**Keeping introns at hand to make starving cells last**

Coping with starvation

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Most genes are interrupted by intervening non-coding sequences or introns that need to be removed through the process of splicing to generate functional messenger RNA. The number and density of introns vary greatly between organisms and are still propagating in certain lineage, while experiencing massive loss in others. Primates have the highest density of introns while lowest number of introns is found in primitive organisms including budding yeast. Strikingly, introns are preserved in the smallest of eukaryotic genomes and a complex splicing machinery is preserved in organisms with only a handful of introns. In human cells introns are usually very large. Introns are often viewed as junk RNA but the huge energetic burden of transcribing and removing the introns argues for a significant evolutionary advantage. Introns are associated directly and indirectly with many functions in the eukaryotic genomes. The direct roles of introns include the regulation of alternative splicing, the stimulation of gene expression, the control of mRNA transport and the regulation of mRNA stability through nonsense-mediated decay. In addition, introns may function as a reservoir for a large number of non-coding RNAs and as a breeding ground for new genes. Indeed, the majority of small nucleolar RNA (snoRNA) and microRNA in human cells are generated from the intron of mostly unrelated genes.

In S. cerevisiae genome there is only 295 introns located in 280 genes and only 9 genes contain more than one intron. Several hypotheses were put forward to explain the simplicity and paucity of splicing in yeast. One hypothesis proposes that introns in yeast have appeared recently and that their full function did not have time to evolve (intron-in model), whereas another and more prevalent hypothesis suggests that introns are on their way out of the yeast genome (intron-out model). Genome-wide analyses of splicing and global surveillance of intron expression suggested that yeast introns improve and regulate gene expression, thereby fueling the debate about yeast intron function and the fundamental value of splicing in eukaryotes. To understand the basic function of introns, we created the first and currently unique collection of ∆i strains. The 295 S. cerevisiae introns and tested the impact of intron deletion on growth. The growth was tested in community cultures where wild type and mutated strains compete for nutrients. Surprisingly, most deletion strains competed well with wild type cells in the early stages of a typical culture growth phase, but they were at a significant disadvantage as nutrients were consumed by the growing culture. Remarkably, the majority of the intron deletion strains disappeared from the cultures during stationary phase. Strikingly, we found no correlation between this intron effect on growth and their effect on the expression of their host genes. Remarkably, mutated alleles of genes that do not produce proteins still completely complement the growth defect of the introns deletion. Therefore, the intron, and not the protein, of the host gene is required for cell growth in stationary phase. Strikingly, introns of one gene rescues the growth defects caused by intron deletion in other unrelated genes and multiple intron deletion was genetically epistatic, suggesting that the introns are working in the same metabolic pathway.

Transcriptomic and genetic analyses indicate that introns promote resistance to starvation through the repression of the nutrient sensing TOR pathway that controls ribosome biogenesis and translation. This evolutionary conserved TOR pathway controls cell growth in response to nutrients. As a principal regulator of cell growth, it is implicated in many diseases including cancer, obesity and diabetes. Interestingly, examining gene expression in intron deletion strains indicated that introns are required for repressing a common set of genes related to translation and respiration in response to nutrient limitations. Strikingly, this intron-mediated effect on cell growth was completely lost upon the deletion of genes implicated in the nutrient-sensing TOR pathway. These findings could therefore directly explain introns preservation and uncover exciting regulatory mechanisms of cell adaptation to nutrient limitation. Indeed, introns can no longer be treated as junk RNA that needs to be removed for genes to function but instead an integral component of the regulatory network that control cell growth and response to fluctuation in growth conditions. Therefore, the work highlights a hidden aspect of nutrients sensing pathway that make use of introns that otherwise may work as break for growth when nutrients are abundant. Indeed, keeping an intron at hand may slow growth when food is ample but would also prolong cell survival when nutrients are depleted.