Invasion

Unraveling the mechanism underlying invasive yeast growth

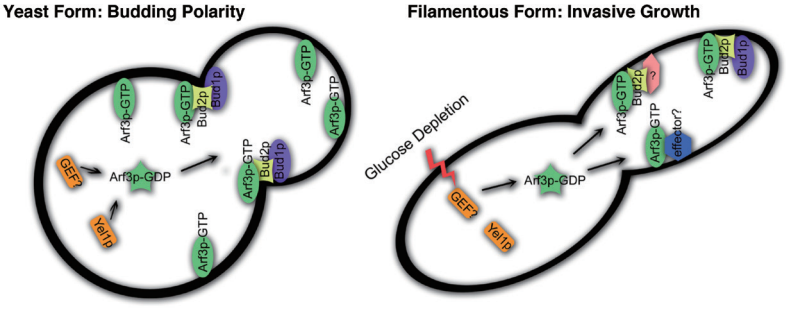
In energy-depleted environments, cells are stimulated to migrate toward nutritional or carbonic sources and, in some cases, may even become invasive.

Why is this so?

Many fungi will switch to filamentous growth to search for nutrients in energy-depleted environments. Filamentous growth is considered invasive and is associated with Arf3p activation in yeast, which is the homolog of mammalian Arf6.

ADP-ribosylation factors (Arfs) are small GTP-binding proteins that can hydrolyze GTP and have critical roles in vesicle transport and actin reorganization. Six Arf isoforms have been identified in mammalian cells, which can be divided into three classes. Class I (Arf1-3) and class II (Arf4-5) Arfs primarily regulate vesicular trafficking between the Golgi and endoplasmic reticulum. Class III Arfs (Arf6) have been implicated in endocytosis, plasma membrane protein recycling and cytoskeleton remodeling. Arf6 also plays a role in cell adhesion, migration, wound healing, membrane ruffling and metastasis.

Similar to other small GTP-binding proteins, the activation of Arf is strictly regulated by guanine nucleotide-exchange factors (GEFs), which facilitate the dissociation of GDP and its replacement with GTP. All Arf GEFs are characterized by a central catalytic domain known as the sec7 domain.



In addition to invasive growth, Arf3p is also involved in polarity development in yeast. During this process, Arf3p activation is mediated by Yel1p, which acts as the GEF; however, further studies have revealed that Yel1p is not responsible for the activation of Arf3p upon glucose deprivation.

Therefore, the key GEF involved in invasive growth was uncertain.

In July 2015, Professor Lee and Doctor Hsu published their study in Nature Communications on the mechanism of Arf3p activation in energy-depleted environments.

In this study, the authors identified a novel GEF named Snf1p. Snf1p is the yeast homolog of mammalian AMP-activated protein kinase (AMPK), which is responsible for Arf3p activation in response to glucose depletion. Snf1p is a key metabolic regulator of energy homeostasis and is involved in yeast invasive growth. Snf1p directly binds to and activates Arf3p through the C-terminal regulatory domain. Unlike other Arf GEFs, Snf1p lacks the sec7 domain and acts independent of N-terminal Snf1p kinase activity.

In conclusion, Arf3p and Snf1p, the homologs of mammalian Arf6 and AMPK, respectively, are associated with yeast invasive growth in glucose-depleted environments. Recent studies have also shown that Arf6 and AMPK may be related to cell migration and invasion in cancer. Understanding the regulatory pathway underlying the mechanism of Arf3p- and Snf1p-mediated invasive growth may facilitate new drug development in the future.

Reference

Jia-Wei Hsu, Kuan-Jung Chen and Fang-Jen S. Lee. Snf1/AMP-activated protein kinase activates Arf3p to promote invasive yeast growth via a non-canonical GEF domain. Nat. Commun. 6:7840 DOI:10.1038/ncomms8840 (2015).

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