Scientists identify 'molecular fossil' in fungi

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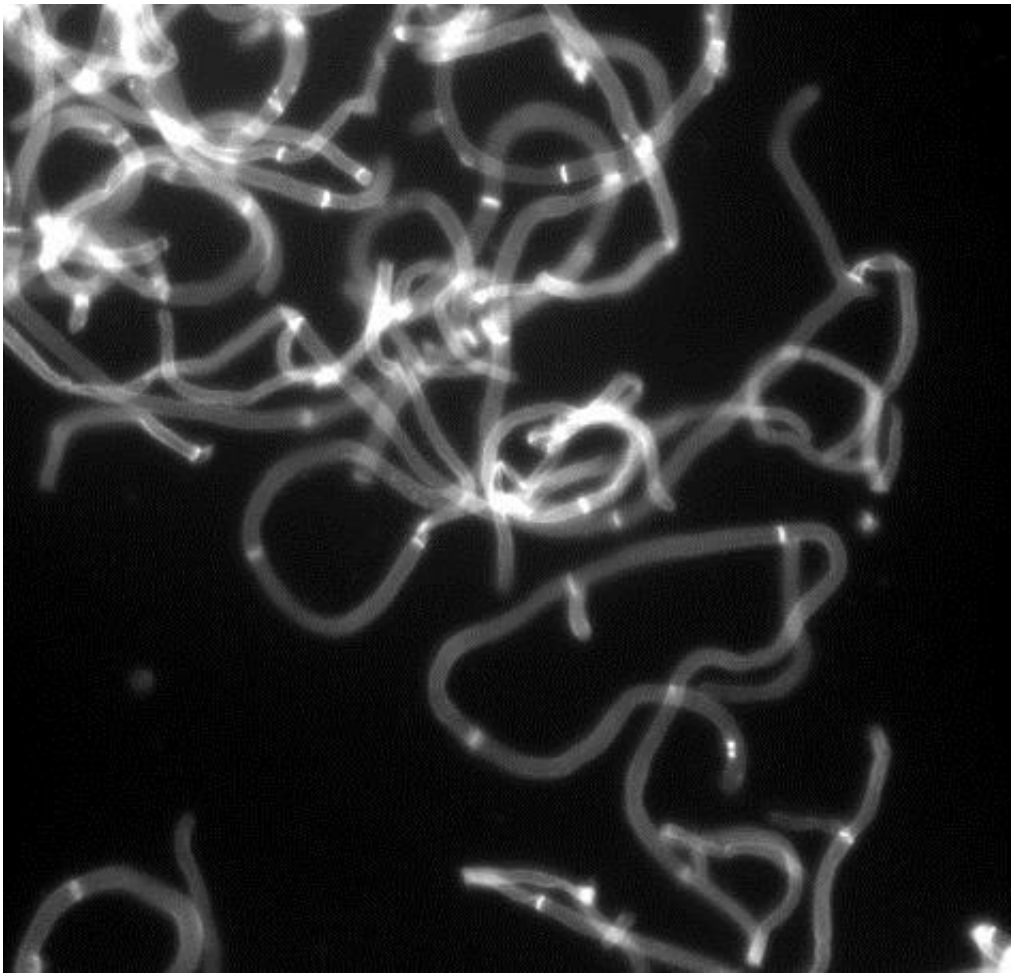

The fungus Yarrowia lipolytica growing in filamentous form in low oxygen conditions. Credit: University College Dublin

(Phys.org) —All but a few eukaryotes die without oxygen, and they respond dynamically to changes in the level of oxygen available to them.

UCD scientists used genetic analysis to pinpoint an evolutionary switch in regulating response to low oxygen levels in fungi.

One example of ancient oxygen-requiring biochemical pathway in eukaryotes is the biosynthesis of sterols, producing cholesterol in animals and ergosterol in fungi.

The mechanism regulating the sterol pathway is widely conserved between animals and fungi and centres on a protein family of transcription activators named the sterol regulatory element binding proteins (SREBPs), which form part of a sterol-sensing complex.

However, in one group of fungi; the Saccharomycotina, which includes the model yeast Saccharomyces cerevisiae and the major pathogen Candida albicans, control of the sterol pathway has been taken over by an unrelated regulatory protein, Upc2.

New research published in *PLoS Genetics* by UCD researchers, in collaboration with colleagues from AgroParisTech, France and the University of Kansas, USA, used comparative genomic analysis to investigate the timing of the evolutionary switch from one regulatory mechanism to another; from SREBPs to Upc2.

Led by Professor Geraldine Butler, UCD Conway Institute and UCD School of Biomolecular & Biomedical Science, the group found that one yeast species, Yarrowia lipolytica is unique in that it contains both SREBP and Upc2 genes. Y. lipolytica is used in the biotechnology industry to produce lipids and lies at the base of the Saccharomycotina group.

Using a mixture of genetic and biochemical analysis, the group showed that Upc2 is the main regulator of the hypoxic response in Y. lipolytica, and regulates the levels of sterols in the membrane, while SREBP

appears to be a "molecular fossil" that has lost its role as a sterol regulator.

The SREBP gene retains some role in the hypoxic response of Y. lipolytica however, and is required for maximal growth when oxygen levels are low. Derivatives of SREBPs are also required for the growth of several yeast species as filamentous forms, which is important for virulence.

Professor Geraldine Butler says, "The analysis showed that the evolutionary switch from SREBP to Upc2 was a two-step process in which Upc2 appeared in an ancestor of Saccharomycotina, and SREBP subsequently lost its sterol-regulatory function while retaining an ancient role in filamentation.

The findings are exciting from a purely evolutionary perspective in that they reveal more about the development of eukaryotes over time but also have tremendous potential for clinical use if they can be applied to the development of more effective anti-fungal therapies".

Many antifungal drugs work by binding with sterols in the cell membrane to damage the integrity of the barrier causing cell death. In recent years with changes in medical practice, there is an increase in resistance to antifungal therapies. A thorough understanding of how pathogenic yeasts respond to hypoxic conditions is essential to the discovery and development of new, more effective anti-fungal treatments.

More information: Sarah L. Maguire, Can Wang, Linda M. Holland, François Brunel, Cécile Neuvéglise, Jean-Marc Nicaud, Martin Zavrel, Theodore C. White, Kenneth H. Wolfe, and Geraldine Butler. Zinc finger transcription factors displaced SREBP proteins as the major sterol regulators during Saccharomycotina evolution. *PLoS Genetics*.

www.plosgenetics.org/doi/pgen.1004076

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