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Review article

PAUL LANGERHANS: A PILGRIM "TRAVELING" FROM FUNCTIONAL HISTOLOGY TO MARINE BIOLOGY

PAUL LANGERHANS: HODOČASNIK KOJI JE "PUTOVAO" OD FUNKCIONALNE HISTOLOGIJE DO BIOLOGIJE MORA

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Summary

The nineteenth century was the time of a real revolution in science and medicine. A lot of seminal discoveries in medicine and biology were done in this time, and many of them were coincident with the introduction of the compound microscope by Hermann van Deijl and the standard histological technique by Paul Ehrlich. The main tissue types and individual cells were characterized and originally classified more than hundred years ago, although less attention was paid to their basic functions. This was mainly due to the modality of tissue specimen processing that allowed particularly detailed descriptive studies. Even so, we can notice some attempts to correlate the structure with the function. The German scientist Paul Langerhans, well-known for the discovery of Langerhans islets of the pancreas and Langerhans cells from the epidermis, tried to change the conventional fate of morphological studies introducing in his works functional hypothesis based on traditional microscopic observations even from the beginning of his scientific career. Paul Langerhans was a complex personality of the second half of the nineteenth century, not only in medicine, but also in other fields of biology. In the present review, presented is the life and research activity of Paul

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Key words: *Paul Langerhans, Langerhans cell, Langerhans islets, marine fauna*

Introduction

The nineteenth century was the time of a real revolution in science and medicine. A lot of seminal discoveries in medicine and biology were done in this time, and many of them were coincident with the introduction of the compound microscope by Hermann van Deijl and the standard histological technique by Paul Ehrlich. The main tissue types and individual cells were characterized and originally classified more than hundred years ago, although less attention was paid to their basic functions. This was mainly due to the modality of tissue specimen processing that allowed particularly detailed descriptive studies. Even so, we can notice some attempts to correlate the structure with the function. The German scientist Paul Langerhans, well-known for the discovery of Langerhans islets of the pancreas and Langerhans cells from the epidermis, tried to change the conventional fate of morphological studies introducing in his works functional hypothesis based on traditional microscopic observations even from the beginning of his scientific career.

Figure 1: Paul Langerhans (1847 – 1888).

Paul Langerhans (Figure 1) was a complex personality of the second half of the nineteenth century, not only in medicine, but also in other fields of biology. In the present review, the life and research activity of Paul Langerhans is presented, not only because of the importance of his discoveries, but also for perspectives that were opened by these findings in unexpected fields of medicine and biology.

Biography

Paul Wilhelm Heinrich Langerhans was born on July 25, 1847 in Berlin. His father was a well-known physician, local politician, and a president of the

Berlin City Council. His mother was Anne Caroline Langerhans, a cousin of the embryologist Franz Keibel. She died of tuberculosis when Langerhans was six years old. One of his stepbrothers, Robert, was an assistant in the laboratory of Rudolf Virchow, and later became professor of pathology. He was the author of a popular textbook of pathology [1]. Paul Langerhans entered the "School of the Grey Monastery", a famous German high school of the time, graduated the Gymnasium when he was 16, and because of his excellent performances as student, he was exempted from the final oral examinations [2].

He studied medicine at the University of Jena for three semesters (1865-1866), then continued in Berlin, and graduated in 1869, with the thesis entitled "Contributions to the microscopic anatomy of the pancreas" [3]. During his studies in medicine, he was strongly influenced by Julius Cohnhem and Rudolf Virchow, and over the years he became a close friend of the last one. After graduation he travelled to Syria, Jordan and Palestine with the geographer Richard Kiepert to study leprosy, and made some interesting anthropological observations. Coming back from the Middle East, he served as physician in an ambulance unit during the Franco-Prussian War [4].

His scientific career was strongly influenced by the famous pathologists of the time: Rudolf Virchow, Ernst Heckel, and Julius Cohnheim. In 1871, Paul Langerhans worked as a prosector in pathology in Freiburg, where he became Privatdozent, and later, an associate professor and full professor (1874). Unfortunately, the career of Paul Langerhans was abruptly interrupted in 1874 because of lung tuberculosis. Repetitive treatments performed in Switzerland and Italy were not effective to cure his disease. He was forced to resign all University duties. This is why he settled in Madeira in 1875, because of its mild climate that improved his health. In Funchal, the capital of Madeira, Paul Langerhans treated a lot of patients with tuberculosis, and this experience is supported by his publications in Archives of Pathological Anatomy [5, 6]. In addition, Paul Lanhergans wrote a book for travelers to the island of Madeira [7], and made some studies in meteorology.

In 1885 he married Margarethe Ebert, which was the widow of one of his patients, and the wedding took place in Berlin. They had a daughter. The Quinta Lambert Villa was their residence in Funchal, and the building is the governor's residence today [8].

Langerhans stopped his medical activities in the autumn of 1887 due to a progressive renal failure. He developed leg edemas, headaches and transient

memory loss. Paul Langerhans died of uremia in Funchal on July 20, 1888, and was buried in the cemetery of an English church. A small cell (read bacteria) caused his death. Other small cells – discovered by Paul Langerhans, made him immortal.

Scientific contributions

Julius Friedrich Cohnheim showed him in 1868 a staining method with gold chloride. Paul Langerhans, still a student at that time, applied this technique on the skin to investigate the innervation, and so, he was able to notice a dendritic non-pigmentary cell in the epidermis [9]. Comparing results obtained by Langerhans using the gold chloride technique with modern methods, we can notice very similar features (Figure 2). Based on their dendritic aspect, Langerhans believed they were nerve cells or intraepidermal receptors for extracutaneous signals [10]. In a paper published in 1882, he wrote that these cells have no apparent connection with nerve endings. Langerhans cell remained an enigma for more than hundred years in terms of its functions and significance in pathology. It was only in 1973 when Inga Silberberg found that Langerhans cell derives from bone marrow-borne monocytes, and is the most peripheral component of the immune system, which plays a role in delayed hypersensitivity [11]. Today, the Langerhans cell of the epidermis is known as antigen-presenting cell, involved in many immunological and pathological conditions of the skin and other organs (like acquired immunodeficiency syndrome, multiple sclerosis, and systemic lupus erythematosus). This particular cell of the skin contains some specific granules in the cytoplasm (Bierbeck's granules), rich in langerin, a protein encoded by CD207 gene. Recently, this cell has been used in the culture to obtain a vaccine against cancer, and there are ongoing clinical trials in breast, lung, prostate, or renal cell carcinoma. The neoplastic proliferation of these cells is

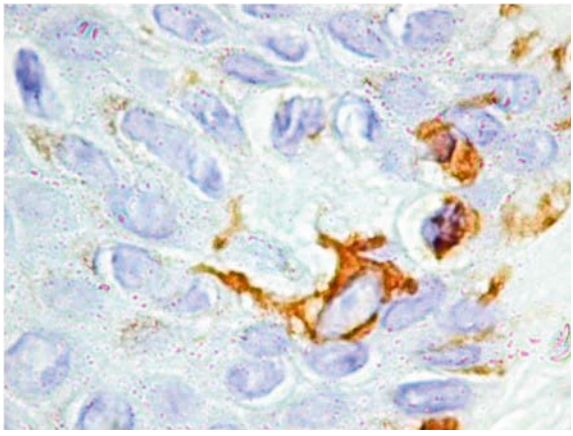

Figure 2: Langerhans cells identified with anti-S100 protein antibody.

also known as Langerhans cell histiocytosis. The term 'Langerhans cell' was first introduced in the literature by Merkel in 1875.

In the paper describing the dendritic cells, Langerhans reported for the first time the granular layer of the epidermis. Now this layer is known as *stratum granulosum*, but for many years it was referred to as layer of Langerhans. He continued his studies on the skin in Freiburg, and he published some interesting observations on tactile corpuscles [12].

Together with Hoffman, he studied in the laboratory of Virchow the storage of cinnabar using an intravital technique in different tissues and organs. They injected the substance intravenously into the rabbits and guinea pigs, and noticed its uptake by leukocytes but not by erythrocytes. In addition, they found deposits of cinnabar in some cells of the bone marrow, capillaries, and some cells of the liver parenchyma (most probably Kupffer cells) [10]. These data allowed Ludwig Aschoff to put the basis of its concept on the reticulo-endothelial system.

Perhaps the endocrine islands of the pancreas represent the best-known discovery of Paul Langerhans. Before Langerhans data about the histology of the pancreas was limited, most probably due to the lack of accurate methods. During studies on the human pancreas he wrote the first complete report on the normal microscopic structure of this organ, and discovered islet cells. In the end of his dissertation thesis, Langerhans mentioned that he had found nothing new and the examiners would look tolerantly to his efforts, but on the other hand, he described pale-stained areas throughout the pancreas, different from the surrounding tissue, supported by a rich vascular network and richly innervated. He measured very accurately these structures (between 0.1 and 0.24 mm in diameter) and described nine different types of cells devoid of granules [10]. Methods that show the presence of alpha and beta granules in these cells were developed many years later. He investigated the structure of the pancreas not only in humans, but also in many animal species and accurately noticed significant differences. He found a broad distribution of the islets in the pancreas by injecting the vessels and the pancreatic duct, and gained the impression of the importance of these structures [1]. Nowadays, we currently use the only accepted term for these components of the pancreas – islets of Langerhans. At that time, Langerhans had no idea how important his observation will be in the understanding of basic function of the human body and in pathology. He only supposed that these unusual structures might be lymph nodes. It was in 1893 when Edouard

Laguesse from Lille hypothesized that these cells might produce some internal secretions ("antidiabetic hormone") and called them for the first time "islets of Langerhans" [13]. The origin of diabetes was demonstrated by pancreatectomy by Von Mering and Minkowski in 1889, but it seems that they did not know about these structures [1]. Only 30 years after the death of Paul Langerhans it was shown that pale-stained islets within pancreas parenchyma are the source for many hormones essential for the metabolism and homeostasis, and because of the term "islets" the first discovered hormone was named "insulin" (Figure 3 a and b). In addition to the islets, in the same seminal study Langerhans described spindle-shaped centroacinar cells of the exocrine pancreas for the first time.

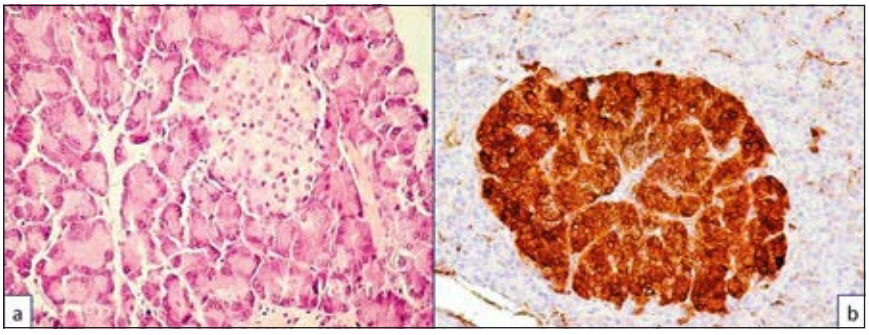

Figure 3: Islets of Langerhans shown with haematoxylin-eosin (a) and chromogranin A reaction (b).

The number of articles directly related to the islets of Langerhans dramatically increased in the second half of the twentieth century, reaching a peak of 1900 in 2004. One hundred forty years after the discovery of islets by Paul Langerhans, *Islets,* a new journal completely dedicated to this micro-organs, was born [14] (Islam, 2009).

He worked in Funchal, and studied tuberculosis and marine fauna of the Portuguese coast. His observations on the classification of invertebrates are extremely important nowadays. Paul Langerhans described hundreds of unknown marine worms and some of them still bear his name. Almost certainly, 57 from them were new species. He proposed the name Virchowia for new genera of worms that he discovered (in the honor of his friend, Rudolf Virchow). He described follicles in the gut of lower chordates that are known today as follicles of Langerhans [4]. These findings were published in a series of papers written between 1879 and 1884 [15, 16, 17, 18, 19]. Based on his own findings, Langerhans gave a lecture on this topic to the Royal Academy in

Berlin in 1887. For his studies on marine fauna he received a prize of 2000 gold marks from the Berlin Academy. Studies of Paul Langerhans on invertebrates are recorded in famous books [20, 21], and methods he used are briefly described by Ebling in the article "Homage to Paul Langerhans" [22]. Based on his important discoveries in marine biology, Czerniavsky established the species Langerhansia in his honor [8].

Instead of conclusion

Paul Langerhans and his contemporaries did not understand or appreciate the importance of these discoveries. His contributions to the biological sciences were related to both human and animal anatomy and he successfully explored the new area of staining technology. His discoveries opened at least three major areas of study: immunology, metabolic diseases, and tuberculosis. He made a partial recovery and besides medical practice, he began the study of marine worms. His findings in this field were thought to be his fourth major contribution to biological sciences. Most probably, Paul Langerhans did not even dream about that his name will be learned and known by all students in medicine and biology.

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Sažetak

Devetnaesto stoljeće bilo je vrijeme prave revolucije u znanosti i medicini. U tom je stoljeću došlo do mnogih otkrića u medicini i biologiji, a mnoga od njih su se podudarala s primjenom mikroskopa (Hermann van Deijl) i uvođenjem standardne histološke tehnike (Paul Ehrlich). Glavne vrste tkiva i pojedinačne stanice karakterizirane su i izvorno klasificirane prije više od stotinu godina, iako je manje pozornosti bilo posvećeno njihovim osnovnim funkcijama. To je uglavnom bilo zbog modaliteta obrade uzoraka tkiva koja je omogućavala posebno detaljne deskriptivne studije. Ipak, primjećuju se neki pokušaji povezivanja strukture s funkcijom. Njemački znanstvenik Paul Langerhans, poznat po otkriću Langerhansovih otočića gušterače i Langerhansovih stanica u epidermisu, pokušao je promijeniti konvencionalnu sudbinu morfoloških istraživanja uvodeći već od početka svoje znanstvene karijere u svoja istraživanja funkcionalnu hipotezu koja se temelji na tradicionalnim mikroskopskim promatranjima. Paul Langerhans bio je složena ličnost druge polovice XIX. stoljeća ne samo u medicini nego i u drugim područjima biologije. U ovom radu predstavljen je njegov život i njegova istraživačka djelatnost ne samo zbog važnosti njegovih otkrića već i zbog gledišta koja su ta otkrića potaknula u neočekivanim područjima medicine i biologije.

Ključne riječi: *Paul Langerhans; Langerhansove stanice; Langerhansovi otočići; morska fauna.*