EU [12], the requirements of Law of Ukraine No. 3447-IV [13], and the expert conclusion of the Commission on Bioethical Expertise and Ethics of Scientific Research at Bogomolets National Medical University (approval of the research implementation plan on 21 November 2022, Minutes No. 164). Animals were kept in vivarium conditions on a standard diet. The opinions expressed in the submitted article represent the views of the researchers and not the official positions of the institution.

RESULTS AND DISCUSSION

The pathological process was accompanied by decreased cell density in the nuclear layers of the retina, the development of diffuse tissue oedema, which was most pronounced in the inner plexiform layer, and the formation of ischaemic areas combined with vacuolisation of neuronal cytoplasm. The vessels of the choroid and inner vascular plexus were dilated, with signs of microthrombus formation in some areas. Numerous vascular abnormalities in the form of microaneurysms were observed along the inner surface of the retina. The number of ganglion cells decreased, and they showed signs of degenerative changes, including cellular oedema and nuclear pyknosis. These morphological changes were progressive over time, from day 7 to 3 months of observation. At the later stages of the experiment, cellular proliferates were detected in the outer nuclear layer as dense clusters of basophilic cells with a tendency towards radial spread beyond the layer. Thickening and compaction of the inner limiting membrane were also noted, accompanied by accumulation of coarse-fibred basophilic structures. Dilation of microvessels along the inner surface of the retina was also observed in intact animals; however, these vessels were characterised by a small diameter, thin wall, and single lumen. By contrast, microaneurysms that formed during the prolonged course of DR had a more complex structure, with several lumens surrounded by a dense membrane. Marked oedema and widespread ischaemic zones were also identified. The number of ganglion cells decreased, and they acquired marked degenerative features. The number and size of Muller cells increased, which corresponded to reactive gliosis.

The use of insulin or sorafenib was accompanied by less pronounced morphological changes. In these groups, no decrease in nuclear-layer cell density was observed, and retinal oedema and ischaemic lesions were minimal or absent. However, individual signs of damage persisted, including a decrease in the number of ganglion cells and the formation of cellular proliferates. The most pronounced protective effect was observed with combined use of insulin and sorafenib. Under these conditions, the retinal structure remained close to normal, and the morphological signs of DR characteristic of the control group were practically absent. In particular, typical manifestations of pathological angiogenesis and cellular proliferative changes were not detected. Specific PMS2-immunopositive staining in the retina of intact rats was practically absent; isolated positive cells were detected mainly in the ganglion cell layer (Fig. 1a).

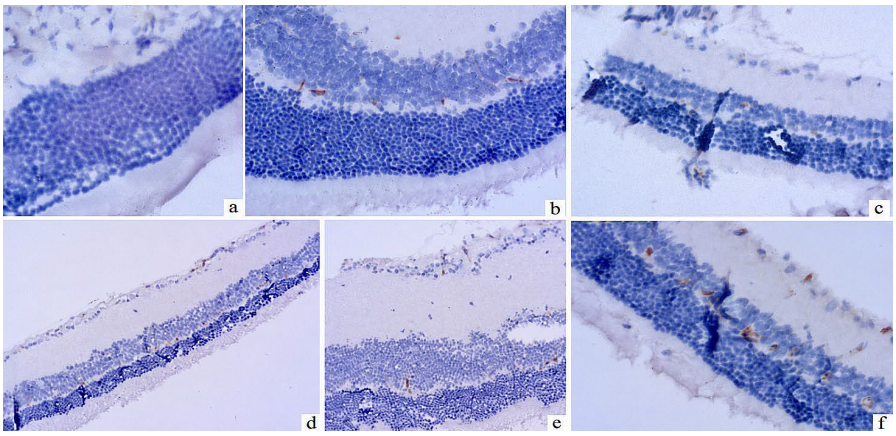

Figure 1. Retinal micropreparations of rats on day 7 and 3 months after modelling diabetic retinopathy: immunohistochemical expression of PMS2 with haematoxylin counterstaining, ×200

Note: a – before streptozotocin administration (intact rat); b – control group (7 days); c – control group (after 3 months); d – insulin administration; e – sorafenib administration; f – insulin and sorafenib administration

Source: developed by the authors

In the control group of animals with experimental DR, PMS2-positive cells were localised mainly along the inner surface of the retina, in the ganglion cell layer and the outer plexiform layer (Fig. 1b, 1c). Immunoreactivity had both nuclear and cytoplasmic localisation, with the intensity of nuclear staining consistently predominating over cytoplasmic staining. Insulin administration was accompanied by an increase in the number of PMS2-positive cells without a change in their predominant localisation (Fig. 1d). A similar effect was observed after sorafenib administration (Fig. 1e). The maximum intensity of PMS2 immunoreactivity was determined after combined administration of insulin and sorafenib (Fig. 1f). A similar pattern was observed for p53 expression (Fig. 2a). p53-positive cells were detected in the ganglion cell layer and the outer plexiform layer. Administration of insulin and sorafenib was accompanied by an increase in the number of positively stained cells (Fig. 2b-2d). However, p53 immunoreactivity was mainly associated with the vascular bed: positive cells were localised along the inner surface of the retina around microaneurysms and in the outer plexiform layer along vessels of the inner plexus.

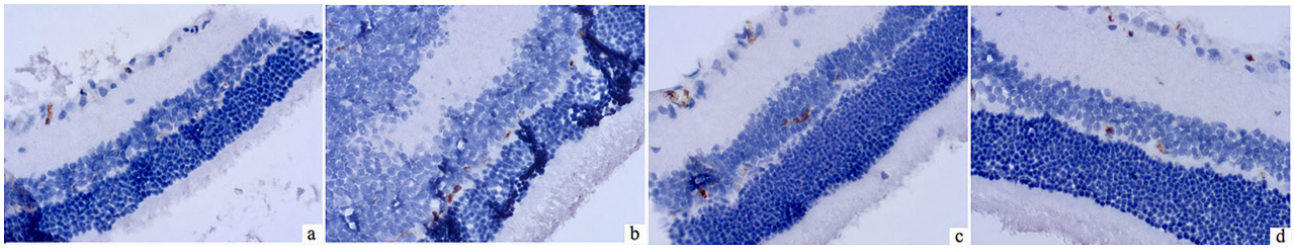

Figure 2. Retinal micropreparations of rats 3 months after modelling diabetic retinopathy: representative results of immunohistochemical staining for p53 with haematoxylin counterstaining, ×400
Note: a – control group; b – insulin administration; c – sorafenib administration; d – insulin and sorafenib administration
Source: developed by the authors

The quantitative characteristics of the proportion of immunopositive cells are presented in Figure 3. In the control group, the proportion of PMS2-positive cells gradually increased during the experiment (1.3-1.8-fold; $p < 0.05$). After 3 months, separate administration of insulin and sorafenib was accompanied by an approximately equal increase in this parameter compared with the control (1.7-fold; $p < 0.05$). The most pronounced changes were observed with combined administration of the drugs, when the proportion of PMS2-positive cells exceeded the control values by 2.5-fold ($p < 0.05$).

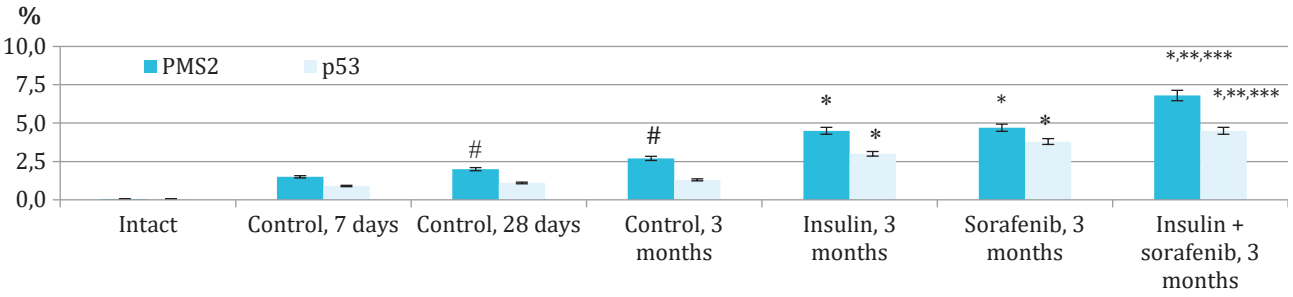

Figure 3. Proportion of PMS2- and p53-positive cells in the retina (% of the total number of cells)
Note: intact – mean data for intact animals; control, 7 and 28 days and 3 months – control-group data; insulin – insulin administration; sorafenib – sorafenib administration; ins+sor – combined administration of insulin and sorafenib; # – $p < 0.05$ compared with the control at day 7; * – $p < 0.05$ compared with the control after 3 months; ** – $p < 0.05$ compared with insulin administration; *** – $p < 0.05$ compared with sorafenib administration
Source: developed by the authors

Similar dynamics were also characteristic of p53, but the changes were less pronounced (Fig. 3). In the control group, a tendency towards an increase in the number of p53-positive cells was observed, but it did not reach statistical significance ($p > 0.05$). Separate use of insulin and sorafenib increased the proportion of positive cells 2.3-2.9-fold ($p < 0.05$), whereas combined administration of the drugs was accompanied by the maximum increase in the indicator, 3.5-fold compared with the control ($p < 0.05$). Thus, the development of experimental DR was accompanied by increased PMS2 and p53 expression in retinal tissues. Treatment with insulin and sorafenib enhanced the immunohistochemical expression of both markers, with more pronounced changes characteristic of PMS2. The highest values were recorded with combined administration of the drugs.

The results reflect increased expression of proteins associated with the cellular response to DNA damage, but they did not allow direct assessment of the functional state of the DNA repair system. This study established increased PMS2 expression in retinal tissues during the development of experimental DR. The results are consistent with data reported by J. Sohn *et al*. [16] and S. Roy *et al*. [15] on the important role of DNA damage and activation of cellular response systems to genotoxic stress in the pathogenesis of diabetic complications. According to M. Zhang *et al*. [9], metabolic stress, hypoxia, tissue acidosis, and excessive formation of reactive oxygen species during hyperglycaemia can directly damage DNA by inducing double-strand breaks and replication errors. Under these conditions, PMS2 activation may reflect involvement of the MMR-associated DNA repair system. The predominance of nuclear localisation of PMS2 immunoreactivity additionally confirmed activation of the cellular response to genetic material damage. PMS2-positive cells were localised mainly in the ganglion cell layer and the plexiform layers of the retina. K.O. Usenko [16] demonstrated that ganglion neurons and Muller cells undergo the earliest and most pronounced changes in experimental DR: degenerative processes progress in neurons, whereas Muller cells enter a state of reactive gliosis. This indicates that DNA damage and activation of repair systems occur most actively in these cell populations. Data reported by J. Ren *et al*. [17] also suggest a possible abortive return of retinal neurons to the cell cycle during neurodegenerative processes, which may be accompanied by activation of MMR-dependent mechanisms.

In parallel with increased PMS2 expression in retinal tissues, p53 expression also increased. W.P. Roos *et al*. [11] noted that activation of p53 is one of the key elements of the cellular response to severe DNA damage and oxidative stress. p53-positive cells were mainly localised along the vascular bed and around microaneurysms, which permits the involvement of endothelial stress and microvascular damage in the formation of this immunoreactivity. However, p53 expression was much less pronounced than PMS2 expression. This dissociation between high PMS2 immunoreactivity and weak focal p53 positivity may suggest predominance of the MMR-associated reparative and adaptive response over the p53-mediated proapoptotic scenario. At first glance, the increase in the number of PMS2- and p53-positive cells under the influence of insulin appears paradoxical. However, reduction of hyperglycaemia and attenuation of metabolic stress under the action of insulin probably create conditions for activation of reparative processes. According to D.D. Liu *et al*. [18], the phenomenon of metabolic memory may be important, since epigenetic changes and DNA damage persist even after normalisation of blood glucose. In this context, increased PMS2 immunopositivity can be regarded as a compensatory mechanism aimed at overcoming accumulated genetic damage in retinal tissues. The substantial increase in the proportion of PMS2-positive cells with combined use of insulin and sorafenib was of particular interest. The results obtained are consistent with the study of A. Callan *et al*. [8] on the role of kinase signalling pathways in the development of DR, including mechanisms of intracellular signalling, neuroinflammation, reactive gliosis, and angiogenic remodelling.

K.O. Usenko *et al*. [19] established that blockade of cellular protein kinases by sorafenib was accompanied by decreased VEGF expression in the retina in experimental DR and suppression of reactive gliosis. The results obtained in the present study supplement these data and suggest the involvement of MMR-associated mechanisms in the protective effect of cellular protein kinase blockade. K.O. Usenko *et al*. also demonstrated that, in experimental DR, caspase-3 expression and Bax protein content in retinal tissues increased sharply, whereas insulin administration, both separately and in combination with sorafenib, reduced the levels of these proapoptotic proteins and inhibited the morphological manifestations of DR. In this regard, increased PMS2 during treatment should not be considered a direct sign of enhanced apoptosis. On the contrary, the data obtained emphasises that treatment with insulin, especially in combination with sorafenib, may shift the cellular response to diabetes-induced damage from a p53-dependent apoptotic scenario towards a reparative and adaptive response associated with activation of the MMR system. According to J.A. Awosika *et al*. [1], PMS2 participates not only in DNA repair processes but also in regulation of p53-dependent apoptosis and the cellular response to severe genetic material damage. This is consistent with data reported by A.J. Barber *et al*. [20] on pericyte apoptosis, neurodegeneration, and ganglion cell death in DR. Thus, increased PMS2 expression may reflect a complex adaptive response of retinal cells aimed at maintaining genomic stability and controlling damaged cells. Notably, PMS2 remains poorly studied in modern ophthalmology. This is because this protein is traditionally considered mainly an oncopathological marker, whereas DR is classically studied in the context of microangiopathy, neuroinflammation, and neurodegeneration [21-22]. However, the current understanding of DR pathogenesis, including studies by J. Sohn *et al*. [14] and S. Roy *et al*. [15], increasingly emphasises the role of DNA damage, cellular ageing, epigenetic alterations, and mitochondrial dysfunction. In this context, assessment of PMS2 immunoreactivity may represent a promising area for studying disorders of DNA repair systems in DR.

CONCLUSIONS

1. During the development of experimental diabetic retinopathy in the retina of rats, a progressive increase in PMS2 expression and, to a lesser extent, p53

expression was observed, which indicated activation of the cellular response to DNA damage.

2. PMS2-positive cells were localised mainly in the ganglion cell layer and plexiform layers of the retina, whereas p53 immunoreactivity was more strongly associated with the vascular bed, which may suggest involvement of both neuronal and microvascular retinal components in genomic stress processes during diabetic retinopathy.

3. The use of insulin and sorafenib was accompanied by increased PMS2 and p53 expression, most pronounced with their combined administration, which may reflect activation of the MMR-associated reparative and adaptive response in retinal cells.

4. The results support considering PMS2 as a promising marker of the cellular response to DNA damage in diabetic retinopathy and justify further study of DNA repair systems in the pathogenesis of diabetic retinal damage.

The limitation of the study is that the assessment of PMS2 and p53 was based exclusively on immunohistochemical analysis without determining the functional activity of DNA repair systems and MMR-associated signalling pathways.

A promising area for further investigation is a comprehensive assessment of the expression and functional activity of PMS2, MLH1, and other components of the DNA repair system in retinal tissues during DR.

ACKNOWLEDGEMENTS

None.

FUNDING

This study was carried out under a budgetary programme of the Ministry of Health of Ukraine, state registration number 0126U001773.

CONFLICT OF INTEREST

There is no conflict of interest. The authors of the article did not take part in the peer-review process or in editorial decisions regarding their own manuscript.

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Експресія протеїнів PMS2 і p53 у тканинах сітківці при експериментальній діабетичній ретинопатії та вплив на неї інсуліну і інгібування клітинних протеїнкіназ

Анотація

Актуальність. Актуальність дослідження полягає у необхідності з'ясування ролі механізмів репарації ДНК та геномного стресу в патогенезі діабетичної ретинопатії для пошуку нових терапевтичних мішеней.

Мета. Визначити експресію протеїнів PMS2 та p53 у тканинах сітківки щурів при експериментальній діабетичній ретинопатії (ДР) та оцінити вплив інсуліну і блокатора клітинних протеїнкіназ сорафенібу.

Матеріали та методи. Дослідження виконано на 50 щурах-самцях лінії Wistar. Цукровий діабет моделювався одноразовим внутрішньоочеревинним введенням стрептозотоцину (50 мг/кг). Через 7 діб тварин зі стійкою гіперглікемією було рандомізовано на групи: без лікування, лікування інсуліном та комбіноване лікування інсуліном і сорафенібом. Тварин було виведено з експерименту через 7, 28 діб та 3 місяці. Імуногістохімічне дослідження виконувалося із використанням антитіл до PMS2 та p53. Частку імунопозитивних клітин визначали на 100 клітин у 5 полях зору.

Результати. У інтактних тварин PMS2- та p53-імунореактивність була мінімальною. При розвитку експериментальної ДР кількість позитивно забарвлених клітин прогресивно збільшувалася. PMS2-позитивні клітини локалізувалися переважно у шарі гангліонарних клітин та плексіформних шарах сітківки, тоді як p53-позитивні клітини були більшою мірою асоційовані із судинним руслом. Лікування інсуліном та сорафенібом супроводжувалося підвищенням експресії обох маркерів, найбільш вираженим при комбінованому введенні препаратів. Через 3 місяці комбінована терапія збільшувала частку PMS2-позитивних клітин у 2,5 раза, а p53-позитивних – у 3,5 раза порівняно з контрольною групою ($p < 0,05$).

Висновки. Розвиток експериментальної ДР супроводжується активацією PMS2- та p53-асоційованої клітинної відповіді на пошкодження ДНК у тканинах сітківки. Підвищення експресії PMS2 при лікуванні інсуліном та сорафенібом може відображати активацію MMR-асоційованих репаративно-адаптивних механізмів. Отримані результати дозволяють розглядати PMS2 як перспективний маркер геномного стресу при діабетичній ретинопатії.

Ключові слова: репарація ДНК; геномний стрес; імуногістохімія; сорафеніб; реплікація.