The shocks in jets from young stars are much slower, at most a few hundred kilometers per second, but the new findings suggest that diffusive shock acceleration can operate even in these puny jets. Thus, jets from young stars could be a new extreme testing ground for the theory of how cosmic rays are made.

Looking ahead, radio astronomy is currently undergoing a revolution. Fiber-optic cables have replaced microwave links, enabling much larger portions of the spectrum to be received and analyzed by radio interferometers. This revolution is akin to the introduction of digital cameras in optical astronomy three decades ago when the efficiency of a telescope at collecting photons was increased from a few percent with photographic plates, to more than 70%. Refurbished radio interferometers, such as the Expanded VLA (EVLA) in the United States (*11*) and the extended-Multi-Element Radio Linked Interferometer Network (e-MERLIN) in the United Kingdom (*12*), will be at least an order of magnitude more sensitive than their predecessors. This will have a major impact on many areas of astronomy, including star formation. Observing jets from young stars is just at the limit of what existing radio telescopes can usefully do. Although most of their radio emission is thermal due to ordinary electrons being released by collisions in the gas, the increased sensitivity of the new radio telescopes should enable the discovery of many more nonthermal (synchrotron) jets from young stars and nonthermal components in previously known, predominately thermal, jets.

The observations reported by Carrasco-González *et al*. finally provide a means of determining the structure and strength of the last poorly known parameter in stellar jets, i.e., the magnetic field, and thus provide a crucial test of the jet-formation paradigm. Ironically while the vast majority of cosmic rays may be generated when stars die, a very small fraction could be produced at their birth.

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CELL BIOLOGY

# The Case for RNA

RNA shows promise for engineering synthetic systems for controlling gene expression.

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A major challenge in cell-based biotechnology is to engineer gene regulatory systems that can detect signals defined by users and then effect desired changes in the expression of targeted genes. On page 1251 of this issue, Culler *et al*. (*1*) take an innovative step toward meeting this challenge. They describe the use of short segments of RNA to create programmable "control devices" that, when triggered by the presence of certain proteins, rewire gene expression pathways and change the behavior of human cells. The work highlights the promise of RNA as a molecular platform for engineering predictable and customized gene regulation systems and potentially using such synthetic systems to treat disease.

Cells are masters of regulating genes in response to environmental cues. They accomplish this through an overwhelming variety of mechanisms, including riboswitches, RNA silencing, protein transcription factors, post-translational modification, and degradation. This mechanistic diversity is represented in differences in the speed, dynamic range, cooperativity, and functional complexity of gene regulation. Bioengineers, however, have had difficulty appropriating such diversity because each mechanism demands a distinct set of strategies in order to tailor it for synthetic systems. From an engineering perspective, it would be more useful to create a simple yet complete framework, ideally based on one molecular system, for building synthetic gene regulation systems. Is such a framework possible?

In the past 20 years, RNA biotechnologists have aimed to answer "yes." They have pursued a general strategy of coupling RNA aptamers (RNA structures that recognize, or bind to, specific small molecules or proteins) to the transcription, translation, or processing of genes (*2*–*5*). They have demonstrated that this approach can produce "user-defined" gene expression control systems (*6*–*8*).

Culler *et al*. present an inventive instantiation of this strategy. Expanding on previous work in engineered alternative splicing systems (*9*, *10*), they place aptamers that bind specific proteins into introns (eukaryotic DNA regions within a gene that are not translated into proteins) and are able to show that the DNA is spliced differently, depending on whether the aptamer is bound to its cognate (matching) protein "signal." When they add a stop codon in an exon that, because of the differential splicing, is either included or excluded in the final messenger RNA (mRNA), a direct change in the translation of the processed gene results (see the figure). This procedure constitutes a versatile method for engineering user-defined gene regulation; in theory, any intracellular protein can be made to trigger an increase or decrease in the expression of any fused gene.

Culler *et al*. demonstrate the function of these systems in human cells with the use of introns containing aptamers for the proteins MS2, β-catenin, or nuclear factor κB (NF-κB), and present an example of combinatorial regulation in which the RNA devices sense two protein inputs. Then, they show that their devices can be used to synthetically rewire cellular behavior. In their proof-of-principle experiment, they link stimulation of the Wnt or NF-κB signaling pathways to the expression of a gene that confers sensitivity to the drug ganciclovir, which induces programmed cell death (apoptosis). This experiment demonstrates the modularity of their strategy and shows that endogenous cellular signaling pathways can be rerouted to guide cells to particular fates. This is an important goal for cell biology and cell-based therapy. It even raises the intriguing possibility of killing diseased cells by using gene therapy

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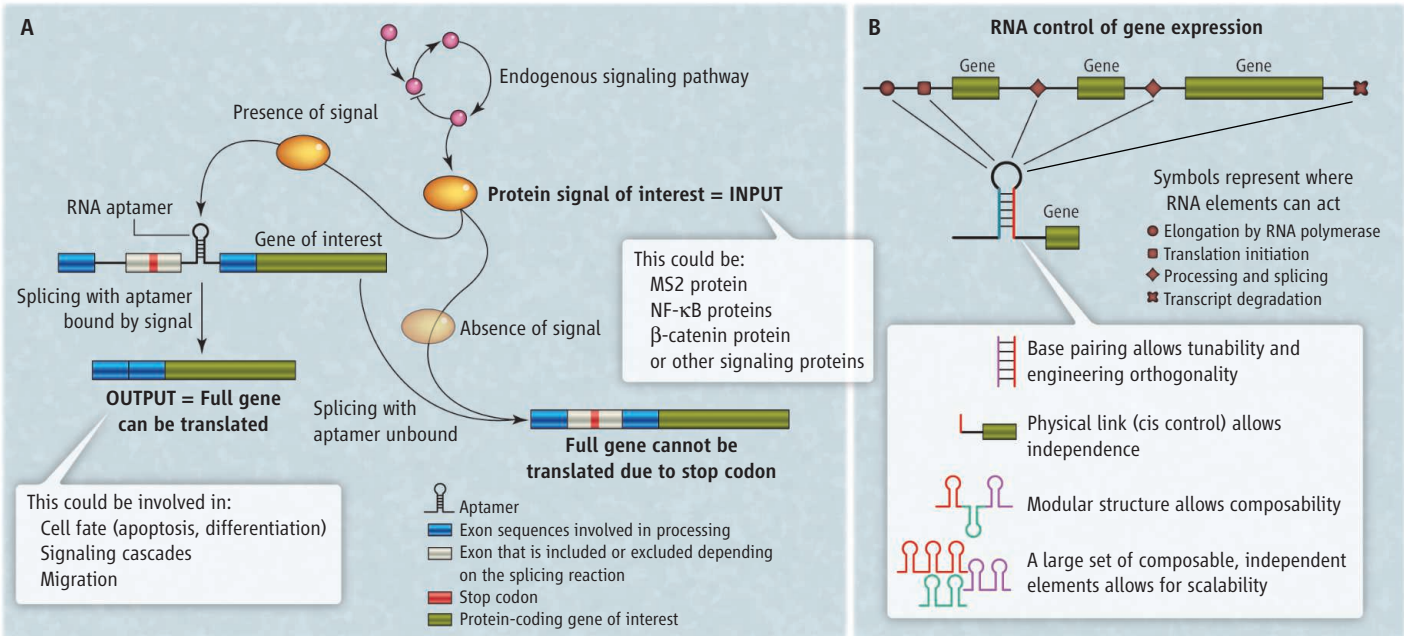


**Engineering RNA controls.** (**A**) Placing an RNA aptamer sensitive to a specific protein signal (orange) into an intron causes the transcript to splice differently in response to the signal. Adding a stop codon (red) within an exon (white) turns this splicing difference into a difference in the translation of the targeted gene (green). In this case, aptamer bound to signal allows full gene to be translated (left), but unbound aptamer prevents complete translation (right). (**B**) RNA elements exhibit a number of properties useful for engineering gene controls—including independence, tunability, orthogonality, composability, and scalability—and are involved in a number of key processes, including elongation, translation initiation, splicing, and degradation.

techniques to synthetically connect disease-associated pathways to apoptosis.

The strategy is not perfect. Because bioengineers do not completely understand the mechanisms underlying the system, combinatorial regulation does not yet produce predictable effects, and gene expression changes in response to the input signals are moderate (a factor of 2 to 4 in the best cases). New developments in analyzing RNA structures, however, should help researchers to overcome these difficulties and tap the great potential this strategy holds for rewiring cellular function.

As for the larger goal of creating a complete framework for the predictable design of gene regulation systems, the choice to engineer RNA is a good one. RNA elements—whether aptamer-based systems, synthetic riboswitches, antisense-mediated regulation, or combinations of these (*11*)—can satisfy the properties required for a complete gene regulation engineering platform. These properties, as defined by Lucks *et al*. (*12*), include independence, tunability, orthogonality, scalability, and composability. For example, RNA elements usually act in cis (on the same molecule), so their effect is physically constrained to the regulated gene(s). This feature gives RNA gene-regulatory elements a good chance of being independent of each other and of other cellular processes. RNA also folds into secondary structures predictably, according to base-pairing rules; hence, it is feasible to engineer variant or new structures and mechanisms either de novo or by manipulating RNA elements naturally involved in gene regulation. RNA parts should therefore be tunable for function at the desired levels. In addition, RNA's structural reliance on predictable base pairing gives bioengineers the ability to take a parent RNA part and systematically create sets of orthogonal variants, meaning that these variants function in a similar manner but do not "cross talk" or interact with each other. These sets can be designed to respond to different inputs, thus turning one RNA part into a family of interoperable parts.

RNA elements are also highly scalable. Powerful in vitro selection techniques can yield custom aptamers that bind to user-defined signals or ribozymes that perform user-defined functions (*13*). These selection techniques, combined with the fact that natural RNA elements are involved in all steps of gene regulation, translate into a huge number of detectable signals and a very wide variety of gene regulation output types that can be engineered. This scalable diversity has the potential to satisfy the demands of any desired synthetic gene-regulatory system. In addition, RNA folds into modular domains, which means that individual RNA parts can be assembled together to achieve combinatorial regulation and higher-order function. RNA parts are therefore composable, and if bioengineers are able to establish general conventions for connecting RNA elements together, they could quickly craft new regulatory units with complex but predictable functions. Finally, the rules for RNA folding are similar across different organisms, increasing the likelihood that systems engineered in one organism will be portable to another (*7*).

Together, these properties suggest that RNA elements may soon constitute a general and highly applicable platform for engineering gene regulation systems that satisfy the needs of cell-based biotechnology (*14*, *15*). Even if individual efforts fall short of this goal, bioengineers should be able to synthesize varying strategies into a unified framework that is more than the sum of its (RNA) parts.


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