Life, but not as we know it

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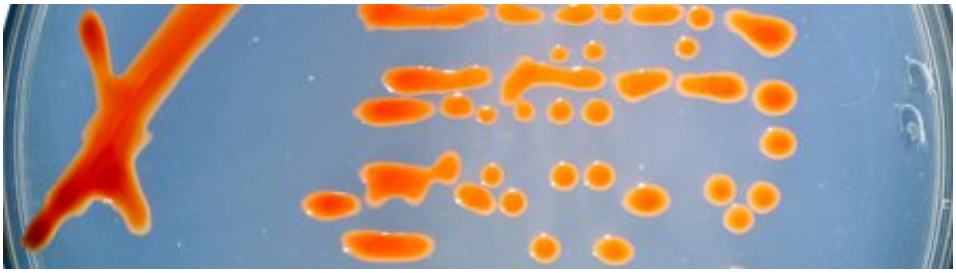

A rudimentary form of life that is found in some of the harshest environments on earth is able to sidestep normal replication processes and reproduce by the back door, researchers at The University of Nottingham have found.

The study, published in the journal *Nature*, centres on Haloferax volcanii—part of a family of single-celled organisms called archaea that until recently were thought to be a type of bacteria.

The findings, led by scientists from the University's School of Life Sciences, could offer new insights into how defective cells can multiply out of control in diseases such as cancer.

Their discovery comes in the same year as the 50th anniversary of a landmark in the field of DNA replication—the presentation of the replicon model at the Cold Spring Harbor Symposium on DNA

Replication in 1963 by François Jacob, who was later awarded the Nobel Prize in Medicine.

Unexpected finding

Dr Thorsten Allers said: "Sadly François Jacob passed away this year, but 50 years after this theory was presented it still guides the investigation of DNA replication.

"Given this anniversary, our paper in *Nature* is rather timely. We have shown that in some organisms, the replication origins—genetic switches that control DNA replication—are not only unnecessary but cells will actually grow faster when these origins are not present. This is totally unexpected and has forced us to re-evaluate one of the cornerstones of DNA biology."

The paper, *Accelerated Growth in the Absence of DNA Replication Origins*, was co-authored by Dr Thorsten Allers, Dr Conrad Nieduszynski and Dr Michelle Hawkins in the University's School of Life Sciences in collaboration with Dr Sunir Malla and Dr Martin Blythe in DeepSeq, the School's state-of-the-art DNA deep sequencing laboratory.

Archaea were originally discovered in extreme environments and can survive at very high or very low temperatures, or in highly salty, acidic or alkaline water. They form one of the three distinct branches of life along with bacteria and eukaryotes, which are multi-celled organisms including humans, other animals, plants and fungi. At a genetic level, archaea have been found to be more closely related to eukaryotes, and therefore humans, than to bacteria. The salt-loving Haloferax volcanii being studied by the Nottingham scientists originates from the Dead Sea.

Fundamental to life?

Dr Allers added: "Although they look like bacteria and behave like bacteria, archaea are actually more closely related to us. Where we really see the similarities is when we look at the enzymes that are responsible for DNA replication and that's why we thought this would be an interesting system to work on. We've got something that's life but not as we know it: on the outside they look like bacteria but on the inside they look like us."

"What we've discovered is that in this type of archaea, François Jacob's replicon model, which was proposed 50 years ago and was thought by everybody to be absolutely fundamental to life, is not necessarily true."

In order to reproduce, all life forms need to copy their DNA before the cell can divide. They do this via a series of 'replication origins' that are located around their chromosomes and to which proteins bind in order to start the replication process.

In eukaryotes such as humans if these replication origins are eliminated it prevents replication and eventually leads to cell death.

However, the Nottingham study, funded by the Biotechnology and Biological Sciences Research Council (BBSRC) and the Royal Society, found that the Haloferax volcanii is able to spontaneously begin a chain reaction of replication all around its chromosomes even when its replication origins have been eliminated.

In addition, the scientists discovered that far from being disadvantaged by having to employ this novel survival method, the archaea without chromosomal origins grew faster.

"The amazing thing that we found wasn't just that deleting the origins

still allowed the cells to grow, but that they now actually grew almost 10 per cent faster. Everybody was thinking, 'where's the catch?' But we haven't found one" Dr Conrad Nieduszynski said.

"The way cells initiates this replication process is to use a form of DNA repair that exists in all of us, but they just hijack this process for a different purpose. By using this mechanism, they kick-start replication at multiple sites around the chromosome at the same time."

Selfish gene

Since it appears that origins are unnecessary in Haloferax volcanii, the scientists believe that replication origins in this organism could be an example of a 'selfish gene'—benefitting the origins by offering the chance to be continually replicated while offering no advantage to the organism itself.

For humans it is very important that we can regulate this process of DNA replication to ensure that our chromosomes are only copied once before the cell divides, otherwise this can lead to genetic diseases including cancer.

When cancer cells develop they no longer regulate the copying of their genome—this happens because of mutations in the genes that control this process. Loss of replication control leads to cancer cells making more than just two copies of their chromosomes, which is something they have in common with what the scientists observed in Haloferax volcanii.

Dr Allers said: "Scientists think that cancer cells revert back to a more primitive state without these forms of control. This is how they resemble Haloferax volcanii. One of the other hallmarks of cancer cells is that grow faster than ordinary cells and can quickly take over the body. This

is similar to what we are seeing—when you don't regulate DNA replication and dispense with the normal checks and balances, you can have unregulated, faster growth."

In the future if we can understand this mechanism it could give us an insight into how cancer cells can escape normal regulation and control. It could even identify new targets for killing cancer cells without harming normal cells.

Provided by University of Nottingham