incomplete knowledge of the instability seeds and their evolution, or both, could be to blame.

In light of this discrepancy, Gopalaswamy *et al.* chose a different approach to optimizing the fusion performance at OMEGA. They posited that, because both the simulations and the experiments have the same inputs (such as the geometry of the capsule and the time dependence of the laser's power), a statistical relationship might exist between simulation outputs and experimental data. The authors trained a statistical model to match an initial set of experimental data using simulation outputs. They then used this model to suggest changes to the implosion design that the model predicted would improve the fusion performance.

By consistently following this methodology to design a series of experimental campaigns, Gopalaswamy and colleagues improved the fusion yield by a remarkable factor of three compared with OMEGA's previous record[3]. Buoyed by this success, the authors expanded their approach to work on increasing the plasma confinement time by increasing the areal density (the mass per unit area) of the imploded fuel. They trained a second statistical model to suggest changes to the time dependence of the laser's power. Such changes led to a 60% increase in the areal density of the fuel, while maintaining the record fusion yield, resulting in a dramatically improved overall implosion performance.

These advances have major implications. For instance, further optimization of OMEGA fusion performance will probably be possible using further refinements of the authors' statistical models. It is also likely that this approach could be extended to other ICF techniques, such as indirect-drive laser fusion, in which laser beams irradiate a small metal cylinder containing the fuel capsule, rather than the capsule itself. Indirect-drive laser fusion has been the highest-performing ICF method so far[4,5].

Gopalaswamy *et al.* extrapolate their results to the energy scale of the National Ignition Facility (NIF) at the Lawrence Livermore National Laboratory in California[6], which has more than 60 times the energy of OMEGA. Although this extrapolation projects that record-breaking fusion yields could be achieved, it is also fraught with peril, because there are considerable uncertainties in how the physics and instabilities scale over such a large energy range. In addition, the laser beams at NIF are not configured to uniformly illuminate the fusion capsule for direct-drive laser fusion, meaning that such experiments could not be carried out without an expensive change to the facility. With an awareness of these concerns, an experimental effort is under way at OMEGA and NIF to better understand the prospects for direct-drive laser fusion as a path to thermonuclear fusion. Gopalaswamy and colleagues' results will greatly aid this effort.

Perhaps the most exciting aspect of the authors' work is the impetus it will give to further understanding the substantial disconnects between what is simulated and what is experimentally observed. It is empowering to know that such large improvements in fusion performance are realizable using trained statistical models, and that powerful insights can be obtained from taking a deeper look at the experimental data. At the same time, it is humbling for scientists dedicated to understanding such complex systems to recognize how much they don't understand. As a quote attributed to physicist Eugene Wigner states[7]: "It is nice to know that the computer understands the problem. But I would like to understand it, too". Gopalaswamy *et al.* have shown us that this statement is even more true for fusion developers than we knew. ■

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MOLECULAR BIOLOGY

Intron RNA sequences promote cell survival

Intron sequences are removed from newly synthesized RNA and usually rapidly degraded. However, it now seems that introns have a surprising role — helping yeast cells survive when nutrients are scarce. SEE ARTICLES P.606 & P.612

SAMANTHA R. EDWARDS & TRACY L. JOHNSON

RNA molecules that are newly transcribed from DNA contain intron and exon sequences. Introns are excised through a process called RNA splicing, during which the remaining exon sequences are joined together (ligated) to form mature messenger RNA, which is then translated into proteins. RNA splicing releases a lariat-shaped intron that is rapidly converted (debranched) to a linear form and degraded. Much of what we know about the molecular machinery — the spliceosome and its associated factors — and the mechanisms of splicing has come from genetic and biochemical experiments using baker's yeast (*Saccharomyces cerevisiae*). Laboratory studies have suggested that most yeast introns can be removed with little consequence for the cell[1]. Parenteau *et al.*[2] (page 612) and Morgan *et al.*[3] (page 606) now challenge this view by showing that introns help yeast cells in culture to sense a lack of essential nutrients in their growth medium and to adjust the rate of cell growth to adapt to this change in the environment.

Although the splicing machinery has been highly conserved during evolution, gene architecture is complex and varies across organisms. The yeast genome is highly streamlined in comparison with those of most other eukaryotes (the group of organisms that includes plants, animals and fungi). Approximately 5% of protein-coding genes in yeast contain introns, and only nine contain more than one. By contrast, 90% of genes in mammals contain introns, with an average of eight introns per gene. In yeast, as in other organisms, introns have been viewed as the dispensable by-product of exon ligation because of their rapid degradation after splicing.

Parenteau *et al.* and Morgan *et al.* shine new light on the role of introns. Each group assessed the roles of introns as yeast cells in culture enter the stationary phase, a period defined by a plateau in growth caused by decreased expression of genes involved in respiration and proliferation in response to limited nutrient availability. For example, expression of components of the ribosome, the cellular machinery that synthesizes proteins when nutrients are abundant, is downregulated during the stationary phase[4]. Both Parenteau *et al.* and Morgan *et al.* find that certain introns accumulate during the stationary phase, and that they have a role in the cells' response to nutrient deprivation (Fig. 1). However, the two groups report different intron forms, each of which might mediate the response to nutrients in distinct ways. Parenteau *et al.* identify a role for unspliced transcripts, whereas Morgan *et al.* identify introns that accumulate after being excised and debranched.

Parenteau *et al.* generated a library of 295 yeast strains, each of which had a single, different intron deleted from its genome, and 9 additional strains whose genes originally contained two introns, both of which had been

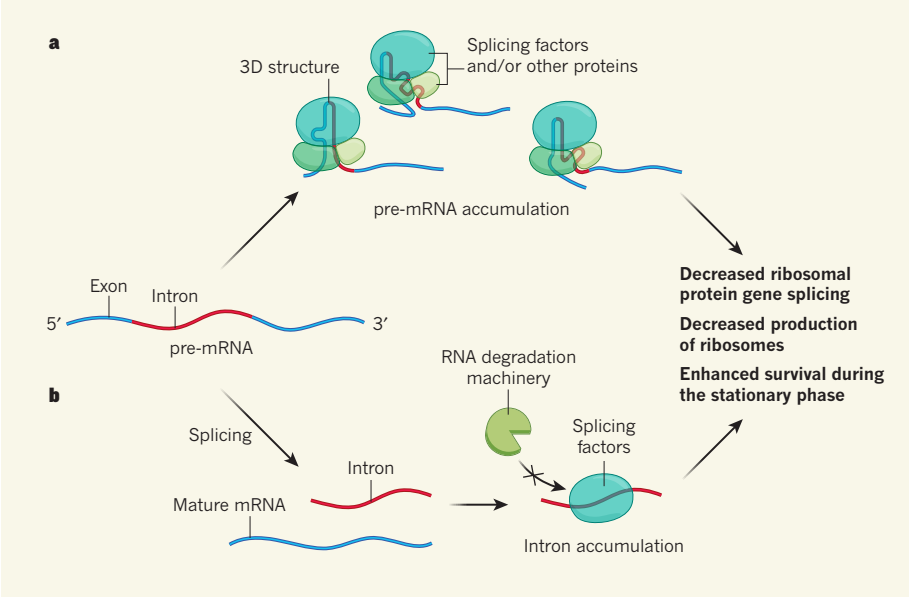

Figure 1 | Role of introns in nutrient-poor conditions in yeast. Precursor messenger RNA (pre-mRNA) molecules undergo splicing to remove intron sequences, which are usually degraded. The remaining exon sequences are joined together to form mature mRNA. Parenteau *et al.*[2] and Morgan *et al.*[3] show that some introns in yeast persist and help the cells survive during the stationary phase, a period of decreased growth due to depletion of available nutrients. **a**, Parenteau *et al.* saw accumulation of unspliced pre-mRNAs that form particular 3D structures at their 5′ ends. These structures affect cellular responses to nutrient deprivation, perhaps by enabling the binding of splicing factors or other proteins. **b**, Morgan and colleagues observed the accumulation of introns that remain stable after being removed from pre-mRNA. They also show that certain splicing factors bind to these introns, and might protect them from degradation and affect cellular responses to nutrient deprivation. Both groups suggest that accumulation of introns might modulate cellular growth by downregulating the production of cellular components — specifically, ribosomes — that are usually downregulated when nutrient availability is low.

removed. When grown together with a wild-type strain in culture, many of the mutated strains were unable to compete with the wild-type strain once the stationary phase had been reached, and these cell populations died out. This growth disadvantage was independent of the function of the gene harbouring the deleted intron.

The authors then created a small DNA molecule containing the gene that produces one of the introns that accumulates during the stationary phase. When they introduced this gene into yeast cells that had intron deletions, it fixed their growth defects. This was true even when the gene had been mutated so that it encoded an RNA molecule unable to undergo splicing or translation. These findings suggest that the element that enables the cells to grow when nutrients are limited is the intron itself, rather than the messenger RNA or the protein encoded by the gene. Intriguingly, this repair of the growth defect happened only when the sequence encompassing the 5′ end and the first exon of the RNA molecule were unmodified. The authors conclude that the 3D structure of the 5′ end of the RNA molecule contributes to the function of introns under starvation conditions.

Morgan *et al.* developed a sequencing workflow to detect introns that accumulate in yeast cells during the stationary phase, and found that these introns were in an excised and debranched form. As in Parenteau and colleagues' study, they observed that strains lacking one or more of these introns were less able to survive in nutrient-poor conditions than was wild-type yeast. Morgan *et al.* isolated one of the accumulating introns, and found that it was associated with a collection of proteins that resembles the intron-lariat spliceosome (ILS) protein complex, which assembles during RNA splicing. The authors suggest that splicing-related proteins bound to the excised intron protect it from degradation. Previous work has suggested that Prp43, a protein involved in splicing, actively disassembles the ILS complex[5]. It will be interesting to determine whether Prp43 activity decreases during the stationary phase, allowing the ILS-like complex to persist — especially because Prp43 also has a role in the production of ribosomes[6], a process that is similarly downregulated during the stationary phase.

Parenteau *et al.* and Morgan *et al.* suggest that intron accumulation might regulate cell growth in the stationary phase by downregulating the splicing of ribosomal-protein genes (RPGs). RPGs make up approximately 90% of the spliced RNAs in yeast cells grown in nutrient-rich conditions, but their production from DNA is repressed during the stationary phase. Previous studies[7–9] in yeast have demonstrated that downregulation of RPG expression enhances the splicing of RNAs encoded by other genes by freeing up the splicing machinery in cells. Morgan *et al.* propose that the accumulating introns might sequester the splicing machinery and downregulate splicing of RPGs. One attractive aspect of this model is that it provides a mechanism for reversing splicing inhibition. Rapid intron degradation could release splicing factors and restore splicing of RNAs encoded by RPGs when environmental conditions can support exponential cell-population growth.

Although the mechanisms by which the 5′ RNA structure described by Parenteau *et al.* promotes survival remain unclear, a possible model, similar to that described by Morgan and colleagues, is that proteins associated with RNA (perhaps spliceosome components) mediate the cell's response to nutrient deprivation. Analysis of the proteins that associate with stable RNA molecules in cells should shed light on these processes.

Both studies make a strong case for the importance of introns under nutrient-poor conditions, although it is not clear whether the two distinct forms of intron RNA identified act in the same or in different ways. Morgan *et al.* report 34 introns that accumulate during the stationary phase. Interestingly, there is little overlap between these and the unspliced RNAs with 5′ structures reported by Parenteau and colleagues. This raises the possibility that two mechanisms, involving different classes of intron and perhaps slightly different conditions, are at work.

By studying yeast under physiologically relevant conditions, these studies generate a new appreciation of the role of introns, and provide compelling evidence that introns help to shape the collection of RNAs in a cell in response to its environment. It will be exciting to uncover other conditions that reveal further roles for stabilized introns in yeast and other eukaryotic organisms. ■

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