A Brief History of the Cellular Slime Molds

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Fungi have been known and their unique character recognized for as long as there has been natural history. They were known to Aristotle which puts an early well established mention of them well over 3000 years ago. By contrast, the cellular slime molds were first discovered a mere 140 years ago. The reason for this great discrepancy is obvious: cellular slime molds are minute and inconspicuous compared to huge, eye-catching mushrooms. And there are other such examples all stemming from the rise of microscopy in the 19th century. Perhaps best of all is the stunning work of Roland Thaxter, who discovered two entirely new groups of organisms: the myxobacteria and the Laboulbeniales, those curious fungi that were previously thought to be the hairs of the insects upon which they lodged. (I have a special feeling about Thaxter for he was the professor of my Ph.D. professor—I am the third generation.)

In 1869 the German mycologist Oskar Brefeld was studying the flora that emerged from horse dung in a moist chamber and he found fruiting bodies that closely resembled those of *Mucor,* yet they were clearly were not a fungus for they had no hyphae but were composed of amoebae. He named the organism *Dictyostelium mucoroides,* presumably to acknowledge its resemblance to *Mucor.* He described the life cycle, starting with the separate feeding amoebae and later their gathering together in streams, but in this first paper he mistakenly thought that the amoebae fused to form a myxomycetes-like plasmodium. This error was first corrected in 1880 by the French mycologist Ph. van Tieghem, who showed that the amoebae always remained discrete and were truly "cellular" slime molds. In 1884 Brefeld described the same property and published in an extensive paper (with no mention of Van Tieghem!) in which he also described a new species with a branched fruiting body (*Polysphondylium violaceum*); this marks the beginning of cellular slime mold taxonomy. Brefeld's paper is illustrated by a series of beautiful drawings that became classics. I still have an elegant wall chart based on one of his drawings that in days gone by was used in teaching (along with the magic lantern—eons before PowerPoint!).

There are a few contributions following this early work, and I refer the reader to the first chapter on the history of cellular slime molds of Kenneth Raper in his splendid monograph, The Dictyostelids (1984—just one hundred years after Brefeld's major paper. In it the reader will find the details of all the early references mentioned here). One especially notable paper was E. W. Olive's in 1902, in which he described all the known species and gave a definitive description of all the phases of the life cycle. It should be noted that Olive was a student of Roland Thaxter and that this paper was his Ph.D. work. Unfortunately, he left biology, and this was his last contribution to science.

From 1900 onward there were two main thrusts in cellular slime mold research: one was systematics that led more recently to phylogeny, and the other is a search for the mechanisms underlying their development and behavior. The first has been carried out by a small group of individuals compared to the latter, which has become an industry.

The discovery of new species has risen steadily. The two of Brefeld and a few others described by others in the latter part of the 19th century were brought together by Olive (with some additions of his own) showing about a dozen species in all. Kenneth Raper, with his discovery of a new species, *Dictyostelium discoideum* in 1935, began the wave of renewed interest in cellular slime molds. He, and later with his student James Cavender who made some of the most significant advances, searched soils from everywhere, not only in different habitats in the Unites States, but Cavender collected all over the world. Their work has been supplemented by the significant contributions of Hiromitsu Hagiwara in Japan. (For references see Raper, 1984.) As a result, the number of recognized species known today is approximately one hundred—quite a leap from Brefeld's two.

Another very significant recent advance has been the building of a molecular phylogenetic tree of most of the recognized species. This was undertaken by Pauline Schaap and Sandra Baldauf (2006) with the help of Cavender and Hagiwara and numerous others. So now we know who is related to whom, and which species are more ancient or more modern.

Turning to the search for mechanisms that underlie their development and behavior, without any doubt all the credit for sparking the initial interest in this goes to Kenneth Raper's work that stemmed from his Ph.D. thesis, published in 1940 (see Raper 1984 for references). The springboard was his newly discovered *D. discoideum* because it had a multicellular migration period in which the cell mass was stalkless (unlike *D. mucoroides* and other species that form a stalk at the end of aggregation of the amoebae and retain it throughout its development). This migrating slug—a mass of amoebae encased in a thin slime sheath, rather like a miniature sausage in its casing—was ideal for experiments, and Raper took full advantage of its properties. He showed that this slug, which behaved as a unit and oriented towards light, was not uniform in its composition, the amoebae in a smaller, anterior portion are destined to become stalk cells (dying in the process), and all the amoebae of the larger posterior portion become spores. Furthermore, through ingenious experiments, he demonstrated a number of other properties. A particularly notable one, one that especially attracted the attention of all those developmental biologists like myself, was his demonstration that if the slug was cut into segments, each segment produced a complete miniature fruiting body with stalk cells and spores. The slime mold showed the power of "regulation," something Hans Driesch (1907) had shown occurred in some animal embryos years ago.

Raper's 1940 paper was published in the *Journal of the Elisha Mitchell Scientific Society,* a fact that has always given me great pleasure. Students are told today they must publish their papers in the most widely known journals but here is proof that rather it is the content that is of paramount importance, and will even shine through if it appears in a relatively obscure journal.

In this splendid paper Kenneth Raper started the study of *D. discoideum* that trapped me and many others that followed. Further advances began with studies in taxis. In 1902 Olive had suggested that the aggregation of the amoebae might be by chemotaxis, but this was only firmly established in the new wave of experimental work. This was followed by a number of studies on the spore and stalk differentiation still very much on the descriptive level. After a few years *Dictyostelium,* as *D. discoideum* came to be called, drew the attention of biochemists for it was an era of great interest in the biochemistry of development. This was led by Maurice Sussman and his students. One of his postdoctoral fellows, John Ashworth, told me many years later that he read an article of mine in the *Scientific American* and immediately decided that that this cellular slime mold was the future: a eukaryotic *E. coli* where one might be able to follow development with the kind of genetic and biochemical success that had been achieved for *E. coli*.

This turned out to be prophetic, but it took many years to achieve for there were mountains that had to be scaled. It would only grow if grown on bacteria, so an axenic culture had to be devised in which all the ingredients were known. After much labor this was finally achieved. Then there was no sexuality known although it was discovered some years later. Unfortunately it turned out not to be possible to germinate the zygote, so simple crossing experiments were not possible. However with the advent of molecular biology and all its ingenious techniques, it became possible to work on the genetics of *Dictyostelium* and there was a great surge of highly productive work on the molecular biology of development, work that continues to be very active to this day. We now know the chemical nature of the aggregation chemoattractant for a number of species, the genes and the proteins that characterize the stalk cell and the spore differentiation pathways and many other interesting and important molecular details of the development.

Perhaps the high point is the recent publication (Eichinger et al., 2005) of the complete genome of *D. discoideum.* All the big advances have placed *Dictyostelium* into the exalted position of being a MODEL organism, along with *E. coli*, *Drosophila, Caenorhabditis*, and others.

A few years ago I tried to measure the progress of research on the cellular slime molds by counting the numbers of publications since Brefeld. There were very few each year until about 1950, and then there was a change in pace. By about 1980 there was a great rise to over 200 publications per year. The vast majority of these are molecular, although there also has been a modest rise in papers on their ecology and behavior. If one looks at the number of scientists involved we started off with one—Brefeld; in the 1940s for a while there was only two—Raper and myself. Today we are well into the hundreds with laboratories all over the globe. When I started, biologists had never heard of them; now they are in every high school text. By any measure it has been a success story.

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