Self or non-self: Social amoeba rely on genetic 'lock and key' to identify kin

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The ability to identify self and non-self enables cells in more sophisticated animals to ward off invading infections, but it is critical to even simpler organisms such as the social amoebae *Dictyostelium discoideum*.

Dictyostelium exists as a single cell when times are good, but when starved, the cells aggregate and become multi-cellular fruiting bodies with a dead stalk and live spores that allow the cells to survive and pass on genes. When the social amoeba aggregates, it prefers to do so with "kin," the cells that are genetically most like it.

Now researchers at Baylor College of Medicine have identified the genetic "lock and key" that enable the amoeba to tell kin from non-kin. A report on their work appears online in *Science Express*).

"We hypothesized that the molecules that enable these cells to tell kin from non-kin would have properties similar to those of membrane-spanning proteins that contain immunoglobulin folds (such proteins are involved in immunity in mammals)," said Dr. Gad Shaulsky, professor of molecular and human genetics and a corresponding author on the report. "One property is that part of the molecule goes through the membrane and protrudes from the cells. It's an extracellular cue."

Just as the uniforms of armies enable soldiers to differentiate foe from friend, these amoeba use the protruding proteins as a kind of flag. In this case, the flag that protruded differs among strains of the *Dictyostelium*.

These differences are critical to the kin/non-kin discrimination.

They identified "suspect proteins" called TgrB1 and TgrC1 that met all their criteria. It was reminiscent of the major histocompatibility complex (MHC) that is part of the immune systems in higher organisms. TgrB1 and TgrC1 were proteins that protruded on the outside of the membrane of the *Dictyostelium* cells.

"Our hypothesis was that TgrB1 on the membrane of one cell recognizes TgrC1 on the membrane of another," said Shaulsky. "The two cells stick together, and the proteins act like a lock and key. If your key matches my lock, you stay and we develop together. If your key does not match my lock, you cannot participate."

Shaulsky credits graduate student Dr. Rocio Benabentos in his laboratory and postdoctoral associate Dr. Shigenori Hirose in the laboratory of Dr. Adam Kuspa with doing much of the bench work in the report. Graduate student Hsing-I Ho in Shaulsky's laboratory also took part. Kuspa, professor of biochemistry and molecular biology, molecular and human genetics and pharmacology and vice president for research at BCM, is also a corresponding author on this report.

In a complicated series of experiments, they removed or added TgrB1 and TgrC1 together or one by one. The result was the same. If the TgrB1 on one cell came from the same strain as the TgrC1 on the other, the cells could cooperate. If either one of the protein or both were from foreign strains, they could not aggregate with cells that had proteins from the original strain they studied.

No matter how they modified TgrB1 and TgrC1 proteins in *Dictyostelium*, those proteins remain key to determining kin/non-kin.

To prove that the TgrB1/TgrC1 complex was truly a lock and key and

not related to some process within the cell itself, they replaced only one of the proteins, producing a strain that had a normal TgrB1 protein and a foreign TgrC1 protein.

"It's as though you had a blue lock and a blue key and a yellow lock and a yellow key," said Shaulsky. "If one cell has the blue lock and the other the blue key, then they can cooperate. They see each other as kin. However if one cells has a blue key and the other a yellow lock, it will not work.

To determine if the cells are actually adhering to one another, they marked one population green and the other red. They separated them into single cells and then incubated the cells together. The cells that had the same TgrB1 and TgrC1 stuck together into red-green aggregates. Those in which the proteins were different separated into red and green populations.

"As long as they have a shared lock and key set, then they can aggregate," said Shaulsky. "This is the first demonstration in a unicellular organism that immunoglobulin-like molecules are participating in self/non-self discrimination."

The molecules involved in the social amoeba are different from those seen in immunity in higher organisms, but the principle remains.

"What it says is that during evolution, there must have been several independent cases where self-recognition evolved and it always used the same concept – a membrane protein that has immunoglobulin folds outside the cells and is polymorphic (looks different in different strains of the bacteria)," he said.

"By revealing the molecular basis of self-recognition, this study elegantly exemplifies the value of single-celled model organisms in uncovering a

fundamental biological phenomenon," said Stefan Maas, Ph.D., who oversees Dr. Shaulsky's and other cell signaling grants at the National Institutes of Health. "These findings provide novel insights into the biology and evolution of complex cellular behaviors for which there are many parallels in multi-cellular organisms with implications for human health."

More information: www.sciencemag.org/content/early/recent

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