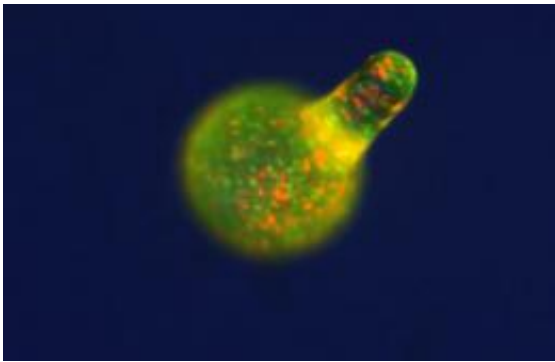


Cells' life and death decisions: lessons from a social amoeba

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Red and green fluorescent labels show the cells destined to become stalk and spore respectively. Credit: Professor Chris Thompson.

Life is full of choices, not only for people but also for the cells that we're made of. Scientists in Manchester are studying a simple life form to uncover the basis of cells' choices, as Michael Regnier reports.

Cells are constantly making decisions about what to do, where to go or when to divide. Many of these decisions are hard-wired in our DNA or strictly controlled by external signals and stimuli. Others, though, seem to be made autonomously by individual cells and yet thousands of independent decisions add up to an apparently organised outcome.

In the developing embryo, there comes a point at which our [stem cells](#) each have to decide whether to become a muscle cell or nerve cell, skin

or bone. This is called differentiation, and it is crucial that we end up with the right proportion of each cell type to develop into healthy human beings.

Researchers working with stem cells have found that, while they can isolate the chemical signals that tells a stem cell to become a nerve cell, for example, adding that chemical to cultures of stem cells does not make them all turn into nerve cells. Only a tiny fraction of the cells do as they are told. The chemical signal is not the deciding factor - there must be other mechanisms involved.

To understand more about how cells make decisions, Professor Chris Thompson, a Wellcome Trust New Investigator at the University of Manchester, is studying an organism called *Dictyostelium* - often referred to as a social [amoeba](#), slime mould, or just plain 'Dicty'. As in the human embryo, Dicty's life cycle includes a stage of differentiation, but rather than having lots of cell types to choose from, Dicty cells choose only whether to live or die.

Chris says: "Dicty is extremely simple, which makes it a good scientific model for studying core cellular processes. Findings in Dicty are translatable to other cells, including human cells, which helps us to learn more about disease and even how we have evolved."

Social life cycle

In the good times, each single Dicty cell works alone, scratching a living down in the soil. However, when food is scarce, their behaviour changes: they club together and form a multicellular organism that moves as one up towards the light and warmth of the surface.

Once at the surface, they form a fruiting body with a stalk and a head of spores at the top. Those cells in the spores are the lucky ones because

they have a chance to be carried by the wind or small animals to new pastures where food may be more abundant. They secure this opportunity at the expense of others: the stalk supporting them is made of dead cells that have sacrificed themselves for the greater good.

"My interest is in the developmental decision to form stalk or spore," says Chris. "We used to think such decisions were made in obvious and predictable ways, But in recent years, research has suggested these decisions are not like that."

Every time Dicty goes through this stage of its lifecycle, the same proportion of cells die: exactly the right proportion required to form the stalk. Which cells form stalk and which spore is determined not by any external or collective intelligence but by each cell making its own life or death decision.

Nothing seems to distinguish the cells that will live from those that will die and there is no obvious pattern to the distribution of emerging stalk and spore cells: they form the same 'salt and pepper' appearance characteristic of differentiating stem cells, which, as Chris says, "only seems random because we can't see the underlying pattern".

Chris is taking two complementary approaches to uncovering the processes by which cells make these decisions and how populations of cells - whether in an embryo or in Dicty - achieve such consistent results from a myriad of apparently independent decisions.

From an evolutionary perspective, he is asking why any Dicty cell would choose to die and join the stalk. On the face of it, there is no benefit, but its altruism means that at least some of its kin will survive, pass on its genes and keep the species going.

If two or more strains of Dicty are present in the multicellular organism,

some strains seem to cheat by making more spores than their fair share, letting another strain die in greater numbers to form the stalk. This rather 'anti-social amoeba' behaviour would seem to offer an evolutionary advantage but, in fact, the 'cheater' strains do not dominate and 'loser' strains must have a reason for not adopting the same strategy.

"There must be a trade-off," says Chris. "Maybe you can't be the best at everything. We need to understand the genetic wiring of the stalk or spore decision."

Do as I say, not as I do

At the same time, Chris is looking at how these cells communicate. This is key: once a cell has made its choice, it releases chemical signals to let its neighbours know what it has decided. This could be part of the mechanism that enables Dicty to form the right proportion of stalk and spores. It could also be the way that cell differentiation is controlled in higher forms of life, including humans.

If the first cells to differentiate send out signals that stop other cells making the same choice of specialisation, that could help to ensure that the embryo produces the right proportion of all the various cell types it needs to develop properly. However, it doesn't explain what prompts the first cell in the signalling chain to make its decision, or why it makes the decision it does. Chris is working to understand this fundamental process at a genetic level.

Having said that it is impossible to predict what decision any one cell will make, it seems there are some transient indicators. Genes are being identified that, when expressed, produce markers that predict which choice a cell will make. These genes are expressed in some cells even when they are growing normally. It is possible that these genes prime the cells so that they are ready to respond in a crisis.

Of course, all the cells in a single strain of Dicty have the same genes and so they all carry the genes for these markers. Why, then, are these genes only being expressed in some of them? One possibility is that the genes are expressed periodically in every cell. However, while all the cells would be expressing the genes at the same frequency, they would not be synchronised, which would explain why only a certain proportion of cells are primed at any one time.

Signal to noise

In Chris's lab, they have begun to identify genes that behave like this in some growing cells: "It gives us a handle for understanding Dicty's decision-making behaviour," he says. "We can generate mutant strains with altered frequencies that lead to different proportions of stalk and spore."

It is possible that the periodic switching on and off of certain genes has been exploited during evolution to control the overall outcome of thousands of cells making individual decisions.

Chris says this is rather a new idea in biology: "Our research suggests that systems may be able to use the noise or randomness inherent in any physical or chemical system to help make decisions."

So the observation that some Dicty [cells](#) try to cheat their cousins might simply be the result of different frequencies of expression of priming genes among different strains, not the act of 'anti-social' amoebae. And in yielding up the secrets of its decision-making process, Dicty is helping us understand how human cells' decisions are regulated through early development, proving itself not just social but positively philanthropic.

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