Вестник РУДН. Серия: МЕДИЦИНА
RUDN Journal of MEDICINE. ISSN 2313-0245 (Print). ISSN 2313-0261 (Online)
2024;28(4)
http://journals.rudn.ru/medicine

ТЕМА НОМЕРА: ОНКОЛОГИЯ
THEME OF THE ISSUE: ONCOLOGY

DOI: 10.22363/2313-0245-2024-28-4-413-426
EDN GKJBSB

REVIEW
ОБЗОР

Molecular genetic signatures of head and neck squamous cell carcinoma and their changes induced by proton irradiation

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Abstract. Head and neck squamous cell cancer (HNSCC) is the seventh most common malignancy in the world. The overall incidence of HNSCC is increasing and is projected to increase by about 30 % annually by 2030. Clinically, HNSCC is characterized by an aggressive course: rapid local spread, resistance to various methods of antitumor treatment, and frequent recurrences. Despite improvements in diagnostic and therapeutic approaches over the last two decades, the outcomes of patients with HNSCC have not shown significant improvements, especially for patients with late TNM stage, with an overall five-year survival rate of 50 %. Approximately 75 % of HNSCC patients are treated with radiation therapy either alone or as part of a comprehensive treatment regimen. To date, one of the main ways to improve the efficacy of radiation therapy in HNSCC is considered to be a combination of maximum allowable increase of radiation dose in the target tumor and minimization of such dose in the surrounding healthy tissues. From this point of view, proton therapy (PT) has a pronounced advantage over various types of photon irradiation. Despite the growing interest of scientists in PT, studies aimed at identifying molecular and genetic changes induced by PT are sparsely, while in our opinion they are very important for understanding intracellular mechanisms leading either to tumor cell destruction or to the development of radioresistance. This review summarizes the available knowledge on the changes in the main signaling pathways of HNSCC tumor cells under the influence of PT.

Keywords: head and neck squamous cell cancer, proton therapy, protons, signaling pathways, signaling cascade, molecular genetic signatures

Funding. This work was supported by the tripartite agreement of the Russian Science Foundation № 24-24-00296 dated 29.12.2023 on the project "The effect of proton therapy on the molecular portrait of the microenvironment of head and neck tumors" of the competition 2023 "Conducting basic scientific research and search scientific research by small individual scientific groups" between RSCF, Lokhonina A.V. and RUDN.

Author contributions. Jumaniyazova E.D. — conception and writing the final manuscript text; Lokhonina A.V. — checking the intellectual content of the manuscript, final approval of the version for publication.; Sentyabreva A.V. — manuscript writing, Kosyreva A.M. — checking the intellectual content of the manuscript. All authors made significant contributions to the conception, conduct of the study and preparation of the article, read and approved the final version before publication.

Conflicts of interest statement. The authors declare no conflicts of interest.

Ethics approval — not applicable.

Acknowledgements. The authors express their gratitude to G.G. Kazaryan for technical support during the preparation of the manuscript.

Consent for publication — not applicable.

Received 24.07.2024. Accepted 03.09.2024.

For citation: Jumaniyazova ED, Sentyabreva AV, Kosyreva AM, Lokhonina AV. Molecular genetic signatures of head and neck squamous cell carcinoma and their changes induced by proton irradiation. *RUDN Journal of Medicine.* 2024;28(4):413–426. doi: 10.22363/2313-0245-2024-28-4-413-426. EDN: GKJBSB

Introduction

Head and neck squamous cell cancer (HNSCC) is the seventh most common malignancy in the world. The overall incidence of HNSCC is increasing and is projected to increase by about 30 % annually by 2030 [1, 2]. The most significant risk factors for the development of HNSCC include smoking, alcohol consumption, exposure to environmental pollutants, and infection with viral agents, namely human papillomavirus (HPV) and Epstein-Barr virus [3], additional predisposing factors include betel nut chewing (a species of tree-like plants of the genus Areca of the Palm family, the use of which is common in Southeast Asian countries), malnutrition, poor oral hygiene [4, 5]. Clinically, HNSCC is characterized by an aggressive course: rapid local spread, resistance to various methods of antitumor treatment and frequent recurrences [6]. Despite improvements in diagnostic and therapeutic approaches over the last two decades, mainly due to the respective heterogeneity of these tumors, the outcomes of patients with HNSCC have not shown significant improvements, especially for patients with late TNM stage, with an overall five-year survival (OS) of 50 % [7]. Therapeutic options for HNSCC include minimally invasive, organ-preserving surgery, radiation therapy (RT), and multimodal treatment strategies. For patients with early-stage HNSCC, both surgery and intensive RT provide comparable results in terms of local disease control and overall survival [8]. After surgery, postoperative RT with or without adjuvant chemotherapy is recommended for patients with risk factors including perineural invasion and/or lymphovascular invasion and when positive resection margins (i.e., resection margins with tumor cells detected in them) are identified. As a rule, a combination of surgery, RT and chemotherapy is required at advanced stages (locally advanced stage, or in the presence of distant metastases) [9]. Approximately 75 % of HNSCC patients are treated with RT as the main or as part of complex treatment [10]. Thus, in the early stages of the disease, RT can replace the need for surgical intervention. In some complex clinical situations, for example, for tumor lesions of the larynx, RT allows

to perform antitumor treatment while preserving the organ, which is a fundamentally important aspect from the psychological point of view for a number of patients [11]. However, the planning and implementation of RT in patients with HNSCC is complicated due to the close proximity of a large number of critical organs at risk (OAR). Even with the introduction of Intensity Modulated Radiation Therapy (IMRT) in the clinic, it is not possible to completely avoid irradiation of nearby organs, which subsequently leads to the development of late postradiation complications [12, 13]. To date, one of the main ways to improve the efficacy of RT in HNSCC is considered to be a combination of maximum permissible increase of radiation dose in the target tumor and minimization of such dose in the surrounding healthy tissues. From this point of view, proton therapy (PT) has a pronounced advantage over various types of photon irradiation. [14, 15]. A number of studies have demonstrated a significant reduction in the radiation dose to OAR with PT compared to IMRT [16–18].

PT is a promising variant of RT, the wide application of which is expected to solve many problems [19]. Protons are positively charged particles that penetrate tissue to a limited depth and give up most of their energy at the end of their path [20]. This physical phenomenon of protons has been called the Bragg peak [21]. The pronounced peak of ionizing radiation, or Bragg peak, occurring at the end of the protons' run through matter causes that the integral dose is almost always lower and the irradiation of healthy tissues is less than in photon therapy [22]. Due to such a dose distribution in the substance, it is possible to carry out irradiation with high effective doses against the background of a reduced radiation load on the surrounding healthy tissues, which improves the tolerability of treatment and reduces the number of postradiation complications in HNSCC patients.

The main effect of protons on tumor cells is DNA damage, including nucleotide base modifications, a basic sites and single-strand breaks, the latter being the most common type of PT-induced direct damage. In addition to direct damage, PT has an indirect cytotoxic effect through the formation of reactive oxygen species (ROS) [23], which activate caspases to induce apoptosis [24], (Fig.1). In a past review article, we noted the biological effects of PT [25], (Table 1).

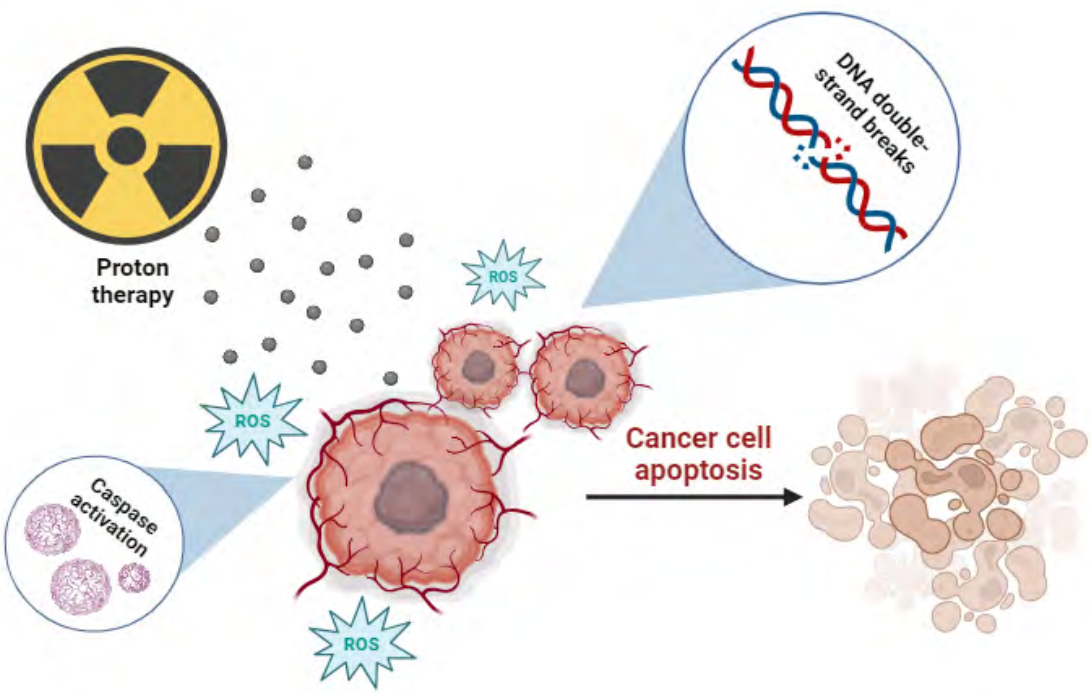

Figure 1. Proton therapy effects on cancer cells

Table 1

Specific features of proton therapy

Evaluation parameters		Peculiarities of proton therapy
Physical properties		Protons emit maximum energy, reaching the "target", i. e. the tumor; while the surrounding tissues (healthy) receive minimal radiation dose [23], [26].
Action on tumor	Cancer cell DNA	Proton irradiation induces clustered DNA damage, with the formation of short DNA fragments that are difficult to repair by the repair mechanism, leading to massive cell death [27].
	Cancer cells as a whole	Proton irradiation leads to the accumulation of ROS, which in turn activate caspases that trigger cancer cell apoptosis [28]. It reduces invasion and migration of cancer cells by inhibiting integrins and matrix metalloproteinases (MMPs) [29].
Tumor microenvironment	Cancer-associated fibroblasts	It reduces protumorigenic properties and induces rapid senescence of cancer-associated fibroblasts [30].
	Macrophages	Proton irradiation stimulates reprogramming of M2 macrophages possessing a pro-tumor phenotype into M1 antitumor ones through activation of NFκB, MAPK and IRF/STAT [31]. It activates the expression of high mobility group box 1 (HMGB1), which is responsible for the activation of antigen-presenting cells [32].
	T-lymphocytes	Proton irradiation activates the recruitment of CD8+ [33], CD4+ and T-reg lymphocytes [32].

Despite the growing interest of scientists in PT, studies aimed at identifying molecular and genetic changes induced by PT are scarce, whereas in our opinion they are very important for understanding the intracellular mechanisms leading to either tumor cell destruction or the development of radioresistance [34]. In this review, we summarize the available knowledge of the changes in the main signaling pathways of HNSCC tumor cells under the influence of PT (Fig.2).

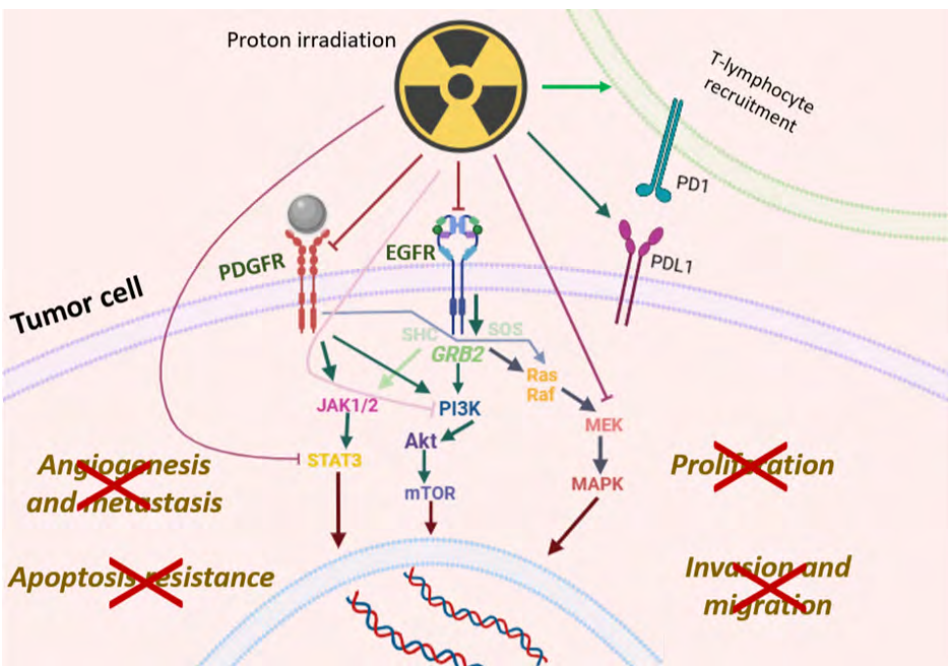

Figure 2. Impact of proton irradiation on cancer cell signaling pathways

P53 signaling pathway

HNSCC is characterized by a high level of genetic instability [35], which is primarily due to inactivating mutations in tumor growth suppressor genes [36]. Like most solid tumors, HNSCC is characterized by mutations in the *TP53* gene, [37] which in "normal" mode of operation provides genomic stability and in case of detecting violations is able to stop the cell cycle and start the process of DNA repair, and in case of impossibility to correct the damage — starts apoptosis [38, 39]. The hallmark of p53 is high sensitivity to DNA damage or oncogene activation in the cell [40]. Inactivating mutations of *TP53* are characteristic of more than 80 % of HPV-negative HNSCC, which necessarily lead to loss of its function [41]. Inactivating mutations in the *TP53* gene are events of early stages of carcinogenesis. The presence of *TP53* mutations in any subtypes of HNSCC is associated with poor overall survival, resistance to therapy, and increased recurrence rates [41]. Talking about RT-induced changes in the *TP53* gene, it is important to note that it is assigned one of the main roles in deciding the "fate" of cancer cells after irradiation. In several studies [42, 43, 44] it has been demonstrated that under the influence of RT, tumor cells die by apoptosis rather than by necrosis or autophagy. Radiation exposure increases the amount of p53 protein in cells, mainly by stimulating its translation and inhibiting its degradation [45].

Activation of the p53-mediated signaling pathway can cause cell cycle arrest followed by DNA repair, which promotes cell survival; if DNA repair is not possible, apoptosis is induced or the cell becomes senescent, which ultimately leads to tumor cell death [44]. Bravata et al. showed on breast cancer cell lines that proton irradiation leads to TP53 pathway activation [46]. Lee et al. demonstrated on the example of three kinds of cancer cells, lewis lung carcinoma cells, hepatoma HepG2 and Molt-4 leukemia cells, that proton irradiation induces an increase in p53 expression with subsequent apoptosis of cancer cells [47]. Taking into the consideration that HNSCC is characterized by a high level of hypoxia (like the above tumors) in the tumor node, similar activation of p53-dependent signaling pathway is likely to occur in this MNs. In addition, proton irradiation activates caspases and increases the generation of ROS via p53. The increase of ROS can activate p53 and vice versa according to the feedback principle [43].

EGFR signaling pathway

A well-known molecular genetic feature of HNSCC is the overexpression of a receptor with tyrosine kinase activity-epidermal growth factor receptor (EGFR) [48]. Thus, EGFR overexpression is thought to be found in approximately 80 % of HNSCC cases, and in terms of disease course, it is associated with a poor prognosis of the disease [49]. The prevalence of EGFR overexpression has led to the introduction of Cetuximab, a targeting drug that is a monoclonal antibody directed against EGFR, into the antitumor therapy of HNSCC.

HER family ligands including epidermal growth factor, heparin-binding, amphiregulin, transforming growth factor-alpha, epiregulin and beta-cellulin have affinity for EGFR. [50]. Upon binding to one of the ligands, activated EGFR activates various intracellular signaling cascades, e. g., JAK/STAT, PI3K/AKT, MAPK [51]. In cancer cells, these signaling cascades are responsible for the processes of cell proliferation, invasion, migration and metastasis [52].

Despite its transmembrane position, EGFR is able to move into the cell nucleus where it functions as a transcription factor. Such a phenomenon can be induced by ionizing radiation and it is associated with the acquisition of resistance to RT by cancer cells. In turn, EGFR inhibition sensitizes radioresistant cancer cells by modulating DNA repair. Overexpression of other receptor tyrosine kinases including HER2 and MET contribute to resistance to agents targeting EGFR [53, 54].

A study by Park et al. demonstrated the efficacy of combining the EGFR inhibitor Gefinitib with proton irradiation on non-small cell lung cancer cells [55]. Promising results were obtained when oral squamous cell carcinoma's cells were irradiated with protons: EGFR suppression was revealed [56]. Irradiation with another type of corpuscular irradiation, carbon ions, also led to a decrease in the activity of EGFR and PI3K/AKT/mTOR pathways [57]. In contrast, Stahler et al.

did not observe activation of EGFR and downstream targets AKT and ERK1/2 after carbon ion irradiation in their experiment [58].

MET signaling pathway

The *MET* proto-oncogene encodes RTK and is a regulator of one of the most important signaling cascades of carcinogenesis, primarily causing epithelial-mesenchymal transition (EMT) [59]. In turn, EMT enhances cancer cell migration and invasion and thereby determines the process of metastasis in HNSCC [54]. Although c-MET has several functional domains, it binds to a single ligand-hepatocyte growth factor (HGF) [60]. The binding of HGF to c-MET affects the catalytic activity of RTC, which activates other cell signaling pathways such as RAS/RAF/ERK, PI3K/AKT/mTOR, JAK/STAT and NOTCH, resulting in uncontrolled proliferation of cancer cells [61]. In HNSCC, *MET* mutations are infrequent, occurring in approximately 2–13 % of cases, whereas *MET* copy number increase and overexpression of its ligand HGF are common [62] and are associated with poor prognosis and poor overall survival [63]. Increased expression of c-MET is associated with metastasis to lymph nodes in HNSCC, and overexpression of HGF is associated with resistance to anoikis (a type of cell death) [64]. Activation of c-Met promotes increased expression of plexin containing domain 2 through activation of ERK1/2-ELK1 signaling. This leads to cancer cell plasticity through the induction of epithelial-mesenchymal transition and an increase in the number of stem cells in the tumor, resulting in RT resistance of HNSCC. Inactivation of c-Met by knockdown or an inhibitory pharmacological agent not only reverses the EMT process, but also diminishes the CD44+CD133 — cancer stem cells (CSCs) population in radioresistant HNSCC, which significantly slows tumor progression [65].

In view of the fact that EGFR and c-MET activate common downstream components of signaling cascades such as MAPK and PI3K/Akt/mTOR, the MET signaling cascade may be considered as a promising target for the treatment of HNSCC in cetuximab-resistant patients [54]. In addition, this signaling pathway is believed to interact with other signaling pathways such as STAT and Wnt, contributing to tumor progression and resistance to antitumor agents and RT [66]. In writing this review, we did not find any studies on how this signaling cascade is altered after proton irradiation. However, there are reports indicating that c-Met is overexpressed in most HPV-negative HNSCC cell lines after ionizing irradiation.

PI3K/Akt/mTOR signaling pathway

Disorders in the PI3K/AKT/mTOR signaling cascade in HNSCC are common, occurring in 90 % of cases [67]. The first constituent member of the signaling cascade-PI3K, which belongs to a class of enzymes that are essential for cell growth, differentiation, and survival-is activated by RTKs (e.g., as mentioned above, such as EGFR). Other members of the pathway include mTORC1, mTORC2 and Akt. mTORC2 is required for phosphorylation of Akt and activation of other signaling molecules of the PI3K pathway [68]. Phosphorylated Akt activates mTOR or inhibits Bad, caspase 9 and other proteins, thereby regulating cell proliferation, differentiation, apoptosis and migration. PI3K is thought to phosphorylate phos phatidylinositol-4,5-bisphosphate and convert it to another form, phosphatidylinositol-3, 4, 5-triphosphate [69]. Phosphatidylinositol-3, 4, 5-triphosphate can be dephosphorylated by phosphatase and tensin homolog, which in turn blocks the PI3K/AKT/mTOR pathway [70, 71].

Activation of this signaling cascade in HNSCC cancer cells leads to the development of resistance to antitumor therapies, especially RT [72], which is associated with the induction of DNA repair [73]. After PT, there is a decrease in AKT phosphorylation followed by inhibition of signaling pathways, leading to decreased radioresistance [74]. Carbon ion irradiation resulted in decreased PI3K/AKT/mTOR activity in non-small cell lung cancer cells [57]. The study conducted on the cell line of glioblastoma multiforme U87 showed that proton irradiation of tumor cells under conditions of acute hypoxia leads to activation of the PI3K/AKT/mTOR signaling pathway [75].

JAK/STAT signaling pathway

Another signaling pathway associated with the malignancy of HNSCC is JAK/STAT. A transmembrane protein called Janus kinase (JAK) perceives information from outside the cell and directs the signal inside the cell by phosphorylating STAT, which is a transcription factor. Activation of this signaling cascade is associated with resistance to various anticancer treatment approaches-chemotherapy, RT, and targeted therapy [76, 77]. It is unusual that activation of the participants of this signaling cascade is associated not only with changes in cancer cells directly, but also in the tumor microenvironment. For example, STAT3 activation leads to changes in the tumor microenvironment: it acquires immunosuppressive potential due to increased synthesis of cytokines TGF-β1, IL-6, IL-10, and VEGF, which, in turn, ensures tumor escape from recognition and lysis by cytotoxic T-lymphocytes [78]. *In vitro* inhibition of STAT3 has been shown to be associated with a less pronounced development of immunosuppressive potential of the HNSCC tumor microenvironment [79]. In contrast, STAT5 activation observed in HNSCC correlates with increased cancer cell proliferation, invasion and EMT activity [80]. In our recent study on transcriptomic changes of HNSCC after PT, we observed suppression of STAT5 activity [81].

MAPK signaling pathway

The mitogen-activated protein kinase (MAPK) signaling cascade has an important regulatory function in cancer cells. Such processes as proliferation of cancer cells, their subsequent differentiation, metastasis, and in addition the processes of angiogenesis and resistance to antitumor treatment are caused by the activation of the MAPK signaling pathway [82]. The MAPK signaling pathway includes RAS (H/K/NRAS), RAF (A-/B-/C-RAF), mitogen-activated protein kinase (MEK, MEK1/2), extracellular signal regulated kinases (ERK, ERK1/2), adaptor molecules (GRB2, SHC1/2/3/4) and dual specificity phosphatases (DUSP3/5/6/7/9), which are negative regulators of ERK [83]. It has been demonstrated that activation of several kinases, including BRAF, KRAS, HRAS and ERK1/2, induces carcinogenesis and stimulates cancer cell invasion [84].

In HNSCC, mutations affecting members of the MAPK signaling pathway occur in about 18 % of cases [85]. These mutations are predominantly localized in BRAF, HRAS, KRAS, and ERK genes [86]; most of the mutations of the MAPK signaling pathway in HNSCC are inducers of carcinogenesis. High intratumoral expression of p-MAPK1/3 (p-ERK1/2) in HNSCC patients correlates with low survival rates [87].

Hyperexpression of one of the participants of the p38/MAPK signaling pathway, MAP2K6, in patients with HNSCC is associated with resistance to RT and poor prognosis of the disease [88]. In a study by Meerz et al., MAPK activation was detected in 3-D cell cultures of HNSCC after proton irradiation. In addition, the authors demonstrated radiosensitization of HNSCC cells when combining PT with selective inhibitors of key members of the MAPK pathway — for ERK1/2 (Ulixertinib); for JNK 1/2/3 (SP600125); for p38α/β/ɣ/δ (Ralimetinib). The most pronounced radiosensitization effect was demonstrated by a selective ERK1/2 inhibitor [89]. Another work devoted to the effects of proton irradiation on the cell line of colorectal cancer, which revealed the inhibitory effect of PT on MAPK phosphorylation in cancer cells, is also noteworthy [90].

NOTCH signaling pathway

The NOTCH signaling cascade starts with 4 receptors (NOTCH1–4) to which 5 ligands (JAG1 and 2 and DLL1, 3 and 4) can bind. After ligand binding to the NOTCH receptor, the γ-secretase complex releases an intracellular NOTCH domain called NICD. NICD moves into the cell nucleus, which activates transcription of NOTCH target genes -HES and HEY [91]. A large-scale genomic analysis conducted in 2015 revealed that NOTCH 1–3 mutations are present in 17 % of HPV-positive and 26 % of HPV-negative HNSCC cases [41, 92].

An increase in the activity of NOTCH signaling pathway participants was observed in HNSCC cells, and their inhibition leads to a decrease in proliferation and invasion of cancer cells [91]. Activation of the

signaling pathway through NOTCH1 by Wnt-signaling stabilizes the population of CSCs, which is associated with frequent recurrences and active metastasis. Hovinga et al. demonstrated that Notch inhibition significantly improves response to radiation by reducing proliferation and self-renewal of CSCs in tumor explants [93]. In addition, survival of CSCs is maintained by activation of Akt and STAT3, which are almost always activated in cancer cells. These together account for tumor radioresistance [94]. On human glioma cell lines it was shown that carbon ion irradiation suppresses Notch signaling at all levels of transcription and translation of proteins participating in this pathway [95]. Proton boron capture therapy in GBM cells induces a Notch signaling activation, able to regulate cell fate through the modulation of autophagy/apoptosis transition [96].

PDGF/PDGFR signaling pathway

The peculiarity of this signaling pathway is that simultaneous expression of platelet-derived growth factor (PDGF) and platelet derived growth factor receptor (PDGFR) is observed in cancer cells, which creates an autocrine loop that promotes aggressive tumor behavior. The PDGF ligand family includes several members: PDGFA, PDGFB, PDGFC, and PDGFD, which form homo- and heterodimers [97]. Upon ligand binding to the receptor, intracellular tyrosine kinases are activated and form multiple binding sites for downstream signaling molecules, thereby activating various signaling pathways such as PI3K/Akt/mTOR signaling cascades, MAPK signaling cascade, JAK/STAT and Notch signaling cascade [98].

The PDGF/PDGFR signaling pathway has been assigned a major role in tumor progression [99]. PDGF has been found to have a stimulatory effect on malignant cell transformation, cancer cell migration, and cancer cell survival [100, 98]. PDGF overexpression promotes tumor cell growth [101] and induces angiogenesis [102], affecting cells in the tumor microenvironment, thereby provoking tumor progression and dissemination [103, 104]. In addition, there is evidence that increased PDGF activity in tumors is associated with resistance to drug treatment, which is associated with impaired blood flow in tumors due to increased interstitial fluid pressure [105]. Aebersold et al. found that more than half of tumor samples from 95 patients with oropharyngeal cancer stained positive for PDGF-BB, and this was associated with an increased risk of metastasis [106]. After proton irradiation suppression of this signaling pathway was observed in HNSCC cells [81].

PD-1/PD-L1 signaling pathway

The PD-1/PD-L1 signaling pathway controls the induction and maintenance of immune tolerance in the tumor microenvironment [107]. PD-L1 is expressed by tumor cells and endows them with the ability to avoid an anti-tumor response by inhibiting activation of T cells (which express the PD1 receptor), reducing cytokine production, and inducing cytolysis of T cells. [108, 109]. Primary tumors and metastases, particularly in HNSCC, and even different regions of the same tumor node can differ significantly in PD-L1 expression levels [110, 111, 112]. There are conflicting data in the literature regarding the prognostic value of PD-L1 expression in HNSCC. A meta-analysis evaluating PD-L1 expression and the association with survival in HNSCC patients, found no significant difference in overall survival between PD-L1-positive and -negative patients [113]. Currently five monoclonal antibodies targeting PD-1 and PD-L1 have been approved by the FDA. Two of them target PD-L1, Atezolizumab and Durvalumab, and Nivolumab, Pembrolizumab and Cemiplimab target PD-1.

Proton irradiation of the KYSE450 (esophageal squamous cell carcinoma) cell line increased PD-L1 expression [114]. The combination of RT with immunotherapy for the treatment of HNSCC has long attracted the attention of researchers. When RT is combined with immune checkpoint inhibitors, it can potentiate the synergistic effects, where RT contributes to the normalization of the tumor vascular system, enhance the expression of leukocyte adhesion molecules on endothelial cells, and stimulate the secretion of chemokines that attract CD8+ T cells [115]. And a recent study revealed a synergistic effect of combining proton irradiation and immunotherapy on mouse oral cancer cell lines [116].

Conclusion

PT is a promising option for RT of HNSCC, minimizing the number of post-radiation complications and significantly improving the quality of life of patients undergoing antitumor treatment. However, radioresistance leads to treatment ineffectiveness in some cases. In the course of writing this review article, we encountered the fact that the described molecular-genetic signatures of this malignancy are not few, but they lack specificity, and the number of works devoted to the description of PT effects at the level of intracellular signaling pathways is limited. This determines the urgent need to search for molecular genetic biomarkers to predict response to PT. The understanding of molecular genetic changes induced by PT in tumor cells of HNSCC will allow to create effective combinations of antitumor therapies to avoid radioresistance.

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Молекулярно-генетические сигнатуры плоскоклеточного рака головы и шеи и их изменения, индуцированные протонным облучением

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Аннотация. Плоскоклеточный рак головы и шеи (ПРГШ) занимает седьмое место в десятке наиболее распространенных злокачественных новообразований в мире. Отмечается рост общей заболеваемости ПРГШ, и прогнозируется, что к 2030 году она будет увеличиваться примерно на 30 % ежегодно. Клинически ПРГШ характеризуется агрессивным течением: быстрым локальным распространением, резистентностью к различным методам противоопухолевого лечения и частыми рецидивами. Несмотря на усовершенствования диагностических и терапевтических подходов за последние два десятилетия, исходы пациентов с ПРГШ, особенно с поздними стадиями заболевания, не улучшились- их общая пятилетняя выживаемостью составляет 50 %. Примерно 75 % пациентов с ПРГШ назначается лучевая терапия в качестве самостоятельного или в составе комплексного лечения. На сегодняшний день одним из основных путей повышения эффективности лучевой терапии при ПРГШ считается сочетание максимально допустимого повышения дозы облучения в опухоли-мишени при минимизации ее в окружающих здоровых тканях. С этой точки зрения протонная терапия (ПТ) обладает выраженным преимуществом по сравнению с различными видами фотонного облучения. Несмотря на растущий интерес ученых к ПТ, исследований, направленных на выявление молекулярно-генетических изменений, индуцированных ПТ, недостаточно; тогда как, на наш взгляд, они очень важны для понимания внутриклеточных механизмов, ведущих либо к уничтожению опухолевых клеток, либо к развитию радиорезистентности. В данном обзоре обобщены имеющиеся знания об изменениях основных сигнальных путей опухолевых клеток ПРГШ под действием ПТ.

Ключевые слова: плоскоклеточный рак головы и шеи, протонная терапия, протоны, сигнальные пути; сигнальный каскад; молекулярно-генетические сигнатуры

Информация о финансировании. Работа выполнена при поддержке трехстороннего соглашения Российского научного фонда № 24–24–00296 от 29.12.2023 по проекту «Влияние протонной терапии на молекулярный портрет микроокружения опухолей головы и шеи» конкурса 2023 года «Проведение фундаментальных научных исследований и поисковых научных исследований малыми отдельными научными группами» между РНФ, Лохониной А.В. и РУДН.

Вклад авторов. Джуманиязова Э.Д. — концепция и написание рукописи, составление иллюстрации; Лохонина А.В. — проверка интеллектуального содержимого рукописи; Сентябрева А.В. — написание рукописи, Косырева А.М. — проверка интеллектуального содержимого рукописи. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Информация о конфликте интересов. Авторы заявляют об отсутствии конфликта интересов.

Этическое утверждение — неприменимо.

Благодарности. Коллектив авторов приносит благодарность Казаряну Г.Г. за техническую поддержку в процессе подготовки рукописи.

Информированное согласие на публикацию — неприменимо.

Поступила 24.07.2024. Принята 03.09.2024.

Для цитирования: *Jumaniyazova E.D., Sentyabreva A.V., Kosyreva A.M., Lokhonina A.V.* Molecular genetic signatures of head and neck squamous cell carcinoma and their changes induced by proton irradiation // Вестник Российского университета дружбы народов. Серия: Медицина. 2024. Т. 28. № 4. С. 413–426. doi: 10.22363/2313-0245-2024-28-4-413-426. EDN: GKJBSB

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