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Spotlight

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EVEN A MONKEY CAN DO IT

The astounding advances in our understanding of early embryos, and our resulting ability to manipulate them, has led to the development of numerous chimeric animals, or those composed of two or more genetically distinct types of cells. While chimeric rodents, rabbits, sheep and cattle have all been produced, our limited access to primates and less established grasp of their stem cell biology has hindered development of chimeric monkeys, baboons, and the like. Now, Tachibana *et al.* (*Cell* 2012, *148*, 285−295) present the world's first three primate chimeras, a set of twin monkeys named Roku and Hex and a single monkey named Chimero.

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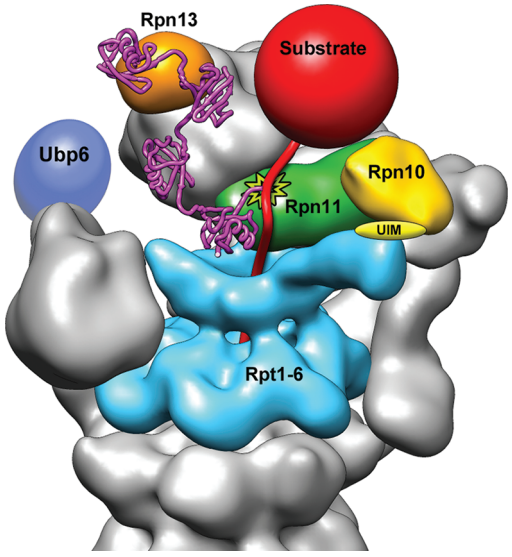
Early embryos contain totipotent cells, which are the precursors to every cell in the organism and even those that develop outside the organism, such as the placenta. Pluripotent cells are another type of embryonic stem cell that can also develop into every cell in the body but cannot make tissues like the placenta. Most strategies for creating chimeric mice successfully employ cultured pluripotent embryonic stem cells. However, when analogous strategies were attempted with Rhesus monkeys, no chimeric animals were produced. Instead, freshly isolated from embryos pluripotent cells formed whole animals when transplanted into a host embryo. Only when several genetically distinct, four-cell embryos, which contain only totipotent cells, were mixed together were chimeric monkeys produced. The authors propose that in monkeys, efforts to create animals using cultured pluripotent stem cells may fail because, unlike in mice, the cells may have already lost some of their pluripotent capabilities and thus no longer have all the mechanisms necessary create a new organism. This impressive study illuminates key differences between embryonic development in primates and other mammals, providing a path forward for the continued exploration of stem cell biology in higher mammals. These discoveries may also inform future efforts to develop embryonic stem cells for therapeutic purposes.

Eva J. Gordon, Ph.D.

PIECING TOGETHER PROTEIN DEGRADATION

Just as proper protein function is critical for fundamental biological processes such as cell growth and gene transcription, so is the ability to get rid of malfunctioning, misfolded, or transient proteins. The proteasome, a colossal protein dismantling machine, is the major cellular mechanism for eliminating proteins once they have been tagged with ubiquitin. This proteolytic behemoth is made up of no less than 32 subunits comprising a regulatory particle, where candidate proteins are recognized, deubiquitinated, and unfolded, and a barrel-shaped core, where protein degradation takes place. Though intensive investigations have revealed much about the proteolytic activities in the core, the structure and function of the regulatory particle is less well characterized. By recreating the subunits of the lid portion of the regulatory particle and using electron microscopy to obtain subnanometer structural information, Lander *et al.* (*Nature* advance online publication January 11, 2012; DOI: 10.1038/nature10774) report new insight into regulatory particle architecture. Identifying the location of all the subunits of the regulatory particle enabled creation of a spatial model for the recognition and degradation of ubiquitin-tagged substrates. For example, it was discovered that a deubiquitinating enzyme is strategically located near several ubiquitin receptors, right above the entrance to the core. In addition, it was observed that major conformational changes occur in the lid when it is bound to the other part of the regulatory particle, the base, suggesting that allosteric mechanisms may be at play to facilitate removal of ubiquitin. Also, it was found that the ATPase subunits of the regulatory particle are arranged in a spiral staircase-like fashion, presenting a potential mechanism for how substrates are transported from the regulatory particle to the core. While numerous questions remain, this exciting work takes our understanding of proteasome function to the next level.

Eva J. Gordon, Ph.D.



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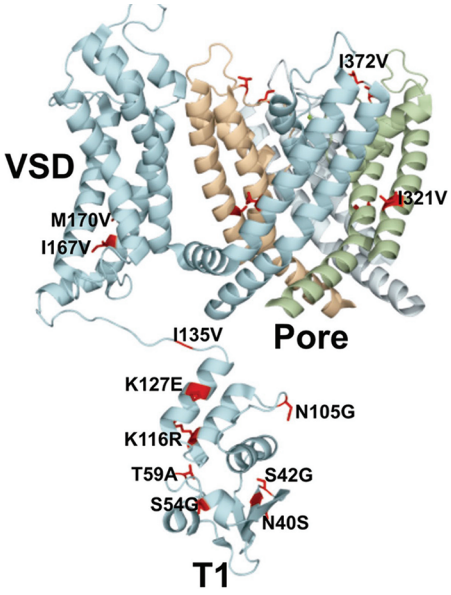
THE OCTOPUS INKS A NEW SCRIPT

In many eukaryotes, RNA editing machinery expands mRNA diversity by catalyzing selected base changes in a post-transcriptional fashion. One type, adenosine to inosine, or A-to-I, editing occurs by a deamination event of the base. In turn, the translational machinery recognizes the inosine base as if it was a guanosine, often resulting in a change in the encoded amino acid. The enzymes carrying out this recoding event in animals are known as ADARs, or Adenosine Deaminases Acting on RNAs. ADARs play an important role in the nervous system of worms, fruit flies, and mammals, where editing events are critical for generating diversity in transcripts involved in synaptic transmission and neural plasticity. As such, ADAR mutants can have profound cognitive or behavioral phenotypes. Now, this fascinating phenomenon meets an unexpected new variable, environmental temperature, in a nervous system deep in the ocean. Garrett and Rosenthal (*Science* advance online publication January 5, 2012; DOI: 10.1126/science.1212795) demonstrate that A-to-I editing plays an important role in tuning the potassium (K^+) channel excitation properties of both an Antarctic and tropical octopus species.



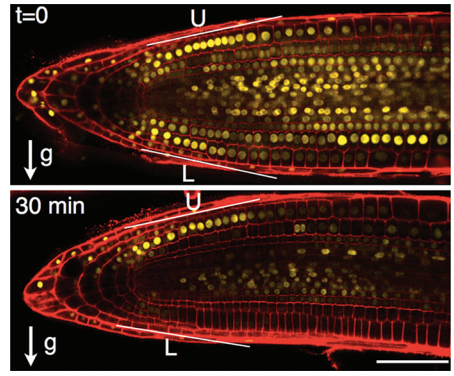
From Garrett, S. and Rosenthal, J. J., *Science*, January 5, 2012, DOI: 10.1126/science.1212795. Reprinted with permission from AAAS.

After sequencing the channel-encoding genomic regions of the two octopi and comparing to cloned mRNA transcripts, they discovered that delayed rectifier K^+ channel mRNAs are extensively edited with some of the dozen edits displaying strong bias toward one thermal environment dweller or the other. One mutation, I321V, was highly edited in the cold water Antarctic octopus and electrophysiology experiments demonstrated that this mutation has a strong effect in increasing the rate of channel closure. This allows the channel to abbreviate the refractory period between channel firings and probably helps to compensate for the handicap of cold temperature. With this curious finding in hand, the authors went on to sample the K^+ channel editing of 6 more octopi living in water temperatures spanning from −2 to +37 °C. They uncovered a very strong correlation between the water temperature and the I321V editing event. As the water temperature dropped, the extent of RNA editing increased. Since ADARs usually act on structured RNA, one new direction will be to study how temperature affects the folding of the mRNAs near the editing site.

Jason G. Underwood, Ph.D.

A BEACON FOR PLANT SIGNALING

Plant hormones known as auxins spur many processes in the development of plants and their response to their environment. Even though these molecules have been studies since the 19th century, researchers have not had accurate tools for monitoring the movement and signaling of these molecules within living plants. In one key step in auxin signaling, these aromatic carboxylic acids trigger the degradation of Aux/IAA repressor proteins. Therefore a fluorescently labeled Aux/IAA repressor provides one way to monitor the real-time effects of auxins within cells.



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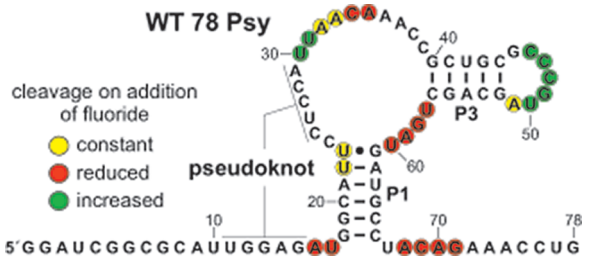
Because of the rapid turnover of the Aux/IAA repressor within plant cells, Brunoud *et al.* (*Nature* advance online publication January 15, 2012; DOI: 10.1038/nature10791, published online 15 Jan 2012) fused the sequence for a fast-coding yellow fluorescent protein, VENUS, in the sequence for several Aux/IAA repressors under the control of an endogenous promoter. Initially the researchers demonstrated that auxins dimmed the signal from the new fusion protein in a dose-dependent manner and similar to the proposed mechanism for the natural protein. Studying roots of the *Arabidopsis* plant that carried this modified fluorescent protein, the researchers demonstrated dimmed fluorescence in response to treatment with the most common auxin hormone, indole-3-acetic acid (IAA). As a result researchers could follow auxin signaling within the structure of the root, shoots, and flowering structures. They also used the fusion protein to examine signaling in a developmental process, a root bending in response to gravity. As auxins assembled on the lower side of the root tip, the fluorescence from the VENUS-labeled protein faded. The results offer a high resolution method for following auxin signaling and a basis for the design of fluorescent sensors for other plant hormones that regulate development.

Sarah A. Webb, Ph.D.

SENSING FLUORIDE

Riboswitches are cis-acting RNA sequences that directly bind a small molecule and affect gene expression. In this manner, the

riboswitch-containing RNA can regulate itself in response to the concentration of a small ligand. Each class of riboswitch possesses a conserved sequence and structure that facilitates specific binding of the cognate signal. Now, Baker *et al.* (*Science*, 2012, *335*, 233−235) report the discovery of a novel riboswitch class present in bacterial and archaeal species that specifically binds fluoride.



From Baker *et al.*, *Science*, 2012, *335*, 233. Reprinted with permission from AAAS.

Fluorine is among the more abundant elements present on Earth and is a potent inhibitor of bacterial growth. As a result this element is commonly used in toothpastes and other oral hygiene-related products. The authors identified a noncoding RNA structure that carried a *crcB* motif that specifically bound fluoride. This observation provides a breakthrough in answering a long-standing question of how microorganisms cope with toxic fluoride. The authors used a 78-nucleotide RNA from *Pseudomonas syringae* that included the *crcB* motif and demonstrated it has specific affinity (K_D ~60 μM) for free fluoride while rejecting other halogen anions. Follow up experiments provided evidence that these riboswitches reduce fluoride toxicity by activating expression of a putative fluoride transporter, CrcB. The wide distribution of these fluoride sensors among bacteria and archaea suggest the means by which these organisms mitigate the toxic effects of fluoride.

Jitesh A. Soares, Ph.D.

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