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Technical Comments

Clathrin: A Matter of Life or Death?

In their Research Article, "Clathrin requirement for normal growth of yeast" (*1*), Sandra K. Lemmon and Elizabeth W. Jones describe the characterization of a yeast strain engineered to contain a deletion in the gene that encodes the heavy chain of clathrin (*CHC*, wild type; *chc*-Δ, deletion). Among the haploid progeny of a single diploid strain, they found a locus, referred to hypothetically as a "suppressor gene," that influences the ability of yeast cells to survive deletion of the *CHC* gene. This locus, genetically unlinked to *CHC*, exists in two forms: one that allows *chc*-Δ cells to live and grow slowly, and another that results in *chc*-Δ cell death. The original diploid contains one copy of each form. Inasmuch as clathrin is held to play important roles in membrane traffic within eukaryotic cells, it is tempting to suggest that the "normal" state of this gene results in the death of *chc*-Δ cells. Hence, "normal" yeast cells, and by extension all eukaryotic cells, would require clathrin to live.

Two years ago we reported results on clathrin deletion (*2*) that are largely confirmed by Lemmon and Jones with one important exception. Our strain of yeast survived deletion of the *CHC* gene, with no evidence of an unlinked genetic character influencing cell viability. We showed that clathrin-deficient cells are sickly, but that at least one aspect of membrane traffic, glycoprotein secretion, is preserved. From these data we argued that clathrin, although important for a normal rate of growth, is dispensable and possibly replaced by other structurally distinct molecules.

Now the question is, Which strain are we to accept as "normal"?

This question would be most difficult to answer with only the two strains that have been reported. For this reason, we have conducted a survey of more than ten strains from our collection and from three other laboratories (*3*). Many of these strains share a common parentage with the original strain used by us and by Lemmon and Jones. Each of the strains we examined survived deletion of the *CHC* gene. Although not mentioned in their article, we would ask if our colleagues also have examined other strains? While it is possible that all strains tested, save the one reported by our colleagues, contain genetic alterations that mitigate the lethal effect of clathrin deletion, we suggest rather that the unusual strain contains a cryptic mutation that is lethal only when clathrin is deleted. This could represent a function that replaces clathrin, or it could affect cell viability indirectly.

Given the large number of strains we have examined, the more representative phenotype appears to be survival of *CHC* deletion mutant cells. For this reason we believe it is appropriate to investigate clathrin function by examining membrane traffic in viable clathrin-deficient cells. To paraphrase Samuel Johnson, "It matters not how a *yeast cell* dies, but how *it* lives."

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Response: We are in the fortunate position of discussing important issues where the two sets of data in question (*1, 2*) are both correct and irrefutable. There seems to be no question that cells can survive clathrin deficiency in some genetic backgrounds and cannot do so in other genetic backgrounds.

Randy Schekman and Gregory Payne raise two issues of substance about the function of clathrin in yeast cells. The first issue is whether the *scd1* (suppressor of clathrin deficiency) allele suppresses the lethality associated with deletion of the clathrin heavy chain gene or whether the *SCD1* allele kills cells bearing the deletion. This is a semantic difference that cannot be resolved by segregational analysis. Only the determination of the molecular basis of *scd1* suppression will resolve this ambiguity.

The second issue raised is whether *SCD1* or *scd1* is the normal allele. Most of the yeast strains commonly used for genetic analysis are closely related to one another (*3*). To sample these strains will merely identify the more common allele in this highly inbred population. In this population, for example, the *ho* and *gal2* alleles (mutant forms of the genes that encode the mating type switching endonuclease and the galactose permease, respectively) are the more common alleles. In one sense it is not even very important which (*scd1* or *SCD1*) is the more common allele in the population at large. The important fact is that cells can survive without clathrin if they carry the *scd1* allele and must have clathrin if they carry the *SCD1* allele. The challenge is to discover the molecular basis that distinguishes these two states.

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