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APPLICATION OF ELECTRON MICROSCOPY TECHNIQUES IN EXPERIMENTAL AND CLINICAL MEDICINE (a review)

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Abstract. This review has summarized the currently available literary information on the possibilities of applying the electron microscopy (EM) in experimental, clinical medicine and in related scientific fields. Concrete results that highlight the role of using EM in highly specialized clinical practice, where ultrastructural studies both complement routine light-optical methods and are their alternative has been presented. Examples of relevant data on virology, toxicology, nephrology, ophthalmology, neuropharmacology, forensic medicine, military and reproductive medicine have been provided. In a number of cases, the results achieved by EM were unique and capable of accurately describing the typical features of certain organs and cells. EM methods are indispensable for identifying, clarifying and recognizing various rare combined defects and pathologies, as well as for investigating the pathogenesis of viral infections and the mechanism of action of drugs.

Keywords: electron microscopy, virology, gynecology. andrology, nephrology, orthopedics, ophthalmology, cardiology, neurophysiology

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ПРИМЕНЕНИЕ МЕТОДОВ ЭЛЕКТРОННОЙ МИКРОСКОПИИ В ЭКСПЕРИМЕНТАЛЬНОЙ И КЛИНИЧЕСКОЙ МЕДИЦИНЕ (обзор)

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Аннотация. Настоящий обзор обобщает имеющиеся на сегодняшний день литературные данные о возможностях применения электронной микроскопии (ЭМ) в экспериментальной, клинической медицине и смежных научных областях. Представлены конкретные результаты, освещающие роль ЭМ в узкоспециализированной клинической практике, где ультраструктурные исследования как дополняют рутинные светооптические методы, так и являются их альтернативой. Приведены примеры соответствующих данных по вирусологии, токсикологии, нефрологии, офтальмологии, нейрофармакологии, судебно-медицинской экспертизе, военной и репродуктивной медицине. В ряде случаев результаты, достигнутые с помощью ЭМ, уникальны и способны точно описывать типичные особенности тех или иных органов и клеток. Методы ЭМ незаменимы для выявления, уточнения и распознавания различных редких комбинированных дефектов и патологий, а также для изучения патогенеза вирусных инфекций и механизма действия лекарственных препаратов.

Ключевые слова: электронная микроскопия, вирусология, гинекология, андрология, нефрология, ортопедия, офтальмология, кардиология, нейрофизиология

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Introduction

Today, it is difficult to imagine a comprehensive experimental study of any material without electron microscopy (EM), comprising a range of experimental techniques for analyzing the microstructure of various objects using electron microscopes, i.e., devices that use an electron beam to obtain images at different magnifications. These techniques allow to study the structure of bodies at micro/ nanoscales at magnifications over 100,000× as well as the local composition of these bodies. This method makes it possible to visualize structures that are far beyond the line of sight of an optical microscope and have dimensions up to several nanometers.

There are two main directions of electron microscopy: transmission (TEM) and scanning (SEM). They are used to obtain qualitatively diverse data about the same object, so both methods are often used together and complement each other.

Scanning and transmission electron microscopes are important, sometimes indispensable, equipment for modern scientific laboratories. They are actively used for biological and medical research, for example, into microorganisms, cells, viruses, implants, clinical, tissue engineering and pharmaceuticals, as well as for elemental analysis of various tissues and detection of foreign matter.

Electron microscopy methods can play an invaluable role in analysis and diagnosis of diseases in various fields of medicine: dentistry, ophthalmology, nephrology, surgery, endocrinology, hematology, pediatrics and neonatology, obstetrics and gynecology, cardiology, gastroenterology, traumatology and orthopedics.

This paper presents a review of the literature data obtained by electron microscopy, considering the results obtained in various fields of medicine.

EM in virology

Since the resolution of electron microscopes exceeds the resolution of optical devices by several orders of magnitude, EM provides extensive opportunities for studying various viruses, in particular after adhesion and invasion into the cells of a macroorganism. EM is capable of monitoring the transformations in the cell after collision between the genetic programs of the virus and its host (cell). Monitoring the ultrastructural changes in infected cells can help inform decision-making for antiviral treatment plans, which is especially important in case of epidemiological outbreaks of new viruses or genetically engineered viral agents [1, 2].

EM studies of autopsy material collected from patients dying of viral infections allows to assess the viral specificity to certain types of cells, for example, neurons, endotheliocytes of renal glomerular capillaries, alveolocytes, providing a range of options to select a strategy for pathogenetic therapy.

Virus particles are characterized by a specific structure and can be verified by electron microscopy. The size and shape of the virion have the property of specificity; localization of the viral particle in the cell, changes in its ultrastructures during absorption of the virion are also of undoubted interest. In particular, since the 1970s, EM has been actively used for visualization and study of the structure of the hepatitis B virus (HBV) and its relationship with the Australia Antigen (HBsAg) [3]. The obtained results helped to form a methodological framework, greatly expanding the scope of research into both HBV itself and the infections it causes. Hypotheses about asymptomatic HBV infection (i.e., transmitted by healthy carriers) and the spread of the virus through sexual contact were formulated and subsequently clinically confirmed. Thus, visualization of HBV by means of electron microscopy played a crucial role in detailed understanding of viral infection, giving a powerful impetus for future research in the field of not only HBV hepatitis, but also other types of viral hepatitis.

Another significant application for transmission electron microscopy is analyzing the effect of human papillomavirus (HPV) types 16 and 18 on the microstructure of the cervical epithelium as well as monitoring the results of contrasting thermo-laser therapy in treatment of this viral infection. Manykin et al. [4] convincingly proved that no HPV DNA was detected in either cervical biopsies or pap smears processed by polymerase chain reaction 1.5 and 6 months after treatment, while the structure of epithelial cells from the biopsy was normal after the end of treatment. Consequently, TEM studies confirmed the high efficacy of contrast thermolaser therapy for eliminating HPV types 16 and 18.

In addition to standard EM methods, electronic tomography is used to study various viruses, making it possible to obtain 3D images of the objects under study. 3D visualization of viral infections clearly shows how and to what extent viruses are capable of modifying the cellular architecture to build their own structures for morphogenesis, replication, exit and spread of the viral genome [5, 6].

EM methods have also been widely used to study the 2020 COVID-19 pandemic, in particular the SARS-CoV-2 virus causing the disease [7]. Both TEM and SEM methods were used to study the new coronavirus infection. The images obtained by the authors of this review using the TEM method at different magnifications are shown in Fig. 1.

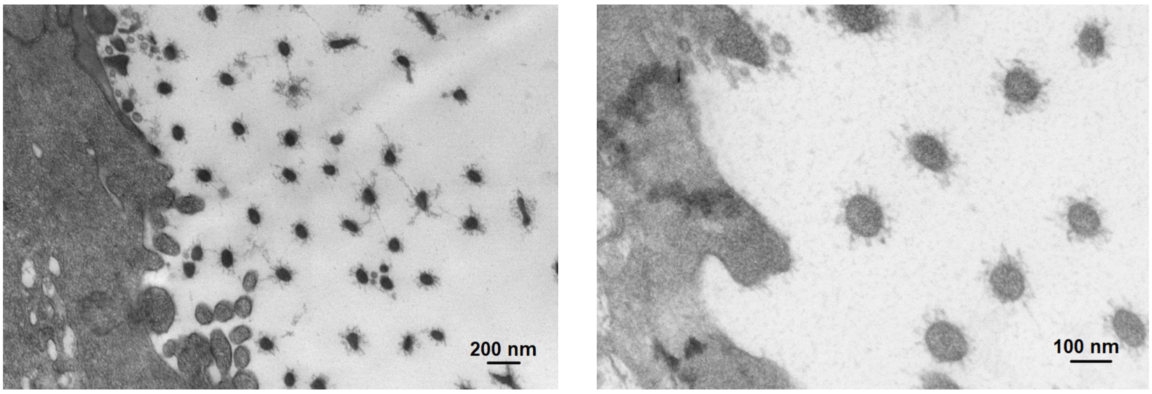

Fig. 1. TEM images (with different magnifications) of viral entry to the surface of oral mucosal epithelial cells in patients infected with SARS-CoV-2 virus

Results of clinical studies showed [8] that all patients had a significant number of circulating endothelial cells (CECs) damaged by the virus in their blood. In addition, numerous holes were found on the CEC membrane for the first time, which were comparable in diameter to the size of the SARS-CoV-2 envelope, suggesting penetration of the virus into endothelial cells, where it replicated and then passed into the bloodstream, while the dead endotheliocytes separated from the vessel wall, also migrating into the bloodstream and exposing the thrombogenic and pro-inflammatory subendothelial surface, which lead to inflammation in the perivascular tissue and induced thrombosis.

EM in obstetrics and gynecology

TEM and SEM methods have also found application in obstetrics and gynecology. In particular, a detailed study [9] was conducted for the ultrastructural elements included in the placental villi in different stages of preeclampsia (a blood pressure condition developing during pregnancy). The results obtained by TEM confirm that the intensity of neoplastic processes in connective tissue of the villous stroma in the placenta increases with an increase in the severity of this disease, morphological changes in the placenta become more pronounced, which ultimately leads to destruction of villi and a deterioration in placental functions. All of this allowed to draw important conclusions for the best measures for restoring fetoplacental blood flow and successful fetal gestation.

The authors of [10] used TEM to visualize decidual cells (DCs) and intercellular contacts to identify predisposing and perpetuating factors and mechanisms of abruption of a normally implanted placenta during pregnancy. EM studies of DCs have convincingly proved the direct involvement of these cells in the pathogenesis of placental abruption. It was concluded that a decrease in the number of basal decidua is accompanied in the case of placental abruption by a transformation of their structure, with an increase in cells of the ‘original’ type, their separation in the epithelial layer due to disruption of intercellular contacts and subsequent replacement with fibrin and collagen fibers.

In addition to TEM, the SEM method is also successfully used to study the placental ultrastructure of the placenta during healthy pregnancy and during the onset of chorioamnionitis (infectious inflammation of fetal membranes) [11], allowing to use the estimates of the placental structure in these cases as reference for changes in the morphofunctional structures of the placenta in various kinds of pathologies. Furthermore, SEM was used in [12] to establish that rupture of fetal membranes in premature pregnancy is associated with a number of morphological changes, namely, damage to the brush border of the amnion, involved in creating an immunological barrier between the fetus and the mother (this border determines the optimal rheological conditions of uteroplacental blood flow).

Furthermore, combining SEM and energy-dispersive X-ray spectroscopy (EDX) made an invaluable contribution to the study of macronutrient composition of the uterus, umbilical cord and placenta tissues, as well as the structural characteristics of red blood cells in the mother-placenta-fetus system in pregnant women diagnosed with type 1 diabetes mellitus, gestational diabetes and various types of thyroid pathologies [13]. It was established that disruption of the macronutrient composition represents a dysfunction of structurally altered tissues in the fetoplacental unit. During the SEM study, it was found that with thyroid pathology and diabetes mellitus in pregnant women, uteroplacental ischemia is detected due to changes in the anatomical and functional state of red blood cells and macronutrient composition, and, as a result, destruction develops in the tissues of the mother-placenta-fetus system, which further enhances tissue and circulatory hypoxia.

EM in andrology

Studies on andrology and reproductive medicine stress the major importance of PEM and SEM methods, since male infertility (with the exception of assisted reproductive technologies) is a challenge yet to be overcome [14–17]. Studies found that using quantitative electron microscopy for analysis of spermatozoa allows to gain a detailed understanding of the morphological substrates of sperm motility and penetrating ability, as well as competition in early embryogenesis. The teratozoospermia diagnosis, characterizing a decrease in the proportion of normal spermatozoa to 4% or less, is made by semen analysis only detecting the abnormal shape of the spermatozoa but not the underlying morphological cause for the dysfunction, especially since normally shaped spermatozoa may be functionally deficient [14]. A special focus is on the fact that electron microscopy of the sperm acrosome is an excellent alternative to invasive techniques, since it allows evaluating the functions and structure of the systems providing motility and penetration ability in the sperm. Visualization of changes in the structure of sperm chromatin can help understand the causes of early fetal growth impairment. The method makes it possible to reliably determine the acrosomal integrity, the state of its enzyme complex and the post-acrosomal region participating in fusion of the sperm with the egg plasma membrane. A possible cause of idiopathic infertility is an increased sperm content in the ejaculate with an abnormal acrosomal region, even with a normal sperm count. Studies of ultrastructural abnormalities in semen allow to identify the causes of male infertility as well as determine treatment tactics.

Special attention was paid in [15] to the involvement of persistent (chronic, constantly present in the body) viral infections, in particular human papillomaviruses (HPV), in the development of male infertility. It was proved that HPV infection significantly reduces motility and disrupts the structure of spermatozoa regardless of the type of HPV and the localization of virions on spermatozoa. The authors stressed the crucial role of electron microscopy of electron microscopy of ejaculate in the diagnosis of HPV-associated infertility, as this method allows not only to detect the virus in the ejaculate, but also to localize it in the sperm and evaluate negative changes in the sperm caused by HPV.

Analyzing the data in [16], we came to the conclusion that TEM is undoubtedly one of the most valuable methods for studying the *in vitro* effects of various drugs (including those with potential spermicidal activity) on the structure of human spermatozoa. The unique results obtained by EM can accurately describe the typical features of sperm necrosis: destruction of chromatin, missing or reacted acrosome, outer dense fibers and fibrous membrane, damage to the plasma membrane, displaced or ruptured axoneme, swollen mitochondria.

In addition, TEM is an indispensable method for detecting various rare combined defects of spermatozoa with a presumably genetic basis, such as an abnormally elongated midpiece combined with the absence of fibrous membrane or outer dense fibers in the main part. EM methods also allow to detect new defects in spermatozoa, including abnormal elongation of the flagella that have a predisposition to disintegrate or coagulate. It is the analysis of TEM data that makes it possible to recognize a rare systemic defect affecting the general sperm population, called acrosomal hypoplasia, or small acrosome. EM-based diagnostics of sperm pathologies can identify the relationship between normal parameters of the semen analysis and prolonged idiopathic infertility. It is noted that only EM analysis is informative for patients with asthenozoospermia (especially with axonemal or mitochondrial pathologies), since routine examination methods show normal results [17].

EM in ophthalmology

Electron microscopy methods are also of major importance in ophthalmology [18–21]. For example, TEM was used in [18] to evaluate the effect of the crosslinking procedure (outpatient surgery) on the ultrastructure of the stroma in the normal cornea to treat keratectasia. Degeneration of normal collagen architecture, increase in interfibrillar spaces and appearance of fibril termination sites in the anterior stroma were observed after corneal collagen cross-linking. A comprehensive discussion of supravital staining of living cells using neodymium (an element from the lanthanide family) is provided in [19, 20]. This approach can significantly speed up and simplify the sample preparation procedures in clinical ophthalmology, in particular, dealing with corneal dystrophies in studies of the corneal and conjunctival microbiome in normal and infectious lesions as well as in studies of the microbiome of the accessory visual structures. Moreover, it was noted that using EM for rapid diagnostics takes significantly less time than microbiological analysis, and this can become critical in a situation of the onset of an infectious process [21].

In addition to detailed study of eye tissues and their transformations in various pathologies, TEM proved extremely useful in studies of lacrimal fluid and vitreous body in both healthy people and patients with various concomitant diseases. Grigorieva et al. [22–24] visualized and

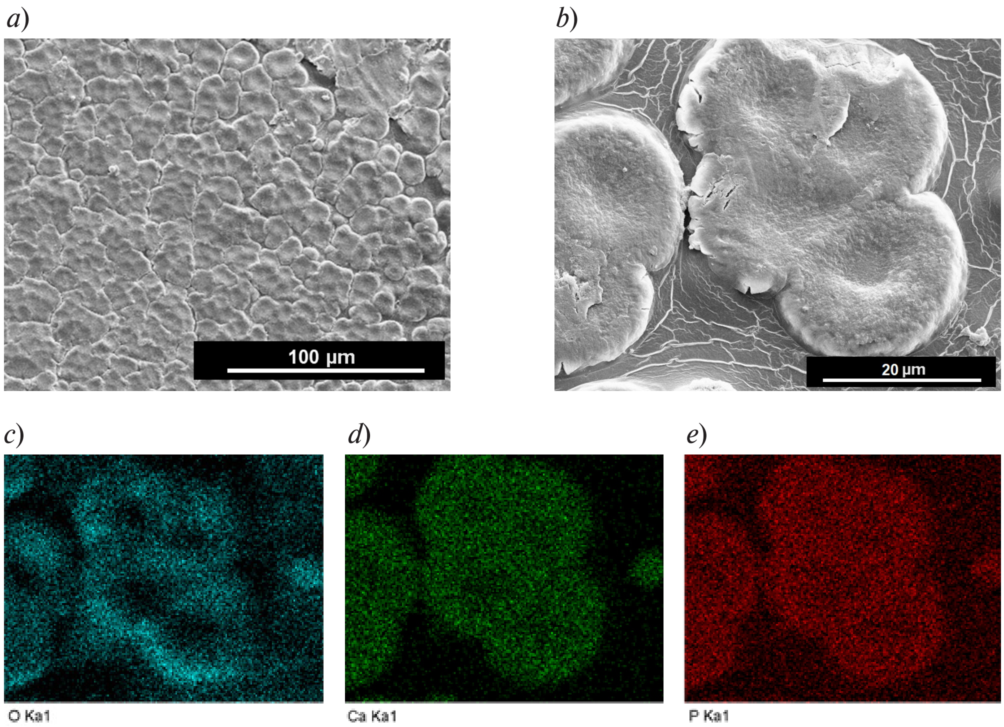

Fig. 2. SEM images of cloudy IOL surfaces obtained at two magnifications (*a*, *b*), and distributions of chemical elements comprising the spherulites inducing the clouding): oxygen (*c*), calcium (*d*) and phosphorus (*e*) atoms
Element distribution maps were obtained by EDX

identified the structural components of human lacrimal fluid. It was shown that the liquid fraction of lacrimal fluid contains microparticles, including exosomes, macromolecular aggregates and fibers, while various types of cells and vesicles as well as an extracellular matrix were found in the sediments of lacrimal fluid. The liquid fraction of the vitreous body contains macromolecular aggregates, collagen and predominantly non-membrane microparticles. Various collagen bundles and rare hyalocytes were found in its sediments. Moreover, an increase in the concentration of exosomes, a change in their morphology as well as a change in the content of other microparticles and macromolecular aggregates were detected in the lacrimal fluid of patients with diabetic retinopathy.

Combining EDX and SEM allowed to identify the cause of intraocular lens (IOL) opacification, i.e., deterioration in transparency, after implantation [25]. In particular, the SEM images obtained by the authors of this review for the surface of hydrophilic acrylic IOL with hydrophobic coating (Fig. 2, *a*, *b*) revealed round protruding structures up to 5 μm in diameter (so-called spherulites), presumably with a crystalline structure and covering the optical part of the lens. As a result of the massive accumulation of such spherulites, the surface of the IOL became rough. The spectra were recorded with an EDX detector allowing to identify the elemental composition of spherulitic deposits on IOL surface, apparently consisting of hydroxyappatite crystals. Fig. 2, *c*–*e* shows the maps for the distributions of chemical elements comprising these crystals: oxygen, calcium, and phosphorus atoms.

No extraneous deposits or changes in the elemental composition were detected in cloudy lenses made of hydrophobic acrylic material. The clouding of the crystalline lens was caused by the microcavities formed. Thus, electron microscopy made it possible to detect significantly different causes of IOL opacification due to different properties of the materials used for manufacturing them.

EM in nephrology

In clinical practice, electron microscopy is also in demand in nephrology. To select the appropriate therapeutic strategy to treat kidney diseases, it is necessary to detect the specific morphological changes in the structure of the glomerular filtration barrier (GFB) of the kidneys. The GFB thickness does not exceed (with the exception of some cases) 1 μm, therefore, it is studied by methods providing ultra-high magnification. Tracing the changes observed in the glomerular basement membrane and in the visceral epithelial cells of the renal corpuscles, the so-called podocytes, makes it possible to monitor renal pathologies and diagnose their type (acquired or hereditary). Detecting and localizing electron-dense inclusions or deposits, tubuloreticular inclusions in tubular or glomerular basement membranes of the kidneys allows to diagnose glomerulonephritis, for example, caused by infection as well as confirm autoimmune diseases such as lupus nephritis, hereditary diseases such as Alport syndrome or thin basement membrane disease [26, 27]. Images of some of these kidney pathologies were also obtained by the authors of this review and are shown in Fig. 3.

a) *b*) *c*)

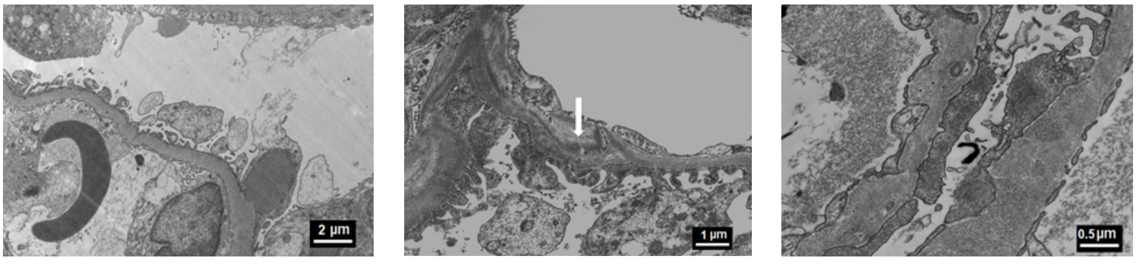

Fig. 3. Examples of nephrological pathologies detected by TEM:
degradation of glomerular basement membrane (GBM) of glomerular filtration barrier (*a*): electron-dense deposit detected in subepithelial position for rapidly progressive post-streptococcal glomerulonephritis; basket-weave structures (shown by arrow) in GBM (*b*), characteristic of Alport syndrome; changes in GBM in post-infectious glomerulonephritis (*c*)

EM in forensic medicine

In recent years, studies have increasingly concentrated on combining SEM and EDX for forensic medical examination [28, 29]. In particular, these methods make it possible to draw conclusions about the shooting distance and detect the transfer of the smallest particles of gunshot residue after their contact with each other, thus providing reliable evidence that the victim was wounded from a firearm shot through an obstacle and by ricochet.

EM in cardiology

One of the most important challenges of modern medicine is timely diagnosis, as well as choosing the right treatment and prevention plan for atherosclerosis, as the success of the fight against a wide range of cardiovascular diseases depends on it. The trigger for this vascular pathology is the imbalance of chemical elements in the body. Apparently, combining SEM with EDX can significantly expand the horizons of research in this field of medicine. It was found that the instability of atherosclerotic plaque (ASP) is mainly due to its chemical and phase compositions, which in turn determines the future strength of the ASP. Evidently, it is not the size or volume, but primarily the ASP composition that determines its instability [30]. Even before vascular stenosis develops, unstable ASP can undergo rupture, erosion, consequently to occlusion, acute thrombosis, and heart attacks. Therefore, improving techniques for elimination of ASP from the blood vessels of patients is inextricably linked with obtaining information about the composition and localization of plaques. SEM and EDX were used in [31-33] to detect the structure, localization, and elemental composition of ASP of coronary arteries to establish the relationship between the calcification process and the key stages of atherosclerosis. Additionally, EDX detected increased contents of silicon, magnesium and potassium on the surface of the ASP compared with its core, which is possible in the case of infiltration of the plaque by these elements from the bloodstream. Furthermore, an increased content of not only calcium but also phosphorus was found in the regions with calcification of asbestos, due to the presence of the largest fractions of calcium and phosphorus in the form of hydroxyapatite. The formation of agglomerates of nano- and micro-sized hydroxyapatite particles serves as a starting point for the development of extensive calcifications in asbestos. The specifics of the size distributions of particles containing calcium indicates a difference in the mechanisms of their genesis within the ASP and in the regions of contact with blood.

EM in orthopedics and traumatology

Aside from the above-described applications of electron microscopic devices and additional detectors for medical research, they have undoubtedly proved to be important and useful in the field of orthopedics and traumatology. In particular, data from structural studies of hip joint and synovial membrane tissues in patients with femoral head avascular necrosis were used in [34] to reveal signs of impaired cellular matrix architecture, changes in synoviocytes (type *A* and *B*) and chondrocytes in femoral head necrosis, as well as synovial lesion sites. SEM and EDX served as the basis for verifying osseointegration in [35], since these methods make it possible to visualize and evaluate the process of bone tissue ingrowth into the surface pores of implants and the formation of mature trabecular bone tissue. The same methods are undoubtedly useful in studying the processes of bone tissue regeneration during the fixation of bone fragments with the Ilizarov apparatus [36]. It was established that healing of fractures is directly carried out by the so-called immature bone tissue of woven and lamellar structure, following the mechanism of primary healing of bone wounds (without the formation of connective and cartilaginous tissues in the bone junction), while bone fusion directly by lamellar bone tissue was not observed in any experiments. Changes in the articular cartilage of the hip bone during tibial lengthening were studied in [37]. It was concluded that the ultrastructural transformations of this cartilage during shin lengthening consist in the destruction of the surface zone of the cartilage, and the severity of such transformations is directly related to the duration of the apparatus application procedure. Diagnosis, examinations and analysis of experimental data confirmed that dynamic loads are a necessary condition for maintaining the structural organization of articular cartilage.

In addition to detecting structural changes in bones and cartilage, it is also important to study the possibilities of using various drugs for the prevention and treatment of pathologies during the regeneration process after injuries and surgery.

For example, combined analysis of the structure and physico-chemical properties of bone tissue under the joint action of natural zeolites and sodium fluoride was carried out in [38]. SEM was used to confirm that natural zeolites consumed by patients as nutritional supplements, combined with fluoride, have an extreme effect on bone tissue through hypermineralization of membranes in osteocyte canaliculi, with a secondary deterioration in the trophic conditions of the bone matrix and a decrease in bone strength characteristics. These circumstances cast doubt on the prospects of using fluoride and zeolite-containing drugs in the treatment of osteoporosis. Another study [39] showed that vancomycin in combination with poviargol (highly dispersed silver) can prolong the antimicrobial activity of bone cement samples, which effectively prevents the formation of microbial biofilms on the surface.

EM in neurology

EM is of particular importance in the field of neuropharmacology and neurophysiology, where the influence of the studied psychotropic and neurotropic pharmacological substances or neuropeptides can often be traced only by monitoring the ultrastructural transformations in nerve cells. EM allows to assess the ultrastructures for the number of dendritic spines, vesicles with neurotransmitters, serving as indicators of the synaptogenesis [40, 41].

Analysis of telocyte structure

Undoubtedly, EM methods (including 3D microscopy) have played a major role in the identification and detailed study of telocytes, that is, Cajal-like interstitial cells [42–44]. Because the long and very thin prolongation of the telocytes are virtually indistinguisgable in an optical microscope, TEM and SEM remain the few methods that can be effectively used to identify this type of cell. Numerous studies (including 3D microscopy) detected the presence of telocytes in various human organs: in the myocardium, connective tissue of the gallbladder wall and other derivatives of the gut tube, stroma of exocrine glands, placenta, fallopian tubes, some vessels, striated skeletal muscle tissue, etc. [42–48]. In particular, it was found that in chronic salpingitis, there is an increase in destructive changes and a further decrease in the number of telocytes, which leads to changes in the 3D architecture of the extracellular matrix in the stromal compartment of the fallopian tube, disruption of intercellular signaling, as well as contractility of the fallopian tube and, as a result, impaired organ motility [47]. A similar decrease in the number of telocytes was observed during inflammation and fibrosis in atrial fibrillation [45], as well as in prolonged (chronic) inflammation of striated skeletal muscle tissue [46]. Analysis of modern data on the ultramicroscopic structure of telocytes, their localization, functions and significance in pathological processes is given in [48].

Novel electron microscopy techniques

Describing the possibilities and undoubted benefits of EM for medical and biomedical research, we should naturally pay close attention to new microscopic methods that have been actively developing in recent decades, namely correlation microscopy, 3D electron microscopy, etc.

Correlation microscopy is the combination of studies in one cycle of samples using, for example, an optical microscope and electron microscopes of various types. This technology opens up additional opportunities for studying various biological objects. Correlation microscopy can combine several microscopes in one device at once, including confocal, fluorescent, electron, helium-ion, etc. [49]. A large overview of the existing applications of correlation microscopy is given in book [50].

Macropinocytosis was analyzed in [51] using ultrastructural approaches of correlation microscopy during infectious processes upon penetration of shigella. The combined imaging techniques presented in are also important for many other bacterial species, including salmonella, brucella, or mycobacteria. In addition, the authors paid special attention to the use of genetically encoded markers and specific liquid indicators for macropinosomes, which allowed to characterize very complex scenarios occurring in shigella invasion sites. These events may be crucial for the further progression of the infection, which means that their study is extremely important for a complete understanding of the basic mechanisms of bacterial infection.

The method of three-dimensional (3D) electron microscopy demonstrates important advantages in obtaining new information. In particular, in the course of studying dynamic processes in cells, it was possible to combine the capabilities of *in vivo* fluorescence video microscopy and electron microscopy [52]. The paper describes an approach allowing to monitor the individual intracellular structure *in vivo* (using markers tagged with green fluorescent protein), and then perform its ultrastructural analysis using EM and 3D reconstruction methods. Tagging of certain markers (for example, antibodies) with various fluorescent proteins makes it possible to detect and control their localization in organs and cells. As a result, images of the cell's fine structure at any selected point in its life cycle could be obtained. This approach has great potential for biomedical research.

Conclusion

Analyzing the most cited sources, we can conclude that electron microscopy methods provide an opportunity to obtain unique data and can play an important role in fundamental and applied research conducted in the field of experimental and clinical medicine. Such studies can be a key factor in the implementation of the National Project Demography and the Strategic Academic Leadership Program Priority 2030.

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