

The young Ramón y Cajal as a cell-theory dissenter

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The intellectual development of scientists normally traverses several different phases as they mature in their professions. In many cases, strong support of certain ideas and theories gives way to more critical, productive views that set the stage for major theories and discoveries. This appears to have been the case of Santiago Ramón y Cajal (1852-1934). In his youth, he supported the protoplasmic theory of life, and as he matured he maintained a critical, yet open view of the cell theory, which postulated that life phenomena could not take place below the cellular level. In later years, however, an older and wiser Ramón y Cajal abandoned all traces of dissent and joined in fully supporting a refined version of cell theory, to which his own discoveries significantly contributed.

Ramón y Cajal's neuron doctrine and cell theory

Santiago Ramón y Cajal was a Spanish multi-faceted academic and researcher. His affinities with the Generation of 1898, the group of Spanish intellectuals whose work revitalized Spain beginning in the early 1900s after the country's defeat in the Spanish-American War (1898), provide a context for his insightful writings in politics and literature [4]. His major scientific contribution was the brilliant demonstration, in the late 1880s, that nervous tissue is composed of

millions of individual cells, i.e., neurons, a finding that played a crucial role in proving cell theory. Using the famous staining procedure developed by Camillo Golgi, Ramón y Cajal was able to describe the dendritic spines of nervous cells. This discovery convinced him of the metabolic independence of neurons and formed the basis of his neuron doctrine [7]. In 1906, Golgi and Ramón y Cajal were jointly awarded the Nobel Prize in Physiology or Medicine, but in spite of their common interests in nervous tissue, their interpretations on its structure diverged. Golgi openly neglected the neuron doctrine in favor of his own reticularian approach, i.e., that nerve cords were a continuous mass devoid of constructive units. Ramón y Cajal continued to gather experimental support for the neuron doctrine, which he modestly attributed to two of his predecessors, Wilhelm His and August Forel [7]. Eventually, neurons were recognized as the structural units of nerves, and the neuron doctrine was broadly accepted. In this context, the work of Ramón y Cajal has been inextricably linked with cell theory, in which the cell is recognized as the minimal part of any living organism and constitutes the fundamental part of any living system [1,3].

The establishment of cell theory

Many developments in biology have been accompanied by modifications of the cell theory. As originally proposed during the 1830s, following the observations of Schleiden, Schwann, and others, cell theory was an open and flexible interpretation supported by many prominent naturalists of that time. The theory proposed that cells were the mutual integrative parts of plants and animals. It therefore provided,

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for the first time, a conceptual framework that united the disparate fields of botany and zoology. The coherence of the theory was initially bolstered by several accessory hypotheses, including the spontaneous generation of cells and nuclei [1]. While these ideas were well-received by most members of the scientific community, their conflicts with the essential tenets of cell theory soon became apparent. The theory of spontaneous generation is a case in point. The likelihood of the sudden, spontaneous appearance of microbial life was cast into doubt in the 1850s by Rudolph Virchow's influential proposal, which declared that every cell derived reproductively from a previously existing one. The theory received a fatal blow with the experiments of Louis Pasteur and John Tyndall [9].

Although cell theory appeared to be firmly established by the 1860s, it continued to be rejected by a significant number of dissident naturalists working in several different fields. Perhaps not surprisingly, the experimental evidence that supported it generated new and often dissenting ideas on the basic nature of life, and thus many heated discussions. The development of organic chemistry combined with attempts by Félix Dujardin, Hugo von Mohl, Ferdinand Cohn, and especially Max Schultze to explain the properties of living systems in physical and chemical terms would soon lead to the so-called protoplasmic theory of life, which stated that the most distinctive qualities of life resided in the protoplasm of cells [2]. Proponents of the protoplasmic theory were convinced that inheritance and vital cellular functions could not be ascribed to the nucleus, cell organelles, cell membrane, or the cell wall; rather, they argued, protoplasm was the unique element capable of controlling every aspect of cellular life [1,2].

Ramón y Cajal's protoplasmic insights

Long before he became a towering figure in academia and prior to his international recognition, Ramón y Cajal pursued several ideas that openly argued against cell theory. Quite surprisingly, he was one of the advocates of spontaneous generation, which he believed was essential for evolutionary processes to take place. As he wrote, "largely influenced by the ideas of [Ernst] Haeckel and [Thomas H.] Huxley and by Claude Bernard's unfortunate theory of the *plason* [*sic*], in spite of the experiments performed by Pasteur, I declared myself, in principle, a believer of spontaneous generation ..." ([7], p. 374). In truth, the concept of *plason* had been introduced not by Bernard but by Edouard van Beneden to describe a hypothetical, primitive, and undifferentiated protoplasm. Ramón y Cajal became increasingly convinced that

protoplasm was the only essential component of all living beings. Moreover, he argued that living protoplasm should be seen as a biological entity that had been maintained over generations of living beings since the very beginnings of life on Earth. "There are no progenitors and no progeny, there are no separate and independent individuals, alive or dead," he wrote, "but only one single substance, protoplasm, which fills the world with its creations, which grows, which ramifies, which [temporarily] individuates, but which never dies. In our own being there still moves that ancient protoplasm of the *archiplason* [*sic*], the starting point, perhaps, of the organic evolution" ([7] referring to [6]).

In 1880, three years after he defended his doctoral dissertation, Ramón y Cajal published his very first scientific paper "El protoplasma" (The Protoplasm) in the Zaragoza journal *La Clínica. Semanario de medicina, cirugía y farmacia*. In this now largely forgotten paper, he showed great sympathy and a deep acquaintance with the evolutionary ideas of previous protoplasmic researchers. Ramón y Cajal did not consider the complete nucleated cell the ultimate structure of life. Form was not a required component of living function; instead, function could exist in a completely independent fashion, one not necessarily subordinated to the cell body: "...life could exist without the attribution of form [...] not always can be found inside the mold of organization, and [...] a very simple *substractum* [*sic*] is enough to manifest its properties [...] even a formless, constantly changing protoplasm is enough to achieve all fundamental properties which are attributed to perfect [or nucleated] cells" ([5], p. 299). Completely committed to the idea of protoplasm as the basis of life, a bold Ramón y Cajal did not shy away from predicting the future status of protoplasmic research in the world: "Being as much the importance, as high the role that protoplasm performs in the theater of [cell] organization, it is easy to understand the unexpected interest [...] in the study of its constitution and to the unraveling of its three major problems, the anatomical one, the chemical one, and the evolutionary one, which are still [waiting] to be clarified [...] [protoplasm will become] the battle field of the forthcoming science, and the discovery of the laws that this matter obeys in its distinct conditions of existence will be the greatest conquest of humanity..." ([5], p. 307).

In 1883, Ramón y Cajal published another paper in the same journal, which he divided in seven parts. This is an amusing text titled *Las maravillas de la histología* (*The marvels of histology*), which he signed using the pseudonymous "Dr. Bacterium." Ramón y Cajal was clearly well-acquainted with Haeckel's ideas on the primary distinction of life forms. Haeckel had argued, in his *History of Creation*, that there was a fundamental separation between cytods, i.e., bacteria, on

the one hand, and genuine cells, i.e., nucleated cells, on the other. Ramón y Cajal was also familiar with the so-called *Bathybius haeckelii*, a “seafloor protoplasmic organism” found and named by Huxley: “...simplification and dispersal of life [properties] reached their ultimate limit in the cytode and the bathybius [*sic*], nevertheless its simplicity, in spite of the absence of a nucleus and a covering, these [living] beings fit perfectly their needs and perform actions [...] identical not only to cells, but to those that the noblest and higher organisms carry out” ([6], p. 81). He thus argued that it was necessary: “... to replace the denomination cellular by the designation protoplasmic, or organic element, changing the name cell theory for the more exact protoplasmic theory, [this is] because of the elements which integrate and are required for the construction of a cell the only truly essential is protoplasm” ([6], p. 82). The bathybius turned out to be an artifact, and Ramón y Cajal abandoned his work on bacteria and on the search for a vaccine that could render immunity against cholera, which had engaged his attention following the 1885 epidemic that had started in Valencia [8]. Until his own histological research led him to acknowledge cell theory in its entirety, Ramón y Cajal remained an enthusiastic supporter of protoplasmic theory. The gradual shift to cell theory led him to new, extraordinary insights, as he became one of the most influential and important figures of Spanish science and of biology [3].

Conclusions and perspectives

Led by his materialistic philosophy, Ramón y Cajal initially joined the ranks of those members of the scientific community who opposed cell theory, by assuming that protoplasm was the only type of matter in which the most basic life properties could reside. Although the protoplasmic theory of life was not easily dismantled, it would soon be cast to the outskirts of science as cell theory became dominant by the early twentieth century. Somewhat nostalgically, the mature Ramón y Cajal would recall in his autobiography the hypotheses that he advanced in his youth. He felt proud of some of his early proposals but lamented others, which he preferred to be forgotten. His ideas on the life properties of protoplasm, which had openly confronted cell theory, clearly belong to the latter category. “My philosophic-scientific temerities and my semiserious critiques” Ramón y Cajal wrote ([7], p. 371). He would come to focus on another set of ideas, which he developed between 1906 and 1914, as part of

his struggle against the more extreme versions of cell theory. These ideas included the so-called neurobiones and inobiones, hypothetical subcellular organisms, which Ramón y Cajal speculated were symbiotic to neurons and connective tissue cells, respectively. These disputable proposals were not included in the last works he published between 1933 and 1935 (some of them posthumously), which were almost exclusively devoted to rescuing the neuron doctrine from the renewed attacks launched, ultimately in vain, by the few surviving reticularians. It is true that some of Ramón y Cajal’s ideas were mistaken or incomplete, but their critical study provides important insights not only into the scientific development of an exceptional researcher, but also into the many historical factors that have influenced our understanding of living phenomena. As such, they deserve to be rescued and analyzed.

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