УДК 616.345-006.63-033.1:576.311.347]-092.6
https://doi.org/10.20538/1682-0363-2025-3-42-51

Ultrastructural aspects of mitochondrial translocation in colorectal cancer as a possible pathway of tumorigenesis

Kit O.I.[1], Shikhlyarova A.I.[1], Frantsiants E.M.[1], Ilchenko S.A.[1], Neskubina I.V.[1], Kirichenko E.Yu.[2], Logvinov A.K.[3], Snezhko A.V.[1], Averkin M.A.[1], Gabrichidze P.N.[1]

[1] *National Medical Research Centre (NRMC) for Oncology*
63 14 liniya St., 344037 Rostov-on-Don, Russian Federation

[2] *Don State Technical University (DSTU)*
1 Gagarin Sq., 344000 Rostov-on-Don, Russian Federation

[3] *Southern Federal University (SFU)*
194/1 Stachki Ave., 344006 Rostov-on-Don, Russian Federation

ABSTRACT

Aim. To study the ultrastructural features of rectal cancer cells and to detect signs of mitochondrial translocation from the tumor to the resection line area with an assessment of the possibility of the formation of new malignant cells.

Materials and methods. The present study encompassed the data obtained from 44 patients with an average age of 66 (58–73) years, who underwent surgical intervention for rectal cancer T2–3N0M0 with differentiation grade G2. A portion of the tumor specimen and intestinal tissue along the resection line were preserved in a formaldehyde-glutaraldehyde fixative solution. Standard methods of section preparation were employed. Sections were subsequently examined using a Jeol JEM-1011 electron microscope (JEOL Inc., Japan).

Results. The ultrastructure of rectal adenocarcinoma was characterized by a high density of arrangement and varying sizes and shapes of tumor cells with a large nucleus and deep invaginations of the nuclear membrane, as well as an accumulation of multiple mitochondria at one of the cell poles. The process of pinching off a cytoplasmic fragment, which was found to be densely packed with mitochondria, was observed. This phenomenon was subsequently identified as a mitochondriome. Following this observation, the mitochondria were found to have translocated into healthy intestinal tissues along the resection line. Electron diffraction data revealed the active movement of mitochondria in the form of small spheroids and mitovesicles along the boundaries of the multilayer structure of the rectal submucosa, and subsequent fusion into large organelles capable of implementing nuclear synthesis from transported mitochondrial and nuclear DNA. We observed the presence of individual nuclear structures in conjunction with groups of mitochondria, followed by the self-assembly of abnormal cells.

Conclusion. The ultrastructural analysis of rectal adenocarcinoma indicates the need for mitochondrial translocation to free up intracellular space and prevent the metabolic threat of reactive oxygen species (ROS) accumulation in tumor cells. It also points to the key role of mitochondria in initiating tumor energy and information transfer as leaders of these processes. This observation suggests the possibility of early recurrence and metastasis in rectal cancer cases.

Keywords: mitochondria, rectal adenocarcinoma, ultrastructural analysis

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The authors declare no funding for the study.

Conformity with the principles of ethics. All patients signed an informed consent to the collection and transfer of biological material for scientific research, state assignments for socially and socially useful purposes. The study was approved by the Ethics Committee of the Federal State Budgetary Institution NMRC for Oncology of the Ministry of Health of the Russian Federation (Minutes No. 1 dated January 30, 2023).

✉ *Neskubina Irina V.,* neskubina.irina@mail.ru

For citation: Kit O.I., Shikhlyarova A.I., Frantsiants E.M., Ilchenko S.A., Neskubina I.V., Kirichenko E. Yu., Logvinov A.K., Snezhko A.V., Averkin M.A., Gabrichidze P.N. Ultrastructural aspects of mitochondrial translocation in colorectal cancer as a possible pathway of tumorigenesis. *Bulletin of Siberian Medicine.* 2025;24(3):42–51. https://doi.org/10.20538/1682-0363-2025-3-42-51.

Ультраструктурные аспекты транслокации митохондрий при раке толстой кишки как возможного пути распространения опухолевого процесса

Кит О.И.[1], Шихлярова А.И.[1], Франциянц Е.М.[1], Ильченко С.А.[1], Нескубина И.В.[1], Кириченко Е.Ю.[2], Логвинов А.К.[3], Снежко А.В.[1], Аверкин М.А.[1], Габричидзе П.Н.[1]

[1] *Национальный медицинский исследовательский центр (НМИЦ) онкологии*
Россия, 344037, г. Ростов-на-Дону, ул. 14-я линия, 63

[2] *Донской государственный технический университет (ДГТУ)*
Россия, 344000, г. Ростов-на-Дону, пл. Гагарина, 1

[3] *Южный федеральный университет (ЮФУ)*
Россия, 344006, г. Ростов-на-Дону, пр. Стачки 194/1

РЕЗЮМЕ

Цель. Изучение ультраструктурных особенностей клеток рака прямой кишки и обнаружение признаков транслокации митохондрий из опухоли в область линии резекции с оценкой возможности образования новых злокачественных клеток.

Материалы и методы. В исследование включены результаты, полученные от 44 больных (средний возраст 66 (58–73) лет), прооперированных по поводу рака прямой кишки T2–3N0M0 со степенью дифференцировки G2. Часть опухолевого материала и ткани кишки по линии резекции помещали в фиксирующий раствор формальдегида/глутаральдегида. Применяли стандартные методы подготовки срезов, которые исследовали с помощью электронного микроскопа Jeol JEM-1011 (JEOL Inc., Япония).

Результаты. Ультраструктура аденокарциномы прямой кишки характеризовалась высокой плотностью расположения и вариабельностью размеров и формы опухолевых клеток с крупным ядром и глубокими инвагинациями ядерной мембраны, скоплением множества митохондрий по одному из полюсов клетки. Было выявлено отшнуровывание фрагмента цитоплазмы, плотно заполненного митохондриями, в виде митохондриома с последующей транслокацией митохондрий в здоровые ткани кишки по линии резекции. По данным электронограмм можно было судить об активном передвижении митохондрий в форме мелких сфероидов и митовизикул вдоль границ многослойной структуры подслизистой оболочки прямой кишки, а затем их слияние в крупные органеллы, способных к реализации ядерного синтеза из транспортированных митохондриальных и ядерных ДНК. Отмечены отдельные ядерные структуры в кооперации с группами митохондрий и последующей самосборкой аномальных клеток.

Заключение. Ультраструктурный анализ аденокарциномы прямой кишки свидетельствует не только о необходимости митохондриальной транслокации для освобождения внутриклеточного пространства и предотвращения метаболической угрозы накопления активных форм кислорода в клетках опухоли, но и указывает на ключевую роль митохондрий для старта опухолевого переноса энергии и информации как лидеров этих процессов. Это приводит к мысли о вероятности индукции процессов раннего рецидивирования и метастазирования рака прямой кишки.

Ключевые слова: митохондрии, аденокарцинома прямой кишки, ультраструктурный анализ

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Все пациенты подписали информированное согласие на взятие и передачу биологического материала для проведения научных исследований, государственных заданий в общественно и социально полезных целях. Исследование одобрено этическим комитетом ФГБУ «НМИЦ онкологии» Минздрава России (протокол № 1 от 30.01.2023).

Для цитирования: Кит О.И., Шихлярова А.И., Франциянц Е.М., Ильченко С.А., Нескубина И.В., Кириченко Е.Ю., Логвинов А.К., Снежко А.В., Аверкин М.А., Габричидзе П.Н. Ультраструктурные аспекты транслокации митохондрий при раке толстой кишки как возможного пути распространения опухолевого процесса. *Бюллетень сибирской медицины.* 2025;24(3):42–51. https://doi.org/10.20538/1682-0363-2025-3-42-51.

INTRODUCTION

In recent years, significant improvements have been made in the treatment of colorectal cancer (CRC) with chemotherapy, molecular targeted therapies, and immune checkpoint inhibitors [1]. However, recurrences and drug resistance prevent successful cancer treatment, resulting in a relatively poor 5-year survival prognosis in approximately 60% of cases [2–4]. Moreover, approximately 20% of patients with CRC have metastasis at the time of diagnosis, whereas 25% of patients develop metastasis at an early stage during follow-up [5]. Therefore, an in-depth study of the key factors and mechanisms of tumor progression, as well as the investigation of new therapeutic targets, is essential.

Metabolic reprogramming is currently the focus of cancer research. Recent evidence suggests that the unique metabolism of tumor cells, characterized by reduced oxidative phosphorylation (OXPHOS) and increased glycolysis, is regulated by mitochondrial dynamics [6–8]. Mitochondria are known as the powerhouses of eukaryotic cells that exhibit dynamic properties such as fusion, fission, and degradation, which is crucial for their optimal functioning in energy production [9]. They play an important role in various cellular processes including cell differentiation, apoptosis, calcium homeostasis, innate immunity, and fatty acid (FA) and amino acid metabolism [10, 11].

Both whole mitochondria and mitochondrial genome or other mitochondrial components are endowed with the ability of intercellular translocation [12]. Mitochondrial transport can be accomplished by tunneling nanotubes (TNTs), gap junctions (GJs), and extracellular vesicles or microvesicles (MVs) ranging from 100 nm to 1µm, which are able to span whole mitochondria, genomic DNA, and mitochondrial DNA [13]. However, mitochondria themselves as active organelles are also transported along the cytoskeleton and can take different shapes, for example, fusing into long or interconnected tubules or dividing into small spheroids, which is regulated by opposing processes of fusion and fission [14]. The continuous processes of mitochondrial membrane fusion and fission help to regulate the morphology and number of mitochondria, ensuring their homogeneity and efficient functioning [15]. In addition, unbalanced mitochondrial fusion and fission during the cell cycle, apparently, may be associated with the processes of mitochondria-dependent metabolic reprogramming, promoting the entry of cancer cells into mitosis, thereby providing an advantage in proliferation and survival [9].

Mitochondrial fusion is defined as the full-collapse fusion of two mitochondria by end-to-end collision [10]. Mitochondria consist of two membranes: the outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM). The fusion of the outer membrane occurs first, followed by fusion of the inner membrane, which occurs in close proximity. The IMM contains the mitochondrial lumen (matrix), an inner fringing membrane parallel to the OMM, and a deep curved polymorphic invagination known as the crista.

The crista increases the surface area of the inner membrane and contains components essential for mitochondrial respiration. When the four lipid bilayers fuse, the contents mix, and the matrix components diffuse to form a single fused mitochondrion [9]. In addition to full fusion, there is the so-called kiss-and-run fusion. In contrast to full-collapse fusion, provisional fusion occurs when two mitochondria join, partially exchange intact membrane proteins, and divide, thereby retaining their original topology. This type of fusion increases the functional stability and plasticity of mitochondria and is necessary to support mitochondrial metabolism [16]. While moderate fusion protects intestinal epithelial cells from mitochondrial damage caused by oxidative stress and prevents CRC, abnormal mitochondrial fusion leads to adenosine triphosphate overproduction and abnormal tumor proliferation.

Thus, taking into account the level of modern knowledge about mitochondria dislocation and transformation and their biological significance in tumor pathogenesis, it seems relevant to visually assess the topographic signs of mitochondria movement from the primary focus of CRC to the resection line. This will help to approach the formation of a hypothesis about the key role of mitochondria in the initiation of new tumor cell conglomerations as a possible basis for recurrence and metastasis.

The aim of this study was to investigate the ultrastructural features of rectal cancer cells and to detect signs of mitochondrial translocation from the tumor to the resection line, taking into account the possibility of formation of new malignant cells.

MATERIALS AND METHODS

The study included the data obtained from 44 patients with rectal cancer T2–3N0M0 with an average age of 66 (58–73) years, operated on without adjuvant therapy. The tumor differentiation grade in all patients was G2. During the operation after laparotomy, we performed mobilization of the tumor-affected part of the intestine by dissecting and dividing the feeding blood vessels, performed lymphodissection and resection of the affected organ in the scope of rectal resection with removal of the malignant tumor. A part of tumor material and a fragment of intestinal tissue along the resection line were immediately placed in the formaldehyde-glutaraldehyde fixative solution.

TRANSMISSION ELECTRON MICROSCOPY

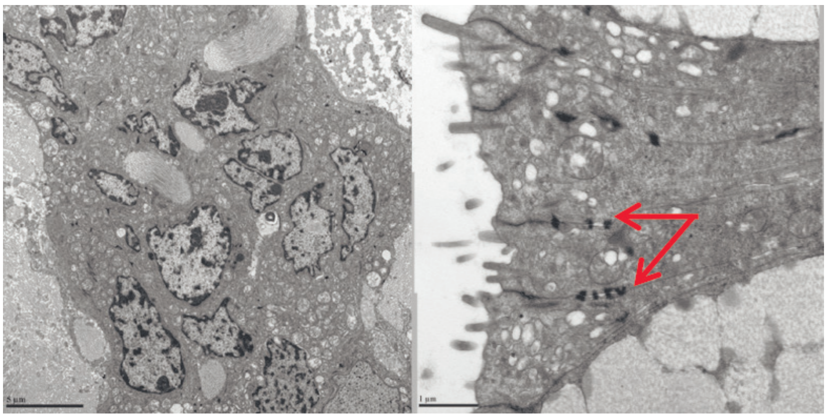
After the pretreatment procedure, the tissue sample was placed in pure Epon-812 resin (SPI Inc., USA) and cured for 72 hours at 70°C. Ultrathin 90-nm sections were obtained using an ultramicrotome equipped with a diamond knife. Sections were mounted on copper slit grids and contrasted with 2% aqueous uranyl acetate solution for 40 minutes and lead citrate for 2 minutes. Sections were examined and photographed using a Jeol JEM-1011 electron microscope (JEOL Inc., Japan).

RESULTS

According to the histopathology report, the rectal tumor was a low-differentiated adenocarcinoma (high grade G2). The most characteristic features of such tumors were the presence of a mucinous component (5%) with invasion of all layers of the intestinal wall, invasion of visceral peritoneum, foci of necrosis, moderately pronounced chronic inflammation, and presence of signs of lymphovascular and perineural invasion.

Ultrastructural study of the tumor tissue showed typical invasive growth of adenocarcinoma cells varying in shape and size (Fig. 1). The cells were tightly adherent to each other without a pronounced intercellular space between the outer layers of cell membranes. At the same time, electron-dense formations of the "interdigitation" type or desmosomes (indicated by arrows in Fig. 1, *b*) were among the noticeable structures demonstrating close intercellular contacts.

Taking into account the fact that desmosomes provide the necessary mechanical adhesion between cells by connecting intermediate filaments, it confirms direct interaction and exchange, allowing to realize the life support of tumor tissue. In cellular polymorphism, we observed diverse nucleus sizes and shapes. The bizarre shape of the nuclei was associated with numerous invaginations of the nuclear membrane. Often the nucleus occupied a significant part, reaching up to 50–60% of the cell surface, and had a multilobed appearance with deep invaginations of the nucleus shell (Fig. 2).



a *b*

Fig. 1. Electron diffraction image of a fragment of a low-differentiated adenocarcinoma with invasion of the rectal wall: *a* – variability in the size and shape of tumor cells with high-density arrangement; *b* – the presence of intercellular contacts in the form of "interdigitation" or desmosomes (indicated by arrows); x10,000. Here and in Figures 2 and 4, images are typical of the preparations of each of the examined patients in the group.

This type of nuclei is characteristic of malignant transformation. The cytoplasm of adenocarcinoma cells was densely filled with organoids, among which the most common ones were mitochondria of different sizes, mainly of irregular round shape with pathological configuration of cristae, and varying electron density of the inner space containing metabolic products (Fig. 2).

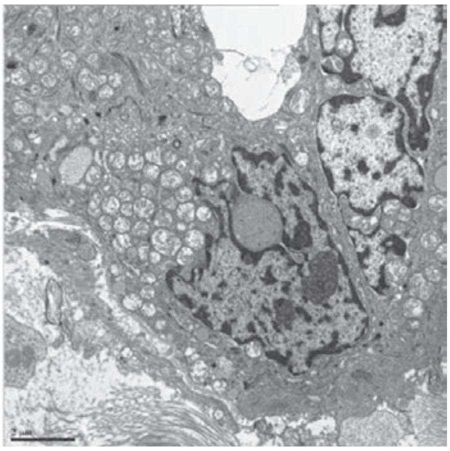


Fig. 2. Electron diffraction image of a fragment of rectal adenocarcinoma tissue. We observe tumor cells with numerous deep invaginations of the nuclear membrane and a cluster of mitochondria at one of the cell poles; ×20,000

It was noticed that in the overwhelming majority of cells the large aggregation of mitochondria as a rule was shifted to one of the cell poles. As a rule, this peculiarity of mitochondria movement to the leading edge of invasive cancer cells is associated with the necessity of energy supply for their movement [17, 18]. It can be assumed that a significant accumulation of mitochondria in the cells could initiate a large mitochondrial transfer, which was realized through the mechanism of cytoplasmic pinching off of the whole aggregation of mitochondria (expulsion) outside the cell as a mitochondriome, as shown in the electron diffraction image below (Fig. 3).

Indeed, it was observed that a separate structure with mitochondria in the area of collagen bundle accumulation was located near the cells. Otherwise, when tumor cells form an excessive accumulation of mitochondria in a state of dysfunction, a large number of ROS can be produced, which poses a threat to cell life [19]. It is under such dangerous conditions that cancer cells tend to displace mitochondria into the intercellular space [20].

Obviously, the separation of the mitochondriome from the cell by pinching off the mitochondria-filled portion of the cytoplasm demonstrates the initial stage of transcellular mitochondrial translocation, which we recorded in our ultrastructural study of rectal cancer. We cannot exclude the assumption that further on, this may represent one of the signaling mechanisms for translocation of mitochondria and associated essential mitochondrial components (mitochondrial DNA and nuclear DNA fragments) into the surrounding space and invasion into the area of healthy tissues. We were able to confirm this by studying electron diffraction images of the intestinal tissue along the resection line of the removed tumor (Fig. 4, 5).

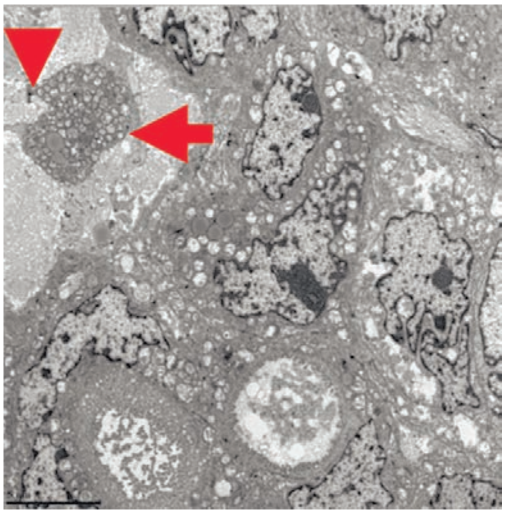


Fig. 3. Electron diffraction image of a fragment of colon adenocarcinoma tissue. It shows pinching off of a cytoplasm fragment forming mitochondriome surrounded by collagen bundles (indicated by an arrow); ×10,000

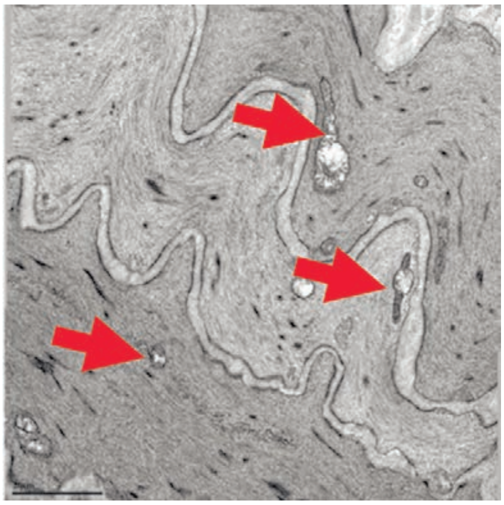


Fig. 4. Electron diffraction image of a fragment of colon tissue along the line of adenocarcinoma resection. The image shows active migration of mitochondria through the layers of the muscularis mucosae. ×25,000

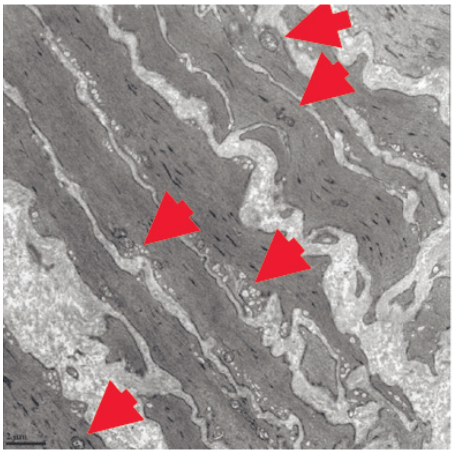
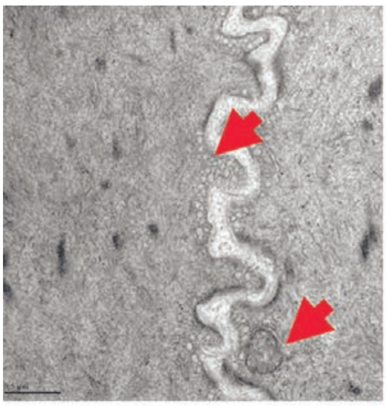


Fig. 5. Electron diffraction image of a fragment of colon tissue along the adenocarcinoma resection line. The image shows movement of many small spheroid-type mitochondria and mitovesicles (indicated by arrows) along the interfaces between the submucosa and the muscularis mucosae. ×12,000

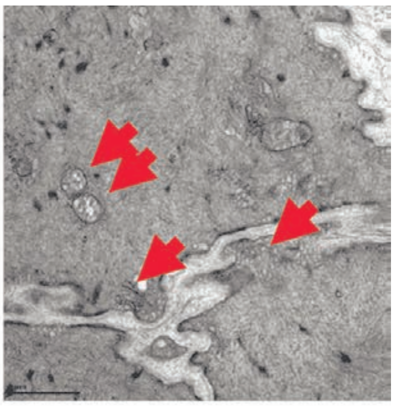
Moving beyond the cell boundaries appeared to enhance mitochondrial migration activity, including the mitochondrial genome to play a signaling role in surrounding intercellular communication, mediating information transfer not only near tumor cells but even over longer distances in the environment of normal healthy tissues.

As can be seen in Fig. 4, mitochondria released from tumor cells show mobility and move independently along the layers of the muscularis mucosae of the colon. Further, it is easy to notice that the overwhelming majority of mitochondria look like small spheroids, which confirms their morphological plasticity and ability to adapt quickly during the transition from tumor environment to healthy tissues (Fig. 5). At the same time, there is a mechanism associated with the formation of so-called mitovesicles, a population of extracellular vesicles of mitochondrial origin during the development of mitochondrial dysfunction. The composition of mitovesicles may include mitochondrial proteins, mtDNA, cytochrome C, and other components.

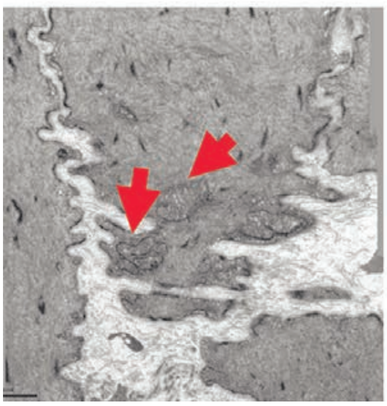
In other words, at this stage of active independent translocation of mitochondria, we visualized the process of their size reduction, known from the literature as the process of fission, providing adaptive efficient functioning of small spheroid forms and mitovesicles during active movement at the boundary with muscle and mucous tissue (Fig. 6, *a*).



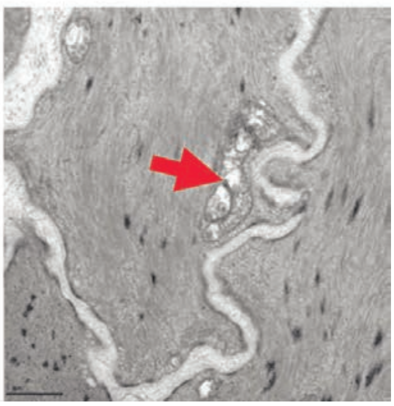
a



b



c



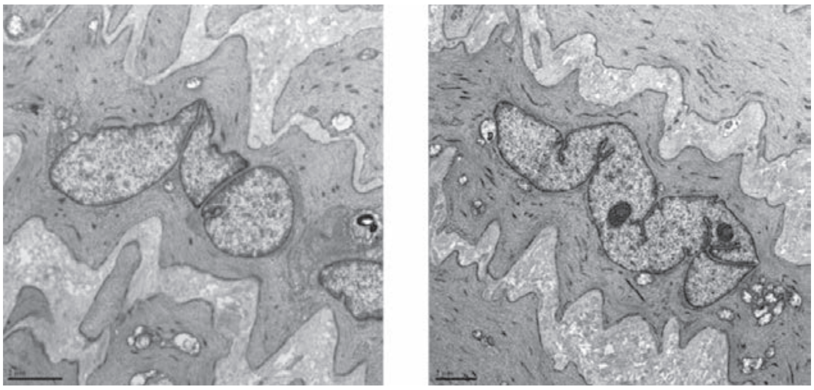
d

Fig. 6. Electron diffraction image of a rectal tissue fragment along the adenocarcinoma resection line: *a* – the presence of small spheroid mitochondria along the healthy tissue interface of submucosa, ×80,000; *b* – accumulation and fusion areas of spheroids and mitovesicles, ×50,000; *c*, *d* – the formation of large abnormal mitochondria in the niches of curved spaces, ×30,000

It was not only the accumulation of a large number of mitovesicles in the curved segments of the boundary but also the presence of single large mitochondria with electron-dense content that drew attention.

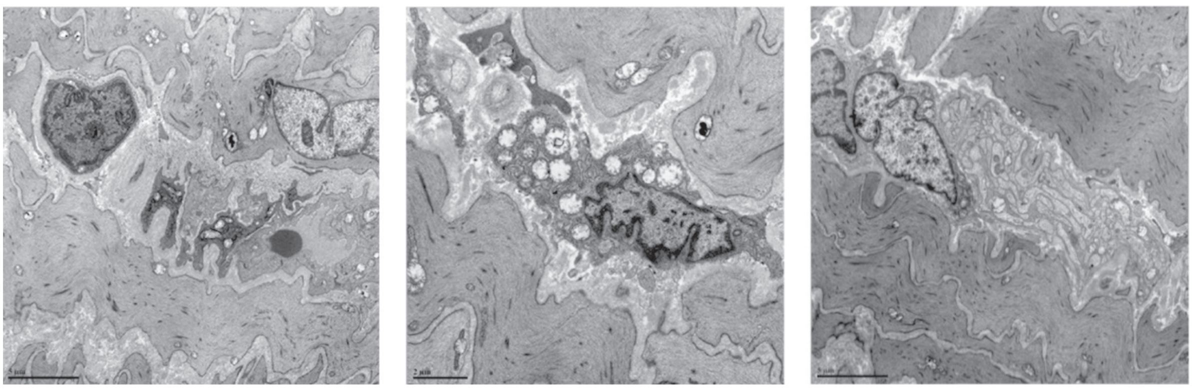
The question arose whether these large mitochondria are the result of fusion as a legitimate process of dynamic shaping according to the implementation program of mitochondrial carcinogenesis.First of all, attention was drawn to the fact that in contrast to the “vertical” movement along tissues, in which the expedient form for the process of rapid mitochondrial movement was fission into small spheroids and mitovesicles, in the presence of folded transverse partitions of tissues, there appeared conditions facilitating “horizontal” displacement into a convenient niche and fusion of small forms of mitochondria into larger ones (Fig. 6, *b–d*). The mechanism of such fusion, as already noted, begins with the outer membranes and is then followed by that of the inner membranes, which form a polymorphic invagination with crista protrusions into the matrix. At the same time, matrix components diffuse to form a fused mitochondrion [9]. It is known that the processes of mitochondrial fission are regulated by Drp1 expression, while mitofusin expression regulates fusion [21, 22]. Apparently, such an abnormal fusion and concentration of metabolic and information factors involved mitochondria-dependent metabolic reprogramming to realize nuclear fusion (Fig. 7).

As can be seen from Figure 7, the connective tissue layers of the colon submucosa along the resection line contain only free nuclei and mitochondria, which are single or assembled in groups. It was not possible to determine the time of nuclear assembly, but, apparently, such electron diffraction images illustrate the role of mitochondria in the initiation of self-organization processes of nuclear structures due to the possibility of nuclear material transfer and fusion processes. Figure 8 demonstrates the process of further abnormal self-assembly of tumor cells with the participation of mitochondria surrounding the object they are assembling or being inside it.



a *b*

Fig. 7. Electron diffraction image of a rectal tissue fragment along the adenocarcinoma resection line: *a* – the formation of nuclei fragments in connective tissue layers surrounded by mitochondria, ×20,000; *b* – an elongated shape of the formed nucleus with nuclei in close contact with mitochondria, ×15,000



a *b* *c*

Fig. 8. Electron diffraction image of a fragment of colon tissue along the line of adenocarcinoma resection: *a* – filling of the dilated area of submucosa with nucleus and unformed fragments of cytoplasm, ×10,000; *b* – the formation of a cellular structure including nucleus and mitochondria, ×20,000; *c* – the formation of a system of tubes and cisterns as a prototype of the Golgi apparatus and endoplasmic network, ×10,000

DISCUSSION

Summarizing the data of the conducted study, it is possible to present the sequence of dynamic events from primary tumor cells to the appearance of a similar image at a remote distance along the resection line and to highlight the main stages of mitochondrial translocation. Our assumption includes several conditional stages, which are discussed below.

First, the ultrastructural study of colon adenocarcinoma cells allowed us to determine the presence of a significant accumulation of mitochondria, the pathological status of which could pose a threat to the tumor cell due to the accumulation of ROS. In fact, this was a signal not only to free up vital space and prevent metabolic threat to the cell, but also to start the most important process of tumorigenic energy and information transfer by mitochondria, which drive these processes. The analysis of electron diffraction images pointed to such a mechanism of mass transfer of mitochondria outside the cell as the formation of mitochondriomas in pinching off a section of cytoplasm containing a conglomeration of mitochondria. It was this extremely simplified mechanism of separation that allowed for further active movement of mitochondria and mitovesicles in a tumor-free direction.

The second stage, which we associate with mitochondrial translocation itself, is based on electron diffraction data indicating the active movement of mitochondria along the borders of the multilayer structure of the rectal submucosa. The high degree of mitochondrial plasticity contributes to the inclusion of the fission mechanism and the formation of small spherical forms. As noted in the literature, in colorectal cancer cells, enhanced mitochondrial fission is a common phenomenon that promotes or prevents tumor progression. Namely, enhanced mitochondrial fission promotes metabolic reprogramming of cells, leading to cell proliferation, invasion, metastasis, and chemoresistance [22].

Then, as mitochondrial microspheres advanced into the depth of the colon wall tissues, the structure of submucosa changed, forming transverse folds and curves, into the lumen of which spheroids and mitovisicles penetrated. The outer membrane is known to act as a permeable platform that facilitates the convergence of other cellular signals that can be decoded and transmitted to mitochondria [14]. Apparently, this served to turn on the mechanisms of mitochondrial fusion and the formation of large organelles capable of realizing nuclear fusion from transported mitochondrial and nuclear DNA.

Indeed, when analyzing electron diffraction images, we identified areas of the colon submucosa along the resection line, in the layers of which we detected only single nuclei and mitochondria in contact with them. The nuclei were both separate fragments without nuclei and whole nuclei in the form of an elongated structure with several nuclei. However, the characteristic circumstance was the obligatory contact or non-contact interaction of nuclei with mitochondria, which confirms the assumption about the establishment of signaling membrane connections between them, as well as between mitochondria and major organelles such as the endoplasmic reticulum.

This may be evidenced by the next stage, which can apparently be characterized as a self-assembly process based on the same unique signaling mechanisms of membrane system interactions and the formation of abnormal tubes and cavities, which may already represent the prototype tumor cell. It can be assumed that the presence of the nucleus and mitochondria, taking into account their signaling role in triggering the protein synthesis system, could facilitate the proliferative activity of the cell as the basis for recurrence or metastasis.

Undoubtedly, the visually observed pattern of mitochondrial movement can be interpreted as a possibility of new foci of rectal adenocarcinoma growth. However, this problem needs further investigation not only by means of electronic visualization, but also in the application of quantitative immunohistochemical, radioisotopic, and other methods of examination. We believe that the findings of this study may lead to consideration of the enormous and dangerous potential of motor and regulatory activities of mitochondria in malignant neoplasm progression.

CONCLUSION

The ultrastructural study recorded the process of mitochondrial conglomeration movement from rectal adenocarcinoma cells into the intercellular space in the form of mitochondriomas (passive transfer). Further independent dynamics of mitochondria promotion in the layers of the rectum submucosa at the level of the resection line (active transfer) was accompanied by the transformation of mitochondria sizes (fission and fusion) and the inclusion of trigger mechanisms of self-organization processes. It is assumed that the mobile nature of mitochondria and regulatory signaling systems of membranes contribute to the reproduction of the processes of nuclear fusion and self-assembly of the prototype tumor cell as possible mechanisms of early recurrence and metastasis of rectal cancer.

REFERENCES

1. Kit O.I., Gevorkyan Yu.A., Soldatkina N.V., Gusareva M.A., Kharagezov D.A., Milakin A.G. et al. The Complete Clinical Response of Colorectal Cancer to Chemoradiation: Tactics. *Problems in Oncology.* 2017;63(6):838–842. (In Russ.). DOI: 10.37469/0507-3758-2017-63-6-838-842.
2. Luo M., Yang X., Chen N.N., Nizza E.C., Huang K. Drug resistance in colorectal cancer: an epigenetic review. *Biochim. et Biophys. Acta (BBA) – Cancer Reviews.* 2021;1876(2). DOI: 10.1016/ j.bbcan.2021.188623.
3. Hossain M.S., Karunyawati H., Jairoon A.A., Urbi Z., Ooi D.J., John A. et al. Colorectal cancer: a review of carcinogenesis, global epidemiology, current challenges, risk factors, prevention and treatment strategies. *Cancer Diseases.* 2022;14(7). DOI: 10.3390/cancers14071732.
4. Kit O.I., Gevorkyan Yu.A., Soldatkina N.V., Kolesnikov V.E., Bondarenko O.K., Dashkov A.V. Modern Strategy of Metastatic Colorectal Cancer Treatment (Literature Review). *South Russian Journal of Cancer*. 2024;5(3):102–110. (In Russ.). DOI: 10.37748/2686-9039-2024-5-3-9.
5. Biller L.H., Schrag D. Diagnosis and treatment of metastatic colorectal cancer: a review. *JAMA.* 2021;325(7):669–685. DOI: 10.1001/jama.2021.0106.
6. Bonnay F., Veloso A., Steinmann V., Köcher T., Abdusselamoglu M.D., Bajaj S. et al. Oxidative metabolism drives immortalization of neural stem cells during tumorigenesis. *Cell.* 2020;182(6):1490–1507.e19. DOI: 10.1016/j.cell.2020.07.039.
7. Sessions D.T., Kashatus D.F. Mitochondrial dynamics in cancer stem cells. *Cell Life Science*. 2021;78(8):3803–3816. DOI: 10.1007/s00018-021-03773-2.
8. Frantsiyants E.M., Neskubina I.V., Sheiko E.A. Mitochondria of Transformed Cell as a Target of Antitumor Influence. *Research and Practical Medicine Journal*. 2020;7(2):92–108. (In Russ.). DOI: 10.17709/2409-2231-2020-7-2-9.
9. Chen W., Zhao H., Li Y. Mitochondrial dynamics in health and disease: mechanisms and potential targets. *Signal Transl. Purpose Tam.* 2023;8(1):333. DOI: 10.1038/s41392-023-01547.
10. Chan D.K. Mitochondrial dynamics and its involvement in disease. *Annu. Rev. Pathol.* 2020;15:235–259. DOI: 10.1146/annurev-pathmechdis-012419-032711.
11. Zhou Z., Fan W., Zong R., Tang Q. Mitochondrial unfolded protein reaction: a multitasking giant in the fight against human diseases. *Aging Editorial.* 2022;81:101702. DOI: 10.1016/j.arr.2022.101702.
12. Singh B., Modica-Napolitano J.S., Singh K.K. Defining the momiome: Promiscuous information transfer by mobile mitochondria and the mitochondrial genome. *Semin. Cancer Biol.* 2017;47:1–17. DOI: 10.1016/j.semcancer.2017.05.004.
13. Davis C.H., Kim K.Y., Bushong E.A., Mills E.A., Boassa D., Shih T. et al. Transcellular degradation of axonal mitochondria. *Proc. Natl. Acad. Sci. USA.* 2014;111(26):9633–9638. DOI: 10.1073/pnas.1404651111.
14. Giacomello M., Pyakurel A., Glitsu S., Scorrano L. Cell biology of mitochondrial membrane dynamics. *Nat. Rev. Mol. Cell Biol.* 2020;21(4):204–224. DOI: 10.1038/s41580-020-0210-7.
15. Kłos P., Dabravolski S.A. The role of mitochondria dysfunction in inflammatory bowel diseases and colorectal cancer. *Int. J. Mol. Sci.* 2021;22(21):11673. DOI: 10.3390/ijms222111673.
16. Wang S., Xiao W., Shan S., Jiang S., Chen M., Zhang W. et al. Multistep dynamics of mitochondrial fission and fusion in living cells. *PLoS One.* 2012;7(5):e19879. DOI: 10.1371/journal.pone.0019879.
17. Cunniff B., McKenzie A.J., Heintz N.H., Howe A.K. AMPK activity regulates trafficking of mitochondria to the leading edge during cell migration and matrix invasion. *Mol. Biol. Cell.* 2016;27:2662–2674. DOI: 10.1091/mbc.e16-05-0286.
18. Schuler M.-H., Lewandowska A., Di Caprio G., Skillern W., Upadhyayula S., Kirchhausen T. et al. Miro1-mediated mitochondrial positioning shapes intracellular energy gradients required for cell migration. *Mol. Biol. Cell.* 2017;28:2159–2169. DOI: 10.1091/mbc.e16-10-0741.
19. Lyamzaev K.G., Nepryakhina O.K., Saprunova V.B., Bakeeva L.E., Pletjushkina O.Y., Chernyak B. et al. Novel mechanism of elimination of malfunctioning mitochondria (mitoptosis): Formation of mitoptotic bodies and extrusion of mitochondrial material from the cell. *Biochim. Biophys. Acta (BBA) Bioenerg.* 2008;1777:817–825. DOI: 10.1016/j.bbabio.2008.03.027.
20. Nakajima A., Kurihara H., Yagita H., Okumura K., Nakano H. mitochondrial extrusion through the cytoplasmic vacuoles during cell death. *J. Biol. Chem.* 2008;283:24128–24135. DOI: 10.1074/jbc.M802996200.
21. Parone P.A., Da Cruz S., Tondera D., Mattenberger Y., James D.I., Maechler P. et al. Preventing mitochondrial fission impairs mitochondrial function and leads to loss of mitochondrial DNA. *PLoS One.* 2008;3(9):e3257. DOI: 10.1371/journal.pone.0003257.
22. Wu Z., Xiao S., Long J., Huang W., Yu F., Li S. Mitochondrial dynamics and biology of colorectal cancer: mechanisms and potential targets. *Cell Commun. Signal.* 2024;22(1):91. DOI: 10.1186/s12964-024-01490-4.

Author Contribution

Kit O.I., Snezhko A.V. – final approval of the manuscript for publication. Shikhlyarova A.I., Ilchenko S.A. – justification of the manuscript and critical revision for important intellectual content. Frantsiyants E.M. – conception and design. Neskubina I.V. – critical revision for important intellectual content. Kirichenko E.Yu., Logvinov A.K. – data analysis and interpretation. Averkin M.A., Gabrichidze P.N. – critical revision for important intellectual content.

Author Information

Kit Oleg I. – Academician of the Russian Academy of Sciences, Dr. Sci. (Med.), Professor, General Director of the National Medical Research Centre for Oncology, Rostov-on-Dov, super.gormon@ya.ru, https://orcid.org/0000-0003-3061-6108

Shikhlyarova Alla I. – Dr. Sci. (Biology), Professor, Senior Researcher, Laboratory of Malignant Tumor Pathogenesis Study, National Medical Research Centre for Oncology, Rostov-on-Don, shikhliarova.a@mail.ru, https://orcid.org/0000-0003-2943-7655

Frantsiyants Elena M. – Dr. Sci. (Biology), Professor, Deputy General Director for Research, National Medical Research Centre for Oncology, Rostov-on-Don, super.gormon@yandex.ru, http://orcid.org/0000-0003-3618-6890

Ilchenko Sergey A. – Cand. Sci. (Med.), Oncologist, Abdominal Cancer Unit No. 1, Deputy General Director for Education, National Medical Research Centre for Oncology, Rostov-on-Don, ilchenkosergei@mail.ru, https://orcid.org/0000-0002-0796-3307

Neskubina Irina V. – Dr. Sci. (Biology), Senior Researcher, Laboratory of Malignant Tumor Pathogenesis Study, National Medical Research Centre for Oncology, Rostov-on-Don, neskubina.irina@mail.ru, https://orcid.org/0000-0002-7395-3086

Kirichenko Evgeniya Yu. – Dr. Sci. (Biology), Acting Head of the Department of Bioengineering, DSTU, Rostov-on-Don, kiriche. evgeniya@yandex.ru, http://orcid.org/0000-0003-4703-1616

Logvinov Aleksandr K. – Cand. Sci. (Biology), Researcher, Laboratory of Molecular Neurobiology, Southern Federal University, Rostov-on-Don, a.k.logvinov@yandex.ru, https://orcid.org/0000-0002-8873-3625

Snezhko Aleksandr V. – Dr. Sci. (Med.), Professor, Oncologist, Abdominal Cancer Unit No. 1, Deputy General Director for Education, National Medical Research Centre for Oncology, Rostov-on-Don, snezhko.sania@yandex.ru, https://orcid.org/0000-0003-3998-8004

Averkin Mikhail A. – Cand.Sci. (Med.), Oncologist, Abdominal Oncology Unit No. 1, Deputy General Director for Education, National Medical Research Centre for Oncology, Rostov-on-Don, mifodiy111@yandex.ru, https://orcid. org/0000-0003-4378-1508

Gabrichidze Petr N. – Cand. Sci. (Med.), Oncologist, Consultation and Diagnosis Unit, National Medical Research Centre for Oncology, Rostov-on-Don, q395273@yandex.ru, https://orcid. org/0009-0003-3918-1945

(✉) **Neskubina Irina V.,** neskubina.irina@mail.ru

Received on February 4, 2025;
approved after peer review on February 19, 2025;
accepted on February 27, 2025