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THE ACTIVITY OF CIRCULATING PROTEASOMES IN TUMOR AND PRECANCEROUS DISEASES OF THE HEAD AND NECK ORGANS

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Abstract

Introduction. Identification of persons with a high oncological risk to squamous cell carcinoma of the head and neck region is an urgent problem for the early diagnosis of this disease. The activity of circulating proteasomes can be a criterion for predicting the risk of the larynx and oral cavity cancers in patients with precancerous diseases of the upper respiratory and gastrointestinal tracts. **The aim of the study** is to investigate the chymotrypsin-like and caspase-like activities of circulating serum proteasomes depending on the localization of precancerous and neoplastic diseases of the larynx and oral cavity. **Material and Methods.** The study population consisted of 35 patients with histologically verified HNSCC (T1–3N0–3M0), 15 patients with chronic hyperplastic laryngitis (CHL) and oral leukoplakia, and 10 healthy volunteers who did not have chronic upper respiratory tract diseases in the acute stage. The median age of the patients was 53 ± 5.3 years. **Results.** An increase in the studied proteasome activities was found in the blood serum of patients with malignant tumors as compared with patients with chronic hyperplastic diseases associated with precancerous changes, as well as in the larynx and oral cavity cancers groups as compared with healthy donors. At the same time, depending on the localization of the pathological process, it was shown that only the chymotrypsin-like activity of the circulating pool of proteasomes significantly differs both in the groups of oral cancer leukoplakia, and in the groups of laryngeal cancer chronic hyperplastic laryngitis with dysplastic epithelial lesions. In addition, differences were found between chymotrypsin-like and caspase-like activities of circulating serum proteasomes in patients with chronic hyperplastic laryngitis with oral dysplasia and leukoplakia. **Conclusion.** The results obtained indicate that the determination of the CTP activity of the circulating pool of proteasomes can be used as a criterion for predicting the risk of the larynx and oral cavity cancers in patients with precancerous diseases of the larynx and oral cavity.

Key words: laryngeal cancer, oral cancer, dysplasia, chymotrypsin-like activity of proteasomes, caspase-like activity of proteasomes.

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АКТИВНОСТЬ ЦИРКУЛИРУЮЩИХ ПРОТЕАСОМ ПРИ ОПУХОЛЕВЫХ И ПРЕДОПУХОЛЕВЫХ ЗАБОЛЕВАНИЯХ ОРГАНОВ ГОЛОВЫ И ШЕИ

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Аннотация

Актуальность. Выявление лиц с высоким онкологическим риском развития плоскоклеточного рака области головы и шеи (ПРГШ) является актуальной проблемой для ранней диагностики этого заболевания. Критерием для прогноза риска возникновения ПРГШ у больных с предопухолевыми заболеваниями верхних отделов респираторного и желудочно-кишечного трактов может быть активность циркулирующих протеасом. **Цель исследования** – изучить химотрипсинподобную и каспазаподобную активности циркулирующих протеасом сыворотки крови в зависимости от локализации предопухолевых и опухолевых заболеваний гортани и ротовой полости. **Материал и методы**. В исследование вошли 35 пациентов с ПРГШ (T1–3N0–3M0) с гистологически верифицированным диагнозом, 15 человек с хроническим гиперпластическим ларингитом (ХГЛ с DIIII), лейкоплакиями полости рта и 10 здоровых волонтеров, не имеющих хронических заболеваний верхних дыхательных путей в стадии обострения. Средний возраст больных составил 53 ± 5,3 года. **Результаты.** Обнаружено повышение изучаемых активностей протеасом в сыворотке крови больных со злокачественной опухолью по сравнению с больными хроническими гиперпластическими заболеваниями, ассоциированными с предопухолевыми изменениями, а также в группах ПРГШ по сравнению со здоровыми донорами. В то же время в зависимости от локализации патологического процесса показано, что только химотрипсинподобная (ХТП) активность циркулирующего пула протеасом значимо различается как в группах рак ротовой полости – лейкоплакии, так и в группах рак гортани – хронический гиперпластический ларингит (ХГЛ) с диспластическими изменениями эпителия. Кроме того, были обнаружены различия между ХТП и каспазаподобной активностями циркулирующих протеасом сыворотки крови больных хроническим гиперпластическим ларингитом с дисплазиями и лейкоплакиями ротовой полости, а также у групп больных злокачественными опухолями этих локализаций. **Выводы.** Полученные результаты свидетельствуют о том, что определение ХТП активности циркулирующего пула протеасом может быть использовано в качестве критерия для прогноза риска возникновения ПРГШ у больных предопухолевыми заболеваниями гортани и ротовой полости.

Ключевые слова: рак гортани, рак ротовой полости, дисплазия, химотрипсинподобная активность протеасом, каспазаподобная активность протеасом.

Introduction

Although most of the head and neck organs can be visually and instrumentally inspected, squamous cell carcinoma of the upper respiratory and digestive systems is characterized by an asymptomatic course, late admission of patients to cancer centers, early onset of metastases and high mortality rate within the first year after diagnosis [1, 2]. In most cases, the development of HNSCC follows an ordered series of steps beginning with epithelial cell hyperplasia followed by dysplasia. Grade II–III laryngeal dysplasia and oral leukoplakia is associated with high risk of progression to carcinoma [3, 4]. Thus, it is important to develop predictive markers that may identify lesions at high risk of progression to malignancy.

Tumor transformation occurs with the participation of many processes, one of which is proteolysis. Intracellular proteolysis occurs mainly in proteasomes, multisubunit complexes. Proteasomes are the main non-lysosomal proteases in eukaryotic cells, which are responsible for the degradation of all short-lived proteins and 70–90 % of all long-lived proteins [5]. Proteasomes are known to be involved in the cleavage of growth factors, their receptors, components of signaling pathways, and transcription factors [6, 7]. The proteasome is made of two subcomplexes: the 20S proteasome and the proteasome activator. All proteasomes have three types of active sites: caspase-like, trypsin-like, and chymotrypsin-like. To date, the existence of extracellular forms of proteasomes

circulating in various biological fluids of the body has been proven [8, 9]. They can be found and transported both as part of microvesicles, in particular, exosomes, and in free form, circulating in the bloodstream [9, 10]. Proteolytic activity is possessed by proteasomes in a free, non-vesicular form. Circulating proteasomes in human plasma are present in the form of a 20S pool, and their levels increase significantly in various pathological conditions, including cancer, autoimmune diseases, trauma, and sepsis [11].

Proteasomes are involved in the pathogenesis of many cancers including breast, endometrial, and thyroid cancers [12, 13]. We previously showed that the the ChTL and CL levels were higher in patients with HNSCC than in patients with chronic laryngeal hyperplasia associated with epithelial dysplasia. The levels of ChTL and CL proteasomal activity did not depend on the tumor stage but depended on the tumor grade [14]. The purpose of the study was to assess the ChTL and CL activities of circulating proteasomes in patients with premalignant and malignant oral and laryngeal lesions.

Material and Methods

The study population consisted of 35 patients with histologically verified HNSCC (T1–3N0–3M0), who had not received previous special treatment, 15 patients with chronic hyperplastic laryngitis (CHL) and oral leukoplakia, and 10 healthy volunteers who did not have chronic upper respiratory tract diseases in the acute stage. The median age of the patients was 53 ± 5.3 years. The study included patients with HNSCC, who were treated at the Head and Neck Cancer Department of Cancer Research Institute, patients with CHL, who were examined at the Endoscopy Department of Cancer Research Institute and patients with oral leukoplakia, who were observed at the Dentistry Department of Siberian State Medical University (Tomsk, Russia). The study was conducted under conditions of voluntary participation and confidentiality in accordance with the World Medical Association's Declaration of Helsinki «Ethical Principles for Medical Research involving Human Subjects», as revised in 2000. This study was approved by the Ethics Committee of the Cancer Research Institute. Prior to the study, serum samples were frozen and stored at -80 °C.

To assess the chymotrypsin-like (ChTL) and caspase-like (CL) activities of circulating proteasomes, blood serum was pre-activated with 10 % SDS according to the technique [15]. The ChTL activity of circulating proteasomes was determined by the hydrolysis of the fluorogenic oligopeptide Suc-LLVY-AMC (Sigma); the CL activity was determined by the hydrolysis of the fluorogenic oligopeptide Z-LLE-AMC (Sigma). The reaction was carried out for 20 minutes at 37 °C. The resulting product was recorded on a Cytation1 multi-mode microplate reader-imager (BioTek, United States) at Exi=360 nm, Emi=460 nm. The specific activity of proteasomes was expressed in units of activity per 1 ml of serum.

Statistical analysis was carried out using the Statistica 10.0 software package. The results shown in the table are presented as median (Me) with an interquartile range (Q1Q3). Using the Kruskal-Wallis test, statistically significant differences were found between the study groups. For further pairwise comparison, the nonparametric Mann-Whitney test was used taking into account the correction for multiple comparisons (Bonferroni correction). Differences were considered significant at $p<0.05$.

Results and Discussion

Table 1 shows the ChTL and CL activities of circulating proteasomes in blood serum of patients with HNSCC, patients with chronic premalignant lesions, and healthy donors. Significant differences in serum proteasome ChTL and CL activities between patients with HNSCC and patients with chronic oral and laryngeal lesions associated with dysplastic changes as well as between patients with HNSCC and healthy donors were found. As the disease severity increased, the serum proteasome ChTL and CL activities also increased. The data obtained confirm our previous findings that the proteasome ChTL activity was higher in patients with HNSCC compared to patients with CHL with grade II–III dysplasia [14]. In addition, a significant increase in the CL level was also observed in the same groups of patients. Thus, the development of oral and laryngeal cancers was associated with significant changes in the proteasome ChTL and CL activities.

We also compared serum proteasome ChTL and CL activities in patients with premalignant laryngeal and oral lesions (table 2).

The levels of ChTL and CL proteasomal activities were significantly higher in patients with CHL (grade IIII dysplasia) than in patients with oral leukoplakia. Among HNSCC patients, the levels of ChTL and CL proteasomal activities were higher in laryngeal cancer patients than in oral cancer patients (table 3). Moreover, the comparison of malignant and premalignant lesions revealed a significant difference in the ChTL proteasomal activity between patients with oral cancer and patients with oral leukoplakia as well as between patients with laryngeal cancer and patients with CHL with epithelial dysplasia.

A significant difference in the ChTL activity of circulating proteasomes between premalignant and malignant lesions shows that proteasomes are likely to be involved in malignant transformation of precancerous lesions into cancer.

The role of circulating proteasomes in the development of cancer is not clear. Increased levels of their activity were shown to correlate with the progression of solid tumors, including laryngeal cancer [14, 16]. Proteasomes are believed can enter the systemic circulation during secretion from cells by the mecha-

Таблица 1/Table1

Химотрипсинподобная (ХТП) и каспазаподобная (КП) активности циркулирующих протеасом сыворотки крови больных ПРГШ и хроническими заболеваниями с предопухолевыми изменениями

The chymotrypsin-like (ChTL) and caspase-like (CL) activities of circulating proteasomes in blood serum of patients with HNSCC, patients with chronic premalignant lesions, and healthy donors

Исследуемые группы/Study groups	ХТП/ChTL (ЕД/мл/U/ml)	КП/CL (ЕД/мл/U/ml)
Здоровые доноры (n=10)/ Healthy donors (n=10)	81.2 (65.0–101.6)	106.2 (86.6–139.5)
ХГЛ с DI–III, лейкоплакии (n=15)/ CHL with grade I–III dysplasia, leukoplakia (n=15)	95.3 (69.2–117.0)	160.0 (153.7–200.0) p=0.030
ПРГШ (n=35)/HNSCC (n=35)	150.0 (117.0–200.0) p=0.001; p1<0.001	253.3 (156.6–310.0) p=0.001; p1=0.020

Примечание: p – значимость различий между здоровыми донорами и группой больных с ПРГШ; p1 – значимость различий между группами больных с ХГЛ с DI–III, лейкоплакии и с ПРГШ.

Notes: p – significant difference in ChTL and CL activities between healthy donors and patients with HNSCC; p1 – significant difference in ChTL and CL activities between patients with chronic premalignant lesions (CHL with dysplasia and leukoplakia) and patients with HNSCC.

Таблица 2/Table 2

Химотрипсинподобная (ХТП) и каспазаподобная (КП) активности циркулирующих протеасом сыворотки крови больных хроническим гиперпластическим ларингитом с дисплазией (ХГЛ) и лейкоплакиями ротовой полости

Serum proteasome ChTL and CL activities in patients with chronic hyperplastic laryngitis (CHL) with dysplasia and in patients with oral leukoplakia

Исследуемые группы/Study groups	ХТП/ChTL (ЕД/мл/U/ml)	КП/CL (ЕД/мл/U/ml)
ХГЛ (DI–III) (n=9)/CHL (grade I–III dysplasia) (n=9)	103.3 (95.3–127,4)	200.0 (183.0–267.0)
Лейкоплакии ротовой полости (n=6)/Oral leukoplakia (n=6)	57.2 (41.2–74.7) p=0.030	128.4 (90.8–159.3) p=0.003

Примечание: p – значимость различий между группами больных с ХГЛ (DI–III) и с лейкоплакиями ротовой полости.

Notes: p – significant difference in ChTL and CL activities between patients with CHL (grade I–III dysplasia) and patients with oral lekoplakia.

Таблица 3/Table 3

Химотрипсинподобная (ХТП) и каспазаподобная (КП) активности циркулирующих протеасом сыворотки крови больных с предопухолевыми и опухолевыми заболеваниями органов головы и шеи

The ChTL and CL activities of circulating proteasomes in blood serum of patients with premalignant and malignant head and neck lesions

Исследуемые группы/Study groups	ХТП/ChTL (ЕД/мл/U/ml)	КП/CL (ЕД/мл/U/ml)
Лейкоплакии (n=6)/Leukoplakia (n=6)	57.2 (41.2–74.7)	128.4 (90.8–159.3)
Рак ротовой полости (n=10)/Oral cancer (n=10)	116.8 (90.0–150.0) p=0.009	146.0 (103.0–183.3)
ХГЛ (DI–III) (n=9)/CHL (grade I–III dysplasia) (n=9)	103.3 (95.3–127.4)	200.0 (183.0–267.0)
Рак гортани (n=25)/Laryngeal cancer (n=25)	160.0 (140.0–217.0) p1=0.010; p2=0.050	281.6 (233.0–338.3) p2=0.040

Примечание: p – значимость различий между группами больных раком ротовой полости и больными с лейкоплакиями; p^1 – значимость различий между группами больных раком гортани и больными с ХГЛ (DI–III)»; p^2 – значимость различий между группами больных с ХГЛ (DI–III) и больными с лейкоплакиями.

Notes: p – significant difference in ChTL and CL activities between patients with oral cancer and patients with oral leukoplakia; p^1 – significant difference in ChTL and CL activities between patients with laryngeal cancer and patients with CHL with grade I–III dysplasia; p^2 – significant difference in ChTL and CL activities between patients with CHL with grade I–III dysplasia and patients with oral leukoplakia.

nism, which has not been established yet [17] or from destroyed microvesicles [13]. Determination of the function and substrates of circulating proteasomes showed that they can degrade albumin [18] and osteopontin [19]. It was found that the processing of osteopontin in the circulating proteasomes produced biologically active peptides with chemotactic activity [19]. It has not yet been determined whether there are other substrates for circulating proteasomes in the systemic circulation and what their significance is in pathological conditions.

The study of proteasomes in various malignant tumors is relevant not only from the point of view of the development of new therapeutic agents, the targets of which are active centers or subunits of proteasomes [20], but also for the search for new predictive cancer markers. The data obtained can serve as a basis for the development of a new method for assessing the cancer risk in patients with precancerous oral and laryngeal diseases.

Conclusion

In this study, we analyzed for the first time the ChTL and CL activities of circulating proteasomes in the blood serum of patients with premalignant and malignant head and neck lesions. It was found that the levels of ChTL and CL proteasomal activities were significantly higher in patients with laryngeal and oral cancer than in patients with laryngeal dysplasia and oral laukoplakia. Moreover, significant differences in the ChTL and CL proteasomal activities between patients with CHL+dysplasia and patients with oral leukoplakia were observed. Thus, the results obtained indicate that the assessment of the ChTL and CL activities of circulating proteasomes can be used as a criterion for predicting the risk of developing HNSCC in patients with premalignant oral and laryngeal lesions.

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ВКЛАД АВТОРОВ

Сиденко Евгения Александровна: исследование показателей в сыворотке крови флуориметрическим методом, статистическая обработка материала.
Михалев Дмитрий Евгеньевич: набор клинического материала.
Какурина Гелена Валерьевна: составление базы данных.
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Olga D. Baidik: critical revision of the manuscript for important intellectual content.
Evgeny L. Choynzonov: study conception and design.
Irina V. Kondakova: study supervision, final approval of the manuscript.

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Conflict of interest

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