MODERN ACHIEVEMENTS OF THE SCIENCE OF HISTOLOGY

Sobirova Dildora Ravshanovna
Tashkent Medical Aacademy - associate professor of histology and
Medical biology department

Abdyvosiyeva Mushtariy Ismoil's daughter
Tashkent Medical Aacademy student,

Saparaliyev Umidjon son of Hasan
Tashkent Medical Aacademy student,

Egamberdiyeva Laylo Yodgor’s daughter
Tashkent Medical Aacademy student,

Mamarajabova Pokizahon Gayrat’s daughter
Tashkent Medical Aacademy student

Omonov Kamoliddin komil ugli
Tashkent Medical Aacademy student

Abstract

Histology refers to the study of the morphology of cells within their natural tissue environment. As a bio-medical discipline, it dates back to the development of first microscopes which allowed to override the physical visual limitation of the human eye. Since the first observations, it was understood that cell shape predicts function and, therefore, shape alterations can identify and explain dysfunction and diseases. The advancements in morphological investigation techniques have allowed to extend our understanding of the shape–function relationships close to the molecular level of organization of tissues, as well as to derive reliable data not only from fixed, and hence static, biological samples but also living cells and tissues and even for extended time periods. These modern approaches, which encompass quantitative microscopy, precision microscopy, and dynamic microscopy, represent the new frontier of morphology. This article summarizes how the microscopy techniques have evolved to properly face the challenges of biomedical sciences, thus transforming histology from a merely qualitative discipline, which played an ancillary role to traditional “major” sciences such as anatomy, to a modern experimental science capable of driving knowledge progress in biology and medicine.

Keywords: digital imaging, dynamic microscopy, precision microscopy, quantitative microscopy

Introduction

Histology refers to the study of the morphology of the cells in multicellular organisms within their natural environment, the tissues, which constitute organs and apparatuses of the body. Histology as a scientific discipline dates back to the development of first microscopes, which allowed to override the physical visual limitation of the human eye, the so-called resolution limit, and observe the cellular architecture of the tissues for the first time. This was a major step of biological sciences, comparable to the almost contemporary Copernican revolution in planetary astronomy: Indeed, it marks the starting point of a plethora of studies on the morphology of cells and tissues, which in turn led to understand that shape predicts function and, therefore, shape alterations can identify and explain dysfunction and diseases, opening the path to Histopathology. The advancements in morphological investigation techniques have allowed to extend our understanding of the shape–function relationships close to the molecular level of organization of organisms, as well as to generate reliable data not only from fixed, and hence static, biological samples but also from living cells and tissues, and even for extended time periods. Nowadays, these techniques, also called precision microscopy and dynamic microscopy, represent the new frontier of morphology.

This article aims at discussing how morphological techniques have evolved under the stimulus of emerging experimental needs, thus transforming Histology from a merely qualitative discipline playing an ancillary role to traditional “noble” or “major” sciences, such as Anatomy, to a modern experimental science capable of driving the scientific progress in Biology and Medicine. This fascinating transformation has made the evolved histological methods and knowledge indispensable not only to answer classical biomedical questions but also to develop new therapeutic strategies such as stem cell-based regenerative approaches and patient-specific therapy.

As stated before, most cells are colorless and nearly translucent under natural conditions, thus requiring to be stained for microscopic observation. The enormous development of dyestuff chemistry for the textile industry that occurred between 1600 and 1800 led to the invention of synthetic dyes: on one hand, this favored the artistic revolution of the Impressionists, who were able to paint in open air, directly inspired by the scenes that they observed; on the other hand, it offered to scientists powerful tools to stain histological samples, and to develop and validate new tissue staining methods. In this field, it is worth mentioning the contribution of the renowned Italian scientist Marcello Malpighi.

The milestone of the histological discoveries of the 19th Century can be considered the formulation of the cellular doctrine by Theodor Schwann in 1839, who first hypothesizes that animals and plants are made up of tissues formed by a distinctive spatial distribution of myriads of single cells (Schwann, 1839). Due to the importance and originality of his contributions, the name of this new discipline devoted to the study of tissues was changed from “tissue Anatomy” to “Histology”: this term had been coined in the early 19th century by

Marie Francoise Xavier Bichat and reprised by Karl Mayer in 1819 (Figure 1). The official recognition of Histology as a medical discipline dates back to 1906, when Camillo Golgi and Santiago Ramon y Cajal were coawarded the Nobel Prize for Medicine owing to their fundamental histological studies on nerve cells.

The 20th Century has been hallmarked by the atomic theory and quantum Physics. From the histological perspective, the discovery that both photons and electrons behave as electromagnetic waves led in early 1930s to the development of the transmission electron microscope (TEM) by Ernst Ruska, in collaboration with Bodo von Borries and Max Knoll; Ruska was awarded the Nobel Prize for Physics in 1986 for his fundamental work in electron optics and for the design of the first TEM. Exploiting an electron beam with very short wavelength instead of photons, this microscope can attain a 100- to 1,000-fold higher magnification and resolving power than optical microscopes operating in the visible spectrum, thus allowing to observe the morphology of subcellular structures, viruses and even large molecular complexes. Electron microscopy also led to improve the existing methods of tissue processing for the specific purposes and characteristics of ultrastructural observation (aldehyde-OsO4 fixation, resin embedding, ultramicrotomy, and electron-dense counterstaining). Few years after the development of TEM, the principle of electron beam imaging was applied to the scanning electron microscope (SEM), in which images result from interactions of the electron beam with the sample surface. The secondary, reflected, or backscattered electrons are collected and their signal used to generate an image of the irradiated surface. However, the use of SEM for biomedical investigations is currently limited. The second half of the 20th century saw the discovery of laser (Light Amplification by Stimulated Emission of Radiation), an invention of uncertain authorship which gave rise to a patent controversy lasted over 30 years, and the application of binary mathematics, theoretically introduced by the studies of Gottfried Wilhelm von Leibniz (1646–1716) and George Boole (1815–1864), to modern informatics and computer technology. These achievements have been the technological key points to develop confocal laser scanning microscope: this instrument exploits a monochromatic laser beam for 3-D detection of specific fluorescence markers of cells and tissues. In early 2000s, significant advancements were made in super-resolution microscopy (in the nanometer range) that exploits a non-linear optical approach to reduce the amplitude of the spot of incident light on the sample and therefore the background noise given by the illumination of the contours of the observed detail (point spread function). Among methods inspired by this approach, the most important are indicated by the acronyms STED (STimulated Emission Depletion) and SSIM (Saturated Structured Illumination Microscopy). Other high-resolution techniques are based on the transitions between the two molecular states (i.e., on/off) of photons with fluorophores, and exploit both spatial and temporal phenomena that allow the precise location of single fluorescent molecules. Such techniques include STORM (STochastic Optical Reconstruction Microscopy and PALM (photo-activated localization microscopy). In the present days, the enormous increase in power of modern computers allows to interface different detection devices in order to analyze the same sample simultaneously, and information obtained can be integrated, nearly in real-time, at micrometric to nanometric resolutions. The simultaneous analysis of this multi-level information discloses new relationships between morphology and function undetectable with conventional methods, giving rise to a new branch of histology called correlative microscopy.

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Conclusion

At the beginning of the 19th century, the average human life expectancy was only 30–45 years. This high mortality was also due to the fact that, until the mid-XX century, the drug repertoire available to physicians was very limited and yet substantially similar to that of the Ancient World. The dramatic increase in life expectancy of mankind that occurred after the Second World War is mainly attributable to the impact on everyday life of a relatively low number of key inventions, innovative processes and discoveries. These include the fridge, which decreased food toxicity; the industrial production of aspirin, which reduced the lethal consequences of inflammation; and the discovery of penicillin, intended as the progenitor of antibiotics, which allowed to eradicate deadly bacterial infections. Since then, the exponential development of pharmaceutical chemistry has led to the synthesis of active molecules specifically directed against a large number of diseases, and thus it appears to represent the main culprit for the incremental increase in life expectancy of the current time. On the other hand, the plethora of molecules, which can be introduced in the human body to modify its pathophysiological processes for curative purposes, has also raised the major health issue posed by unwanted side effects. Therefore, a major challenge for the incoming years will be to set-up new effective therapies that minimize the drug adverse effects, with the goal to improve the patients' quality of life. In this view, the research for diagnostic and therapeutic innovations is shifting from the molecules to the target cells. Thanks to the scientific and technological advancements summarized in this article, Histology can be rightfully considered a “major” science and is ready to play its prominent role in the future challenges of modern medicine.

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