РЕЗЮМЕ

ВЫДЕЛЕНИЕ И СРАВНИТЕЛЬНОЕ ИССЛЕДОВАНИЕ КОМПЛЕКСА ТЕРМОСТАБИЛЬНЫХ БЕЛКОВ ИЗ КОСТНОГО МОЗГА ВЗРОСЛЫХ МЫШЕЙ

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Из клеток костного мозга взрослых мышей изолирован и частично охарактеризирован рост-ингибирующий термостабильный белковый комплекс (ТБК). Для сравнительного анализа компонентов ТБК применялся метод электрофореза в полиакриламидном геле.

Установлено, что белковый комплекс, выделенный из костного мозга взрослых мышей, как и комплексы, ранее полученные из других органов, содержит две субфракции белковых компонентов - относительно высокомолекулярную и низкомолекулярную. При этом, в ТБК костного мозга обнаружено незначительное содержание низкомолекулярных компонентов.

Установлено, что ТБК клеток костного мозга взрослых мышей не обладает способностью подавлять пролиферацию гомотипических клеток, что, по всей вероятности, обусловлено незначительным содержанием в комплексе ингибирующего рост активного начала (низкомолекулярная субфракция), а также структурными и функциональными свойствами постоянно возобновляемой кроветворной ткани: свойство факторов, регулирующих пролиферацию, экспрессия мембранных рецепторов и их афинность к действующим факторам.

რეზიუმე

ზრდასრული თაგვების ძვლის ტვინიდან ზრდის შემაკავებელი თერმოსტაბილური ცილების კომპლექსის გამოყოფა და შედარებითი შესწავლა

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ზრდასრული თაგვების ძვლის ტვინის უჯრედებიდან გამოყოფილია და ნაწილობრივ დახასიათებულია ზრდის შემაკავებელი თერმოსტაბილური ცილების კომპლექსი (თცკ). ჩატარებულია თცკ-ს კომპონენტების შედარებითი ანალიზი პოლიაკრილამიდის გელში ელექტროფორეზის გზით. დადგენილია, რომ ზრდასრული თაგვების ძვლის ტვინიდან გამოყოფილი ცილოვანი კომპლექსი, სხვა ორგანოებიდან მიღებული კომპლექსების მსგავსად, შეიცავს ცილოვანი კომპონენტების ორ, შედარებით მაღალმოლეკულურ და დაბალმოლეკულურ ქვეფრაქციებს. ამასთან, ძვლის ტვინის თცკ-ში გამოვლინდა დაბალმოლეკულური კომპონენტის მინორული შემცველობა. დადგენილია, რომ ზრდასრული თაგვების ძვლის ტვინის უჯრედების თერმოსტაბილური ცილების კომპლექსს არ გააჩნია ჰომოტიპური უჯრედების გამრავლებაზე დამთრგუნველი ზემოქმედების უნარი. ეს შეიძლება განპირობებული იყოს კომპლექსში აქტიური საწყისის (დაბალმოლეკულური ქვეფრაქცია) მინორული შემცველობით და მუდმივად განახლებადი სისხლმბადი ქსოვილის სტრუქტურული და ფუნქციური თავისებურებებით, როგორებიცაა: პროლიფერაციის მარეგულირებელი ფაქტორების ბუნება, მემბრანული რეცეპტორების ექსპრესია და მათი უჯრედებისადმი განსხვავებული წვდომა.

LASER INDUCED FLUORESCENCE OF SKIN: SUPERPOSITION OF SPECTRAL INTENSITIES

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Optical methods are widely used in biology and medicine as they allow to study objects in real-time. In particular, in those cases, the diagnosis is made by an effective non-invasive method. A large number of works are devoted to the determination and monitoring of the state of body health by determining the tissues states by their optical parameters (see for example [1-

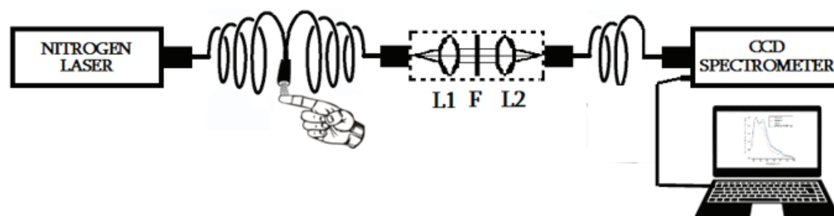

Fig. 1. Schematic view of the experimental setup for in vivo measurements of human skin fluorescence

5] and references cited there). Among human body fabrics, the skin has an important function. The main function of the skin is to maintain homeostasis despite daily environmental exposure. It creates a barrier for body fluids and protects the underlying tissues from the affects of microorganisms, harmful substances and radiation. Accordingly, it is a relevant object for effective diagnostics [6].

A functional model of human skin consists of three layers: epidermis, dermis (skin itself) and subcutaneous tissues. The outermost layer of the epidermis is thin, devoid of blood vessels, and is divided into two sub-layers: the outer corneal layer, which consists of dead keratinized cells, and the inner layer of cells, where melanin and keratin are formed. The dermis is located under the epidermis. The dermis is well-supplied with blood. It contains connective tissue, sebaceous glands, sweat glands, and hair follicles. The dermis merges with the subcutaneous tissue. The color of normal skin (absorption and scattering) depends on the following main chromophores: melanin, β-Carotene, oxyhemoglobin, deoxyhemoglobin and collagen. The absorption coefficient of the dermis depends on the blood filling of the capillaries, and the fluorescence intensity depends on both: the fluorescence quantum yield (keratin, collagen, NADH) and the extinction coefficient (oxyhemoglobin, deoxyhemoglobin and melanin) [8]. Many works have been published on skin optics and spectroscopy ([8-11] and references cited there). However, the spectra were not investigated for the validity of the "Principle of Superposition" [4]. This principle was demonstrated by us for the thyroid tissue and allowed us to represent the fluorescence spectrum of the tissue of any patient as a linear superposition of the LIF (Laser-Induced Fluorescence) spectra of two extreme tissue states. Therefore, it was interesting to check the validity of this principle for human skin.

Materials and methods. In Fig. 1 the scheme of the experimental setup is presented. A MNL 100 Nitrogen Laser (Lasertechnik Berlin, Germany) was used to excite autofluorescence. λ=337 nm; Power – 0.15 mW per pulse; Pulse duration - 3 ns; pulse repetition rate - 1–30 Hz; LIF spectra were recorded on a CCD spectrometer (AvaSpec-ULS 2048CL-EVO-RS, Netherlands). The transfer of exciting radiation to the sample and the transfer of the fluorescence signal from the sample to the spectrometer was carried out using a special Y-type UV probe (R400-7-UV/VIS Ocean Optics, United States). The fiber optics reflectance probe had six illuminating and one detection 400-micron diameter fibers bundled together. A 6-fiber leg was connected to the light source and reflected light was fed into the spectrometer via a single-fiber leg.

To remove laser radiation scattered from the sample and surfaces, a collimated fluorescence signal (using lenses L1-L2) was passed through a band-pass filter (transparency: λ = 337 nm less than 1%; λ=380 nm - 50%; λ 475 nm more than 80%).

In the dominant absorption case, a great deal of absorbed radiation energy transforms into the heat increasing the tissue temperature by approximately 1 K during 10^3 s [7]. In our experiments, the laser radiation exposure time on tissue did not exceed a few seconds. Thus, the temperature increment did not affect the spectral measurements.

The experiments were performed on volunteers' finger pads and nails. In particular, on the dorsal side of the proximal phalange and fingernail of the middle finger of the volunteer's left arm. For more clarity, in this article we presents 7 characteristic spectral curves selected from the spectra recorded from 32 volunteers: 5 physiologically healthy and 2 diabetic (type 1 and type 2). LIF spectra Experiments were performed with consent from the Medical Ethics Commission of Georgian National Center for Disease Control & Public Health (Protocol # 2019-43), and informed consent from these 32 volunteers.

Results and discussion. Under normal conditions, ultraviolet excitation (337 nm) induces fluorescence in the visible region, which is a superposition of fluorescent emission from the three main natural fluorophores. These are collagen, keratin and NADH. The ratio of these three organic fluorophores varies depending on the site of the human skin.

The observed fluorescence line shape and intensity depend on the penetration depth, absorption and scattering of both exciting and fluorescent lights. On that is also influenced skin color, age, health status and many other additional factors of the observed person.

Fig. 2 represents the fluorescence spectra of 7 volunteers' fingerpads. As already noted, among the volunteers who participated in the experiment were both healthy and people with a diagnosis of diabetes mellitus. The figure shows that the volunteers' spectral lines differ from each other. Among them, one stands out as the spectral line belongs to a volunteer with type 1 diabetes (dashed line). The spectral lines are characterized by two main peaks (about 417 nm and 460 nm), obtained by absorption and fluorescence of various chromophores (oxyhemoglobin, deoxyhemoglobin, collagen, NADH). The spectral lines are normalized to the signal amplitude at 417 nm, which is very convenient for comparing them.

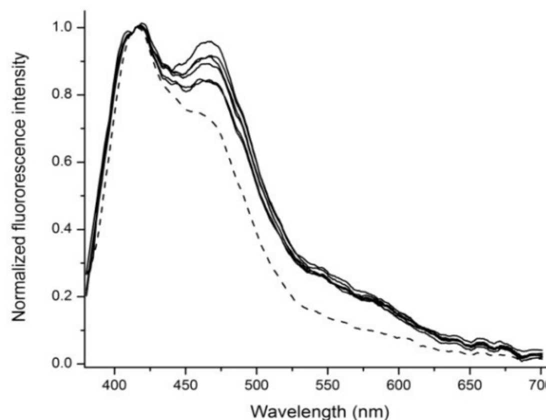

Fig. 2. The autofluorescence spectra from pads of a human finger

In Fig. 3 represents the nails fluorescence spectra of the same volunteers. The naked eye can see that the spectrum of all volunteers is practically identical, which is explained by the fact that the building material of nails is a homogeneous structural material - keratin. The graphs given do not show the effect of hemoglobin, which confirms the point of view stated in the reference [2] that the hemoglobin contribution in the fluorescence of the nail is negligible.

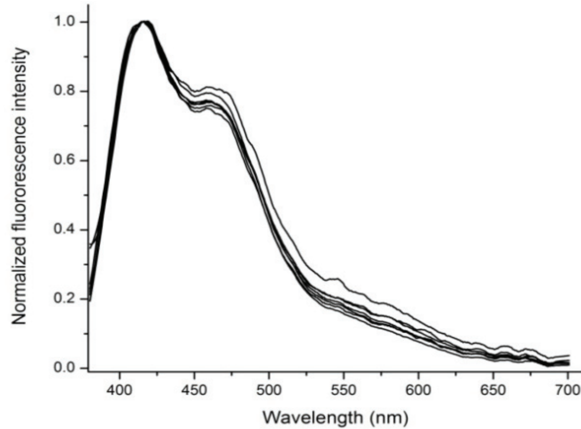

Fig. 3. The autofluorescence spectra from the nail of the human hand

In Fig. 4, represents the fluorescence spectra of the skin and nails of only two volunteers with a diagnosis of diabetes (type 1: nail2, skin2 and type 2: nail1, skin1). This selection of spectral lines gave us an interesting result. It was found that when diabetes was present in the studied volunteers, the individual spectra of their skin and nails literally coincide. In our opinion, such a coincidence of the skin and nails fluorescence spectra is associated with increased content of collagen in the skin of patients with diabetes mellitus, which characterisis the diabetes.

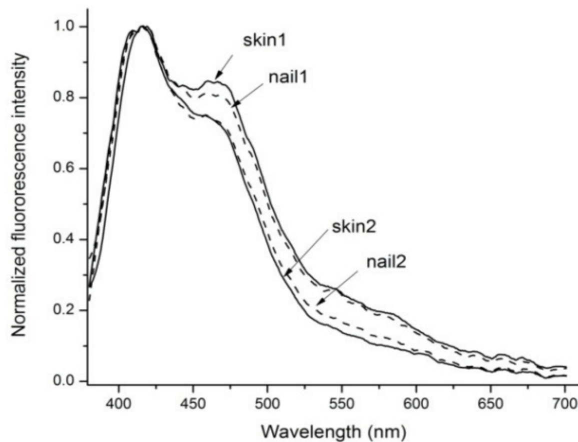

Fig. 4. The comparison of autofluorescence spectra of skin and nail from diabetic volunteers

In Fig. 5 there are shown the spectra of two volunteers – healthy (nail3, skin3) patients and type 1 diabetes (nali2, skin2). Here is the fluorescence spectrum of a healthy volunteer with the maximum difference between the intrinsic spectra of the nail and the skin. It should be noted that the spectrum of the "healthy nail" coincides with the spectrum of the nail and finger of a patient with type 1 diabetes.

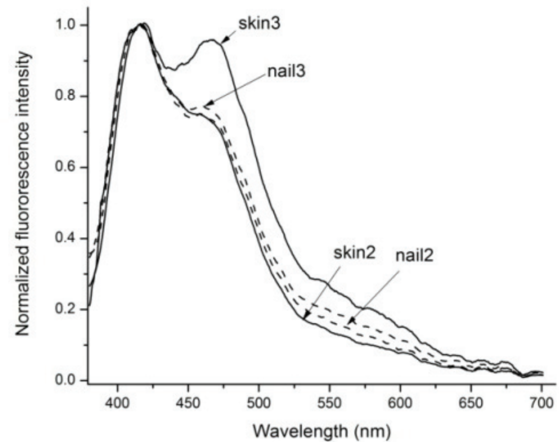

Fig. 5. The comparison of autofluorescence spectra of skin and nail from healthy and diabetic volunteers

The fluorescence spectra of the two volunteer fingers, which are different as much as possible from each other, are selected in figure 6. With the help of their superposition, it is possible to obtain the fluorescence spectra of the skin of any of the volunteers (superposition model). In this particular case, the spectra measured on one volunteer and the same spectrum calculated by using the superposition method of "extreme spectra" are shown. As can be seen from the graph, the agreement between the experimentally observed and calculated spectra (superposition model) is very good.

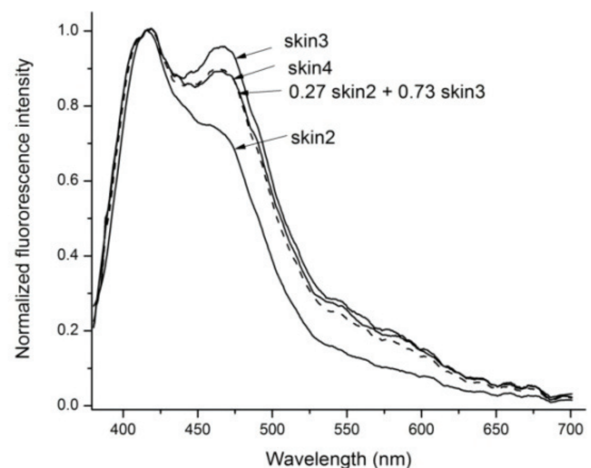

Fig. 6. Superposition of LIF spectra

For discussion, it is important to recall the generally accepted optical model of the skin as a multi-layer multi-scattering medium, in each layer of which chromophores are homogenously distributed [8].

In our analysis, the simple skin model is used [12]. In this model LIF intensity of skin is defined by the total fluorescence intensitiesand arisings from the epidermal (NADH, keratin) and dermal (collagen) skin layers, respectively (Fig. 7).

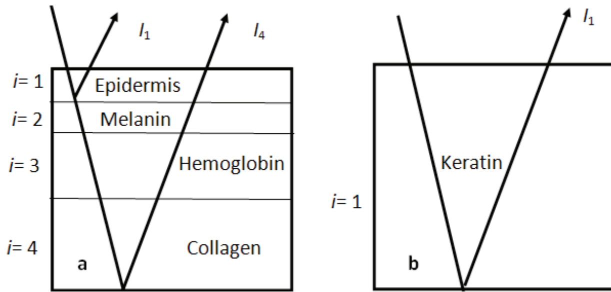

Fig. 7. Simple models of LIF: (a) skin and (b) nail. Adapted from [12]

In the one-dimensional approximation, the intensity of escaping fluorescence from the dermal layer can be presented as [8]:

$$I_4(\lambda_{FL}) = I_0(\lambda_{EX}) \cdot \eta(\lambda_{FL}, \lambda_{EX}) \cdot \exp\left\{-\sum_i [\varepsilon_i(\lambda_{EX}) + \varepsilon_i^*(\lambda_{FL})] \cdot d_i\right\}, \quad (1)$$

where λ_{EX} and λ_{FL} are the excitations and emission wavelengths $\eta(\lambda_{FL},\lambda_{EX})$; is the fluorescence quantum yield; $I_0(\lambda_{EX})$ is the intensity of excitation light incident on the skin/nail surface as a collimated beam; $\varepsilon_i^*(\lambda_{FL})$ is the absorption of the *i*'th layer with thickness d_i at the wavelength of fluorescence emission λ_{FL}, and $\varepsilon_i(\lambda_{EX})$ is the extinction coefficient of the *i*'th layer at the wavelength of the excitation light λ_{EX}.

In earlier work, we empirically introduced a superposition model for fluorescence spectra [4], which states: If we have two basic fluorescence spectra, then any intermediate spectrum is calculated by the linear superposition of these basic spectra. Judging by the obtained experimental results, this principle is valid in this case as well. Then escaping fluorescence generally can be calculated as follows:

$$I_4(\lambda_{FL}) = I_0(\lambda_{EX}) \cdot \sum_j C_j \cdot \eta_j(\lambda_{FL}, \lambda_{EX}) \cdot \exp\left(-\sum_i [\varepsilon_{j,i}(\lambda_{EX}) + \varepsilon_{j,i}^*(\lambda_{FL})] \cdot d_{j,i}\right). \quad (2)$$

Where C_j is the superposition coefficient of the chromophore spectra and $\sum_j C_j = 1$. However, this expression is still not correct. The following condition must be satisfied for (2) to describe the superposition:

$$\sum_i [\varepsilon_{j,i}(\lambda_{EX}) + \varepsilon_{j,i}^*(\lambda_{FL})] \cdot d_{j,i} = \sum_i [\varepsilon_{k,i}(\lambda_{EX}) + \varepsilon_{k,i}^*(\lambda_{FL})] \cdot d_{k,i} \equiv f(\lambda_{EX}, \lambda_{FL}), \quad (3)$$

Where *j* and *k* denote the same chromophore in different human subjects. Taking this into account in (3), in the end we get:

$$I_4(\lambda_{FL}) = I_0(\lambda_{EX}) \cdot e^{-f(\lambda_{EX}, \lambda_{FL})} \cdot \sum_i C_j \cdot \eta_j(\lambda_{FL}, \lambda_{EX}). \quad (4)$$

If we choose the expression (4) for our task, it will be simplified. Considering the existing chromophores $j = 1, 2, 3, 4$. Only two of them are fluorophores: collagen and NADH. The other two chromophores, blood and melanin, do not fluoresce, at least in the visible spectrum. Accordingly, the quantum yield of melanin and blood in the visible spectrum $\eta_{hemoglobin}(\lambda_{FL},\lambda_{EX}) = \eta_{melanin}(\lambda_{FL},\lambda_{EX}) = 0$. Therefore, for the spectrum of fluorescence intensity we can write:

$$I_4(\lambda_{FL}) = I_0(\lambda_{EX}) \cdot e^{-f(\lambda_{EX}, \lambda_{FL})} \cdot [C_1 \cdot \eta_1(\lambda_{FL}, \lambda_{EX}) + C_2 \cdot \eta_2(\lambda_{FL}, \lambda_{EX})], \quad (5)$$

Where C_1 and η_1 correspond to collagen/keratin and C_2 and η_2 correspond to NADH.

Formula (5) explains the result of our experiment - the validity of the principle of the linear superposition of spectra.

Thus, the analysis of our experiments showed that:

1. When excited by an ultraviolet (337 nm) laser, two main natural fluorophores appear in the fluorescence of human skin - collagen and nicotinamide adenine dinucleotide (NADH), the total spectra of which are modulated by the absorption of oxyhemoglobin and deoxyhemoglobin.
2. Fluorescence in nails is not modulated by blood. The fluorescence spectra of nails are practically the same for all volunteers, while the fluorescence of the skin of the same people differs significantly from each other.
3. The fluorescence spectra of nails and skin of human subjects with diabetes mellitus do not actually differs from each other.
4. For each of any three experimentally recorded fluorescence spectra of human skin $I_1(\lambda)$, $I_2(\lambda)$, $I_3(\lambda)$, the principle of superposition of spectral intensities is valid: each spectrum is a linear superposition of the other two, $I_1(\lambda)=C_{11} I_2(\lambda)+C_{12}I_3(\lambda)$, $I_2(\lambda)=C_{21}I_1(\lambda)+C_{22}I_3(\lambda)$, $I_3(\lambda)=C_{31}I_1(\lambda)+C_{32}I_2(\lambda)$.
5. Based on the principle of superposition, it is possible to obtain the fluorescence quantum yields of basic cromophores.

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SUMMARY

LASER INDUCED FLUORESCENCE OF SKIN: SUPERPOSITION OF SPECTRAL INTENSITIES

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The aim of the work was to determine the possibility of assessing the state of human health by the method of optical spectroscopy of skin and nail. To achieve this goal, Laser-Induced Fluorescence (LIF) spectroscopy was used. A special probe was designed, which makes it possible to record differential spectra and, as a result, to compare the shapes of spectral fluorescence lines.

In vivo spectra of LIF intensities of the human finger pad and nail were measured. These spectra can be used to determine and characterize the state of human health, and it's also further monitoring in real time.When processing the spectra of different volunteers, it was found that the fluorescence spectra of the skin of physiologically healthy and pathological (in this case, type 1 and 2 diabetes) volunteers significantly differed from each other. Moreover, the analysis of these spectra makes it possible to assess the degree of pathology. It was also found that any of the three experimentally recorded fluorescence spectra is a superposition of the other two. A theoretical analysis of the multilayer model of human skin fluorescence has shown that this principle is always valid when the same chromophores are involved in fluorescence.

Keywords: laser spectroscopy, laser-induced fluorescence, superposition of spectral intensities, human skin.

РЕЗЮМЕ

ЛАЗЕРНО-ИНДУЦИРОВАННАЯ ФЛУОРЕСЦЕНЦИЯ КОЖИ: СУПЕРПОЗИЦИЯ СПЕКТРАЛЬНЫХ ИНТЕНСИВНОСТЕЙ

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Цель исследования - оценка состояния здоровья человека методом оптико-спектроскопического исследования кожи и ногтей.

Для достижения этой цели использована спектроскопия лазерно-индуцированной флуоресценции (LIF). Разработан специальный зонд, позволяющий снимать дифференциальные спектры и, как следствие, сравнивать формы спектральных линий флуоресценции. Определены спектры LIF интенсивностей ногтей и подушечек пальцев *in vivo*, что может быть использовано для определения и характеристики состояния здоровья человека и дальнейшего мониторинга в режиме реального времени.

При обработке спектров волонтеров обнаружено, что спектры флуоресценции кожи физиологически здоровых и имевших патологию (в данном случае диабет 1 и 2 типа) волонтеров существенно различаются между собой. Более того, анализ этих спектров позволяет оценить степень патологии. Выявлено, что любой из трех экспериментально зарегистрированных спектров флуоресценции является суперпозицией двух остальных. Теоретический анализ многослойной модели флюоресценции кожи человека показал, что этот принцип всегда справедлив, когда в флуоресценции участвуют одни и те же хромофоры.

რეზიუმე

კანის ლაზერით ინდუცირებული ფლუორესცენცია: სპექტრალური ინტენსივობების სუპერპოზიცია

[1]ზ. ჯალიაშვილი, [1]თ. მედოიძე, [1]ზ. მელიქიშვილი, [2]ა. ჭანიშვილი, [3]გ.პეტრიაშვილი, [4]ლ. ლომიძე

საქართველოს ტექნიკური უნივერსიტეტის ვლადიმერ ჭავჭანიძის სახ. კიბერნეტიკის ინსტიტუტი, [1]კოჰერენტული ოპტიკისა და ელექტრონიკის განყოფილება, [2]ოპტიკურად მართვადი ანიზოტროპული სისტემების განყოფილება, [3]ოპტიკურ-ქიმიურ კვლევათა ლაბორატორია; [4]ესთეტიკის ცენტრი კლინიკა კანულა, თბილისი, საქართველო

კვლევის მიზანს წარმოადგენდა ადამიანის კანისა და ფრჩხილის ოპტკურ-სპექტროსკოპიული კვლევით მისი ჯანმრთელობის მდგომარეობის შეფასება. კვლევაში გამოყენებული იყო ლაზერით ინდუცირებული

ფლუორესცენციის (LIF) სპექტროსკოპია. დამზადდა სპეციალური ზონდი, რომლის საშუალებითაც შესაძლებელი გახდა დიფერენციული სპექტრების გადაღება და შესაბამისად ფლუორესცენციის სპექტრალური ხაზის ფორმების შედარება.

გაიზომა ადამიანის თითის ბალიშისა და ფრჩხილის LIF ინტენსივობის *in vivo* სპექტრები, რომლებიც გამოყენებული იყო ადამიანის ჯანმრთელობის მდგომარეობის დასადგენად, მის დასახასიათებლად ამ მდგომარეობის შემდგომი მონიტორინგისათვის რეალური დროის რეჟიმში. სხვადასხვა მოხალისეების სპექტრების დამუშავებით დადგინდა, რომ ფიზიოლოგიურად ჯანმრთელი და პათოლოგიის მქონე (ამ შემთხვევაში – დიაბეტის 1-ლი და მე-2 ფორმა) მოხალისეების კანის ფლუორესცენციის სპექტრები საგრძნობლად განსხვავდება ერთმანეთისგან. მეტიც, აღნიშნული სპექტრების ანალიზი იძლევა პათოლოგიის ხარისხის შეფასების შესაძლებლობას.

აღმოჩნდა, რომ სამი ექსპერიმენტულად ჩაწერილი ფლუორესცენციის სპექტრიდან ნებისმიერი ერთი წარმოადგენს დანარჩენი ორის სუპერპოზიციას. ადამიანის კანის ფლუორესცენციის მრავალშრიანი მოდელის თეორიულმა ანალიზმა აჩვენა, რომ აღნიშნული პრინციპი ყოველთვის სამართლიანია, როდესაც ფლუორესცენციაში მონაწილეობენ ერთი და იგივე ქრომოფორები.

"AMPHICEZINE": NEW APPROACHES TO FIGHTING CANCER PRELIMINARY THEORETICAL AND EXPERIMENTAL (*IN VITRO*) MESSAGE

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Fibrin content is increased in human tumor tissue, which, being the result of overall reactions of so-called "Machabeli Syndrome" present in oncologic patients, occupies the central place in the process of tumor metastasis [8-11]. The decrease of membrane potential of tumor cells allows them to sharply limit the penetration of foreign bodies into them to only a few components. This significantly hinders the effectiveness of anti-tumor medications.

Tumor cells secrete enzyme Hyaluronidase, which supports their break-off from primary site and attachment to the walls of other organ's blood or lymph vessels [4].

The emergence of metastasis is closely related to the interrelation of tumor cells and endothelium of blood and lymph vessels at physical-chemical level. Along with the increase of malignancy degree of tumor cells comes increase in their negative electronic charge, which due to its well-known life-giving qualities, increases their vital capacity. Significantly, it is the carcinogenic substances that support the increase of negative charge of cells [6-8].

Herewith, it seems interesting to use existing differences between electrostatic potentials of normal homologous cells and cancer cells to fight against cancer.

Our proposal is as follows: the use of new perspective class of respective drugs ("Amphicezine") for inhibition of metastasis of malignant cells – negative multi-charged long-chain organic ions. The proposed drugs are substances with macromolecule having polar-distributed qualities, one side charged (polar), another –hydrophobic, non-polar [3,6].

Hydrophilic qualities of macromolecules are preconditioned by number of functional groups, which in various biological environments are dissociated by producing long-chained organic anions [1,2,5], which interact simultaneously with lipophilic, as well as hydrophilic structures, that defines their biological activity. The proposed organic anions are characterized by heparin-like and fibrinolytic activities, which hampers the adhesion of tumor cells that break off from the primary site onto the endothelium. While regulating the penetration processes of the cell membrane in addition they support anti-tumor drug transportation to through cell. The above mentioned organic anions are not complexions by direct meaning, but separate fragments of their molecules could perform the role of chelating agents and take part in blocking of carcinogenic ions of heavy metals (chrome, cadmium etc.). Besides, the usage of these organic anions as carriers of cesium and rubidium ions to penetrate through tumor cells gives us opportunity to alkalinize internal environment of these cells. This process, in its turn, causes full destruction of these cells. Furthermore, it is significant that cesium and rubidium cations do not harm normal cells.

Taking into account the potential of the new class of synthetic inhibitors for tumor metastasis chemotherapy and radiotherapy strategies for malignant tumors are altered: it becomes possible to decrease the treatment-prophylaxis dosage or even not to use them at all. It is worth mentioning that the new class of proposed drugs considerably differs from traditional chemo-drugs, which are characterized by high cytotoxicity in relation to the normal cells [12].

Obviously, the authors well understand how complex and wacked pathology is the cancer, but we do hope that we are on the right path to find the "Achilles heel" of the cancer metastasis process. It is remarkable, that the usage of electric charge for treatment-prophylaxis goals in experimental and even in clinical oncology is not mentioned in worldwide scientific research literature as of today.

It is well known, that various new approaches in the treatment of malignant tumors, which gave good results in lab experiments (in vitro), have been unsuccessful in clinical settings. In our opinion, one of the reasons of above mentioned is, that it is not taken into account, that each proposed medication (in our case - metastasis inhibitor) should target and affect cancer cells only and should not damage the normal ones. We have all reasons to consider that the new approach discussed in our article will give us opportunity to solve this problem.