Synopses of Research Articles

Quiet Time: Gene Program Prevents Division but Keeps Cells at the Ready

Richard Robinson | DOI: 10.1371/journal.pbio.0040085

Because uncontrolled cell division is so dangerous for an organism, the well-behaved cell must know not only when to divide, but also—crucially—when not to. Shutting down cell division prevents tumors and maintains the proper form of tissues such as muscle. Many cells, though, including fibroblasts, must also retain the ability to start dividing again when conditions are right—when the organism must grow, or a damaged tissue must be repaired. A cell in such a temporary, nondividing state is said to be “quiescent.” Signals that send a cell into quiescence include loss of contact with the underlying surface, too much contact with neighboring cells, and not receiving specific growth factors from the surroundings.

Despite its importance, little is known about the quiescent state. In a new study, Hilary Coller, Liyun Sang, and James Roberts define the genetic underpinnings of quiescence, showing that it is actively maintained by a host of genes. Different signals induce genetically different quiescence states, but all share a core set of genes that define a “quiescence program.” They also show that these genes changes distinguish quiescent from irreversible nondividing states, such as the terminal differentiation of a mature muscle.

The authors began by treating fibroblasts with one of the three quiescence signals, and used DNA microarrays to identify genes whose expression increased or decreased as a result of the treatment. Fourteen hours after treatment, the three signals had induced three distinct gene profiles, with only a handful of overlapping genes. The common genes included several powerful transcription factors, each of which regulate multiple other genes. Over time, however, the number of overlapping genes increased. After 20 days, there were over 100 genes whose change in expression linked them to quiescence. These included not only those that regulate metabolism and cell division, as might be expected, but also genes that suppress the transition to two other cell fates—differentiation and programmed death. The expression of these genes (along with many others) was increased, indicating the active nature of the quiescent state.

The reversibility of quiescence contrasts with the cell cycle arrest induced by inhibition of cyclin-dependent kinase (CDK), a key regulatory protein. When the authors treated fibroblasts with a CDK inhibitor, division stopped, but the quiescence program was not activated, and the cells could be induced to irreversibly transform into muscle precursor cells by treatment with the differentiation signal, MyoD. Quiescent cells, on the other hand, were resistant to MyoD-induced differentiation, in keeping with the reversible nature of quiescence.

The identification of different quiescent states, induced by the three different signals, may lead to a better understanding of context-specific control of cell growth during development and repair, not only in muscle, but perhaps in other tissues as well. Identification of specific genes that enforce quiescence may also lead to better strategies for controlling cell division, including the unchecked division of cancer.

Coller HA, Sang L, Roberts JM (2006) A new description of cellular quiescence. DOI: 10.1371/journal.pbio.0040083

Marsupial Genome Sheds Light on the Evolution of Immunity

Emma Hill | DOI: 10.1371/journal.pbio.0040075

All organisms need defense systems to ward off infection. These defenses typically mobilize in response to antigens, bits of protein fragments derived from a pathogen. Vertebrates have a superbly efficient system of adaptive immunity that uses proteins to recognize and bind billions of different antigens via a process known as antigen presentation. Ultimately, this process leads to removal of the antigen. Antigen binding proteins are encoded within one large genomic region known as the major histocompatibility complex (MHC). The high level of polymorphism, or variation, in this genomic region allows the adaptive immune system to keep pace with an ever-changing array of antigens.

Genes in the MHC region are subdivided into Class I, Class II, and Class III based on their structure and function. The organization of MHC genes in present-day species can provide insight into how immunity has evolved. To date, maps of the MHC are available from eutherian (placental) mammals and nonmammalian species, including birds, bony fish, and cartilaginous fish such as sharks. But MHC organization and complexity differ substantially between which regulate multiple other genes. Over time, however, the number of overlapping genes increased. After 20 days, there were over 100 genes whose change in expression linked them to quiescence. These included not only those that regulate metabolism and cell division, as might be expected, but also genes that suppress the transition to two other cell fates—differentiation and programmed death. The expression of these genes (along with many others) was increased, indicating the active nature of the quiescent state.

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mammals and nonmammals, making it difficult to infer the region’s evolutionary history, or phylogeny.

Using available marsupial opossum (Monodelphis domestica) genome sequences, Katherine Belov, Robert Miller, and their colleagues present a detailed map of the opossum MHC. These data from a noneutherian mammal help bridge the gap between nonmammals and eutherian mammals, to enable a more comprehensive phylogeny of the MHC.

In eutherian mammals, the MHC is large and dense, with 264 genes and pseudogenes (remnants of once functional genes) scattered over 3.6 Mb and ordered as Class I–III–II in adjacent gene blocks in humans. In nonmammals, the MHC has fewer genes (the chicken has only 19 genes over 92 kb) ordered as Class III–I–II. The authors found that the MHC in the opossum is flanked at either end by the same marker genes that border the human MHC. This noneutherian mammalian MHC spans 3.95 Mb and encodes 114 genes (identified via sequence similarity to genes from other species), sharing 87 with the human MHC. The authors have provided a Web-based genome browser (http://bioinf.wehi.edu.au/opossum) for viewing an annotated map of the opossum MHC region.

Belov et al. found that while the size and complexity of the opossum MHC is closer to eutherian mammals, its organization is closer to fish and birds: in the opossum, Class I genes are interspersed with the Class II genes—this has not been seen in any other animals. This similar grouping of Class I and II genes implies that they may have been arranged this way in the mammalian ancestor (supported also by the presence of the Class I pseudogenes in the human Class II region).

Humans and mice have a conserved framework region, consisting of a set of genes that are interspersed among the Class I loci. The opossum also contains these genes next to the Class III region. The authors deduced that this framework region assembled in the ancestral mammalian MHC before Class I genes moved to this location in eutherians.

Only one of the opossum MHC genes, UA1, has the characteristics of what’s known as a classical Class I gene—high polymorphism and ubiquitous expression. The authors saw transcripts of this gene in all tissues tested. Expression of a single classical Class I gene is unusual in mammals but has been seen in the chicken and the frog. Contrary to a previous hypothesis that Class I gene evolution is constrained by their proximity to antigen processing genes, the Class I genes in the opossum are significantly diverged.

The authors identified three marsupial-specific classical Class II gene families (DA, DB, and a newly discovered family designated DC). They also found that sequences responsible for regulating Class I genes—SXY motifs—known to be important in the eutherian MHC, have diverged in the opossum. Conversely, the Class II SXY regions are quite well conserved. This is logical given that Class I genes are more likely to evolve new functions while Class II genes are typically coexpressed.

Significantly, the authors also found data supporting the idea that there was an ancient relationship between the MHC and another critical component of the immune system, the natural killer complex (NKC), which contains natural killer (NK) cell receptor loci. Two NKC genes, OSCAR and MIC, are present in the opossum MHC. As MHC Class I molecules are ligands (activators) for NK cell receptors, it makes sense that these two gene families coevolve.

The authors conclude that vertebrates once possessed an “immune supercomplex” that performed the MHC functions. While this complex no longer exists in modern genomes, scientists can probe its remnant traces for clues to its history. Gaining a better understanding of how our mammalian immunity evolved will lead to a much broader appreciation of how organisms’ internal defense systems work across a wide range of species.

Belov K, Deakin JE, Papenfuss AT, Baker ML, Melman SD, et al. (2006) Reconstructing an ancestral mammalian immune supercomplex from a marsupial major histocompatibility complex. DOI: 10.1371/journal.pbio.0040046

Reading the Evolutionary History of the Woolly Mammoth in Its Mitochondrial Genome

Liza Gross | DOI: 10.1371/journal.pbio.0040074

The woolly mammoth (Mammuthus primigenius) disappeared along with the last ice age over 10,000 years ago, yet scientists can glean insight into its evolutionary history by studying its frozen remains. Three recent independent studies applied different methods to isolate and sequence multiple DNA fragments from mammoth specimens. Two teams, reporting in December 2005, used mammoth bones extricated from the frozen permafrost of Siberia. One team, reporting in Nature, analyzed the mitochondrial DNA (mtDNA)—genetic material found in the cell’s energy-producing organelles and transmitted only through the mother—of a 12,000-year-old specimen and concluded that the mammoth’s closest living relative is the Asian elephant. The other team, reporting in Science, analyzed a portion of nuclear and mitochondrial DNA from a 28,000-year-old specimen, using a new method that increases the quantity of DNA fragments that can be extracted and sequenced from ancient specimens.

Ancient DNA studies have traditionally focused on mtDNA, but these investigations have relied on mostly short fragments of mtDNA. In the third and most recent study, Evgeny Rogaev, Yuri Moliaka, and their Russian colleagues sequenced the complete mitochondrial genome of a 33,000-year-old mammoth specimen. (Radiocarbon dating indicated that the mammoth lived 32,850 years ago, plus or minus 900 years.) This is the oldest sequenced mitochondrial genome and—at 16,842 base pairs—the longest stretch of sequenced DNA from an extinct Pleistocene species. This analysis, like the Nature study, points to the Asian elephant as the mammoth’s closest relative. Interestingly, the Rogaev et al. study also suggests that genetic diversity among mammoths living in northeastern Siberia during the late Pleistocene was low.

Having complete mitochondrial mammoth genomes will greatly aid...
The restored right back leg of a 33,000-year-old woolly mammoth found in northeastern Siberia.

...and African (Loxodonta Africana) cousins, the authors also sequenced the complete mtDNA genomes of the two modern elephants from Africa and Asia. Rogaev et al. used the mammoth and elephant genomes, along with previously published mtDNA Asian and African elephant genomes, to construct an elephant evolutionary tree. They used two other placental mammals, the dugong and hyrax, to calibrate the tree, and show that the mammoth and Asian elephant are more closely related to each other than either is to the African elephant. Additional analysis using nuclear DNA and more closely related mammals could help refine the tree.

The authors also compared their sequence with other available mammoth sequences (including the recently published Nature sequence) representing populations from different locations and time periods. This analysis revealed the relatively low genetic diversity in the maternal lineage of mammoths in northeastern Siberia through the roughly 20,000-year period of the late Pleistocene. The population structure of mammoths living at that time appears less complex than that seen in the genomes of Asian and African elephants.

The mammoth and Asian elephant may have diverged around 4 million years ago, splitting soon after their lineage diverged from the African elephant. The authors point out that, given the inherent differences in mutation rates and mode of inheritance between nuclear and mitochondrial DNA, studies focusing on one or the other may produce different dates for the last common ancestor.

But these results, together with the Nature and Science studies, demonstrate the tractability of recovering large amounts of high-quality DNA from ancient extinct Pleistocene animals. Rogaev et al. found that relatively large, nondegraded DNA fragments may be extracted from animals preserved in the permafrost for many thousands of years, allowing complete genes (at least from mitochondrial genome) of extinct animals to be cloned. As scientists continue to mine the DNA-rich permafrost, they will be able to weave together the missing pieces of the evolutionary story of a long-lost, fabled creature and its modern relatives, sequence by sequence. To learn more about ancient DNA research, see the related primer (10.1371/journal.pbio.0040078).

Rogaev EI, Molika YK, Malarchuk BA, Kondrashov FA, Derenko MV, et al. (2006) Complete mitochondrial genome and phylogeny of Pleistocene mammoth Mammuthus primigenius. DOI: 10.1371/journal.pbio.0040073

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Jumping for Dear Life with a Giant Neuron and a Single Receptor

Françoise Chanut | DOI: 10.1371/journal.pbio.0040093

Flies are jumpy, prone to buzzing away at the slightest moving shadow or breeze. This reflexive “jump response” is a lifesaver for the tiny insects, whose only defense against predators is a quick escape. In flies, as in many animals, evolution has forged efficient reflex circuits that transmit nerve impulses from sensory organs to muscles within milliseconds.

The centerpiece of the fly’s jump response circuit is the giant fiber. The large cell body of this prominent nerve cell resides in the brain and its axon extends into the fly’s thorax. There, it connects with motor neurons that innervate the jump muscles in the leg and the flight muscles that power the wings. In the brain, the giant fiber receives visual inputs, caused by moving shadows, from the eyes while mechanical inputs, caused by wind or vibrations, come from the antennae. Neurons communicate via specialized contact points called synapses, where they exchange electrical or chemical signals. The small molecule acetylcholine is a widespread chemical neurotransmitter in the fly brain that could mediate various steps in the jump response. Acetylcholine binds to a large variety of transmembrane receptors. In a new study, Amir Fayyazuddin and Hugo Bellen find that a membrane...
protein belonging to the nicotinic class of acetylcholine receptors, Dα7, is required within the giant fiber to link the jump response to sensory inputs.

Acetylcholine receptors clump together at neuron synapses, forming pores that open in the presence of extracellular acetylcholine. When a synapse fills with acetylcholine, the pores of the receiving neuron open and let in positively charged ions. A massive electrical impulse ensues that elicits signal release at the next synapse downstream. Fayyazuddin and his colleagues used a small piece of mobile DNA that had inserted next to the Dα7 gene in the fly genome to generate several fly strains devoid of part or most of their Dα7 gene. In the laboratory, scientists elicit the jump response in captive flies by simply turning off the light briefly. Normal flies jump while mutant flies stay put. The Dα7 mutants failed to jump in response to the light-off signal, even though additional tests showed they had normal vision and locomotion.

In immobilized and partially dissected flies, scientists can fire up the giant fiber with an electrical stimulus and follow the nerve impulse all the way from giant fiber to twitching jump and flight muscles. Fayyazuddin and his colleagues found that in Dα7 mutants, the flight muscles failed to respond to stimulation by the giant fiber. This result was not unexpected, as earlier observations had shown that a particular neuron that connects the giant fiber to flight muscles uses acetylcholine as its messenger. By contrast, in this assay, the jump muscle behaved normally in Dα7 mutants. This was surprising, because jump precedes flight in the escape response, and the Dα7 mutants have a clear jump deficit.

The researchers reasoned that the Dα7 mutations silenced synapses farther upstream in the circuit. The Dα7 protein is abundant at brain synapses between the giant fiber and neurons that relay sensory inputs from the eyes and antennae. Acetylcholine is also found at these synapses, though its function has been unclear. Introducing an active Dα7 gene in the giant fiber of mutant flies was sufficient to restore activation of the giant fiber. This result demonstrates that the giant fiber uses its Dα7 receptor (and acetylcholine) to trigger the jump reflex in response to sensory inputs.

Nicotinic acetylcholine receptors are notoriously difficult to study, because various family members can substitute for each other and attenuate the consequences of the loss of a single representative. It is therefore remarkable that disrupting the Dα7 gene of Drosophila could have such a profound effect, especially on a behavior as vital as escape. The fly’s Dα7 receptor may have evolved special properties that enhance the effectiveness of the escape reflex, properties that now warrant further investigations.

Fayyazuddin A, Zaheer MA, Hiesinger PR, Bellen HJ (2006) The nicotinic acetylcholine receptor Dα7 is required for an escape behavior in Drosophila. DOI: 10.1371/journal.pbio.0040063

A Key Tumor Suppressor Protein Ensures Proper Chromosome Segregation during Cell Division

Mary Hoff | DOI: 10.1371/journal.pbio.0040065

Cell division in animals is an exquisitely exact process. Before a cell splits, it has one set of chromosomes and one centrosome, a structure just outside the nucleus that plays an important part in the process. The chromosomes replicate, the centrosome duplicates, and the resulting two centrosomes migrate to opposite sides of the nucleus. Each centrosome then sends out threads that grab onto and reel in one of the two sets of chromosomes. The result: two identical “teams” that go on to make up the nuclei of the two daughter cells.

Or that’s the ideal, anyway. Sometimes when cells divide they make more than two centrosomes. And sometimes cells with more than two centrosomes have daughter cells with more or fewer than the normal allotment of chromosomes. Scientists have suspected for a century that the two phenomena—“supernumerary” centrosomes and the wrong number of chromosomes, called “aneuploidy,” a common feature of cancer and premalignant cells—are causally linked. But, like the proverbial chicken and egg, it hasn’t been clear which comes first. Do extra centrosomes sometimes cause aneuploidy? Or does aneuploidy create changes that make cells go overboard when duplicating centrosomes? The answer could help shed valuable light on the process that turns normal cells malignant.

Kimberly McDermott, Thea Tlsty, and colleagues explored these questions in a series of experiments reported in a new study. Using laboratory techniques that allowed them to observe the number and distribution of chromosomes and centrosomes at various stages of cell division, the researchers showed that the production of supernumerary centrosomes can in some cases lead to aneuploidy. They also unraveled the process by which supernumerary centrosomes develop, and showed that when supernumerary centrosomes are present, cell division produces lopsided teams of chromosomes that aren’t able to play by the rules of normal cells.

To accomplish all this, the researchers focused their attention on human mammary epithelial cells (HMECs). Most HMECs can only be grown in culture for a limited amount of time, after which they stop dividing; however, a subpopulation of these cells, called vHMECs (for “variant” HMECs), can divide for longer—but eventually end up with chromosome abnormalities, including aneuploidy. The researchers discovered that if they temporarily paused
chromosome replication with a reversible chemical treatment in vHMECs, some cells ended up with extra centrosomes—as though the original two centrosomes had not gotten the message that things were on hold, and duplicated again while the chromosomes sat. Knowing from other studies that a protein called p16INK4a (which normally plays a role in suppressing tumor formation) is silenced in vHMECs, they tested its possible role in the generation of extra centrosomes by blocking its expression in HMECs. As they predicted, some of the HMECs in which p16INK4a was blocked developed supernumerary centrosomes. And when they altered vHMECs to make them express p16INK4a, the tendency to produce supernumerary centrosomes was reduced.

How does the absence of p16INK4a lead to too many centrosomes? A normal centrosome contains two assemblages of microtubules, called a centriole pair, that split up and make new centriole partners when a cell divides. Looking closely at the supernumerary centrosomes, the researchers discovered a significant portion with only one centriole. This, along with the fact that cells rarely end up with more than four centrosomes, led them to speculate that p16INK4a acts as a sort of centriole pair “policeman”—when it’s around, the centriole pair splits once as it is supposed to, but if it’s disabled, the centriole pairs can split more than once to generate supernumerary centrosomes.

To clearly link production of supernumerary centrosomes resulting from loss of p16INK4a activity to aneuploidy, the researchers looked at cell division in vHMECs and in HMECs with and without blocked p16INK4a. They found that pausing replication was associated with increases in supernumerary centrosomes and aneuploidy in vHMECs and in HMECs with blocked p16INK4a, but not in normal HMECs. To prove a causal connection, they observed cell division using time-lapse microscopy. They found that vHMECs with more than two centrosomes were more likely to produce aneuploid daughter cells than were vHMECs with two centrosomes.

The researchers tested other cell types and discovered that loss of p16INK4a activity produces supernumerary centrosomes and aneuploidy in them as well. And, using human fibroblasts, they showed that p16INK4a prevents inappropriate centriole pair splitting by working with a gene called p21 that inhibits the activity of Cdk, a type of protein needed for centrosome duplication.

Cells with inactive p16INK4a are found in normal human breast tissue. This study suggests that if DNA replication gets held up—which it can if DNA needs repair due to exposure to chemotherapy—such cells would produce supernumerary centrosomes. These supernumerary centrosomes could lead to aneuploidy, loss or gain of genes regulating cell division and death, and may result in the beginning stages of a tumor.

McDermott KM, Zhang J, Holst CR, Kozakiewicz BK, Singla V, et al. (2006) p16INK4a prevents centrosome dysfunction and genomic instability in primary cells. DOI: 10.1371/journal.pbio.0040051

When Less Is More: Losing Genes on the Path to Becoming Human

Liza Gross | DOI: 10.1371/journal.pbio.0040076

Students of human evolution got a big boost when the draft sequence of the chimp genome was published in 2005. Now their challenge is to comb through the combined 6 billion nucleotides for clues to the evolutionary forces that made humans odd man out in the primate family tree. Chimp and human DNA nucleotides differ by just 1.23%, sufficient genetic variation for natural selection to create a bipedal, big-brained primate lineage but small enough to suggest that every mutation has an evolutionary tale to tell.

Natural selection, it’s typically thought, mostly favors “gain of function” mutations, which increase an organism’s fitness while jettisoning “loss of function” mutations, which are considered deleterious. An alternative hypothesis proposes that gene loss—which can occur when mutations render functional genes inactive in a process called pseudogenization—can also confer selective advantage and promote evolutionary change.

In a new comparative analysis of the human and chimp genomes, Xiaoxia Wang, Wendy Grus, and Jianzhi Zhang find support for this “less is more” hypothesis. They analyzed 80 human pseudogenes—many involved in immunity and chemoreception—and show that positive selection explains how

Analyzing “pseudogenes” that lost their functionality since humans and chimps diverged over 6 million years ago promises to shed light on the genetic basis of human origins. (Photo: Curt Busse, Gombe National Park, Tanzania)
one pseudogene spread throughout human populations. Humans with the CASP12 pseudogene, which retains its immune function in other mammals, are less susceptible to severe sepsis. Several cases of gene loss have been proposed as adaptive opportunities for human evolution. To look for potentially momentous gene losses, Wang et al. turned to a human pseudogene database. Most of the 19,000 human pseudogenes in the database are “processed” pseudogenes, which derive from reverse-transcribed RNA that was reinserted into the genome, usually without the regulatory elements necessary for gene activation. Most processed pseudogenes never functioned. And nearly half of the 1,781 “nonprocessed” pseudogenes lack the mutations that would make them clearly nonfunctional. So the authors focused on the 887 “nonprocessed” pseudogenes that had the requisite loss-of-function mutations.

Comparing these human pseudogenes with the chimp genome flagged 83 sequences as closest matches—assumed to be chimp orthologs (derived from an ancestral gene during speciation). After ascertaining that the human pseudogenes have chimp orthologs and are truly nonprocessed pseudogenes, the authors whittled their list down to 67.

Most of the 80 pseudogenes studied (including 13 found in previous studies) play a role in immune response or chemoreception and belong to rapidly evolving gene families with species-specific members. Interestingly, mice lacking one of the pseudogenes, MblI, show higher resistance to sepsis and increased survival. Though this pseudogene likely spread through the human population too long ago to detect signs of selection (about 6–7 million years ago), the authors reasoned that if mice gained an advantage from losing an immunity gene, humans might, too.

To test this possibility, they focused on another sepsis-related pseudogene, CASPASE12 (CASP12) that is still undergoing pseudogenization. In the nonfunctional (null) allele, a mutation replaces a C with a T nucleotide (called a C/T polymorphism), producing truncated, nonfunctional CASP12 proteins. The null T allele is linked to sepsis resistance in humans. All non-Africans (that is, individuals of Asian or European descent) carry two copies of the T allele, which occurs with 89% frequency in individuals of African descent. The authors used population genetic techniques to test whether positive selection drove the high frequency of the T allele. If it did, sequences surrounding the T allele should have lower variation than those flanking the C allele. And that’s just what the authors found. While the T allele existed at a much higher frequency than the C allele in the sampled populations, it had far fewer polymorphisms across nine noncoding regions adjacent to the C/T polymorphism. Wang et al. modeled different demographic scenarios and mutation rate estimates using the polymorphism data to explain the source of the observed low diversity. Their simulation results “strongly suggest” that positive selection drove the spread of the T allele. Since non-Africans and Africans carry identical T alleles, the null mutations likely share a common ancestor, originating sometime before modern humans left Africa 40,000–60,000 years ago. Assuming that selection acted on the variant as soon as it appeared, the allele would need about 51,000–55,000 years to reach its current frequency, suggesting that the adaptive pseudogenization started shortly before the African emigration.

These findings show that gene loss provides not just the opportunities but the means for selection to act. Since pseudogenization in vertebrate and other eukaryotic genomes is common, the authors speculate that adaptive gene loss may be as well. As the chimp genome sequence becomes more refined, researchers will have fresh opportunities to explore how gene loss shaped the unique traits that define human biology—and formulate new hypotheses to test the breadth of a “less is more” strategy in evolutionary change.

Wang X, Grus WE, Zhang J (2006) Gene losses during human origins. DOI: 10.1371/journal.pbio.0040052
confronted with a set of independent, noisy responses, the visual system tends to base its decision on the largest response. Since each stimulus generates a noisy internal representation, and subjects monitor all the distracters to search for the target, as the number of distracters increases, the chance of perceiving a distracter as being more tilted than the target also increases. The authors predicted that the rule also applies to the confidence observers have in such “high magnitude” perceptual errors.

To test this prediction, the authors asked ten observers to indicate the direction and magnitude of the tilt of a target grating patch (small patches of blurred parallel black and white lines) tilted clockwise or counterclockwise. The target was briefly presented either alone or embedded in a circular array of vertical distracter patches. Though perceived magnitude is known to reflect observer confidence, the authors also got a direct measure by asking observers to report their level of confidence about each decision. Adding magnitude to the tilt discrimination task, the authors explain, helps shed light on the internal mechanisms that drive observers’ decisions. As predicted by the Signed Max Model, estimates of perceived tilt increased with set size, as did the observers’ confidence in their decisions. The authors conclude the visual system combines the outputs of noisy detectors and settles on the maximum signal.

These results suggest that the probability of being sure you saw something you didn’t increases in chaotic environments, and could have far-reaching implications. The authors explain that while their study focused on “simple perceptual decisions about a single stimulus attribute,” the same type of processes may also apply to complex cognitive tasks involving problem solving and memory. If people find themselves confronted with multiple events in a chaotic, confusing environment, they may decide about some aspect of the situation and be totally wrong even though they have full confidence in their decision. The consequences of such a phenomenon could be relatively trivial, explaining why professional athletes often end up wasting their time arguing questionable calls with an official. Or they could prove a matter of life and death, perhaps accounting for why eyewitness testimony is so unreliable—or why soldiers sometimes can’t tell friend from foe in the heat of battle.

Baldassi S, Megna N, Burr DC (2006) Visual clutter causes high-magnitude errors. DOI: 10.1371/journal.pbio.0040056

The probability of being sure you saw something you didn’t increases in chaotic environments like this 2003 peace rally near the Campidoglio in Rome. (Image: Stefano Baldassi)
retina, leading to retinal degeneration (in humans, retinal degeneration is a prominent part of the disease). In this study, they examined the cell architecture of the degenerating rod cells, and found that the nucleus was highly swollen due to dramatically increased “decondensation” of the chromatin, or nuclear material.

Decondensation occurs when histones, which help package DNA in the nucleus, are chemically modified by acetylation (adding a two-carbon acetyl group). Acetylation opens up the chromatin, allowing the gene-transcribing machinery to gain access to genes within. Rod cell degeneration was directly correlated with the degree of decondensation, suggesting that aberrant decondensation might be the primary event leading to cell death.

Decondensation usually leads to increased gene transcription, but the authors found instead that transcription of rod-specific genes was decreased, in many cases by 90% or more. This was due to any inability of the mutant protein to become incorporated into its two transcriptional coactivator complexes, which appeared to be unchanged. Instead, the authors show that these complexes worked too well, hyperacetylating their rod-specific target genes, accounting for the increased decondensation they observed. But this hyperacetylation comes at a price—the disruption of the normal chromatin architecture of the mature rod nucleus.

The authors suggest that this disruption is the likely explanation for the loss of rod-specific gene transcription. A growing body of research has shown that within the nucleus, the arrangement of chromatin is not random, but is correlated to cell type. Some evidence suggests that highly expressed genes are preferentially located at the nuclear envelope, where they may have better access to the raw materials that sustain rapid transcription. The loss of this structure in the SCA7 mouse retina may prevent the very high levels of transcription of rod-specific genes needed to maintain normal rod function.

This is not likely to be the last word on disease mechanisms in the polyglutamine diseases, a field full of strong and competing hypotheses of pathogenesis. It does, though, highlight the importance of understanding the role of the normal protein, and strengthens the case for altered nuclear architecture as a key event in neurodegeneration.

Helmlinger D, Hardy S, Abou-Sleymane G, Eberlin A, Bowman AB, et al. (2006) Glutamine-expanded ataxin-7 alters TFIIA/STAGA recruitment and chromatin structure leading to photoreceptor dysfunction. DOI: 10.1371/journal.pbio.0040067

Switching Drugs for Livestock May Help Save Critically Endangered Asian Vultures

Liza Gross | DOI: 10.1371/journal.pbio.0040061

In just ten years, tens of millions of vultures have vanished from the Indian subcontinent. Since the early 1990s, white-backed (Gyps bengalensis), long-billed (G. indicus), and slender-billed (G. tenuirostris) vulture populations have dropped by over 95%. In Europe, it was clear that human persecution eradicated bearded and griffon vultures from some countries (reintroduction and protection efforts are now restoring populations). But in India, where it is illegal to kill wildlife and the bird is valued for its ecological role, their unprecedented decline was puzzling. Dead birds found in India, Pakistan, and Nepal had extensive visceral gout (a buildup of uric acid crystals in the internal organs associated with renal failure). The birds often appeared sick and lethargic, some showed prolonged severe neck drooping, before collapsing—sometimes from their perches.

Intensive testing failed to implicate infectious disease, pesticide poisoning, starvation, and other possible causes. Then, finally, in 2004 a team of scientists from the United States–based Peregrine Fund made a breakthrough. In the mid-1990s, livestock farmers in India began treating their cattle and water buffaloes with the nonsteroidal anti-inflammatory drug (NSAID) diclofenac—a known kidney toxin in mammals. Vultures, it turned out, were highly sensitive to the drug, which they ingested while feeding at carcass dumps, the traditional method of livestock disposal in South Asia. Diclofenac later came into widespread use in Pakistan and Nepal. A subsequent concentrated research effort demonstrated that diclofenac use was on a sufficient scale to fully account for the declines. As a consequence, the Indian government announced its intention to ban veterinary use of the drug in March, but progress has been frustrated in part by the lack of a safe yet effective alternative. In a new study, toxicologist Gerry Swan and a team of colleagues from South Africa, Namibia, India, and the United Kingdom show that they have found that alternative.

The consequences of the vulture collapse have already reverberated across the subcontinent. Americans and Europeans once persecuted vultures, thinking they transmitted disease, but vultures help control brucellosis, anthrax, and other livestock diseases by consuming infected carcasses. In their absence, feral dog populations have exploded, likely increasing the risk of human attacks and the spread of rabies. If rats follow suit, bubonic plague and other rodent-transmitted diseases may also increase. And because these scavengers can’t match vultures’ efficiency as flesh-eaters, many carcasses—including human—lay rotting. In sky burials, Zoroastrian Parsis (and Tibetans, in a slightly different ritual) leave their dead on platforms for vultures to devour, to avoid defiling earth, water, or fire with an unholy corpse. Where corpses once attracted 300 vultures—which could pick a body clean in half an hour—today so few remain that many Parsis must find new ways to send off their dead.
Imagine a race of people with tiny torsos, arms, and legs, but gigantic fingers, lips, and tongues. That’s what we would look like if each of our body parts were sized proportionally to the brain area that processes their sensory inputs. Each of our body parts is represented in the somatosensory cortex on a map (called the somatotopic map), which expands the representation of the more sensitive body parts. Sensory inputs travel from touch receptors in the skin to neurons in the appropriate sectors of the somatosensory cortex.

As much as neuroscientists know about these neural projections for touch, surprisingly little is understood about the neural correlates of conscious tactile perception. In a new study, Felix Blankenburg, Jon Driver, and their colleagues turn to a classic somatosensory illusion—called the cutaneous rabbit—that is perfectly suited to decoupling real and illusory touch. In the illusion, a rapid succession of taps is delivered first to the wrist and then to the elbow, which creates the sensation of intervening taps hopping up the arm (hence the illusion’s name), even when no physical stimulus is applied at intervening sites on the arm.

Blankenburg et al. took advantage of this somatosensory illusion to investigate which brain regions play a role in illusory tactile perceptions. Previous studies had implicated the somatosensory cortex in the rabbit illusion, but did not directly test this possibility. To do this, the authors used state-of-the-art functional magnetic resonance imaging technology (called 3T fMRI) to scan the brains of people experiencing the illusion. With the enhanced image quality and resolution phase, the dose just exceeded the estimated maximum likely exposure for wild vultures.

Though the difference in mortality risk between meloxicam and diclofenac was statistically significant—all vultures in Phases I–III survived meloxicam treatment while both G. africanus vultures treated with diclofenac in a previous study died—the small sample size can’t preclude all risk. But strong corroborating evidence of safety comes from comparing blood samples of treated and control birds from both studies: diclofenac-treated vultures had a marked and dose-dependent elevation of uric acid levels compared to controls; meloxicam-treated vultures showed no such differences.

The authors next expanded the number of birds receiving the highest dose of meloxicam, treating 11 captive and 21 wild G. africanus vultures (plus captive and wild birds as controls). The wild birds were captured on a special expedition to Namibia, held in temporary facilities, and released after the experiment. All the vultures survived and showed no changes in blood uric acid levels. In the fifth phase, captive G. africanus vultures ate liver and muscle tissue from cattle treated with above-standard doses of meloxicam, to mimic the natural route of exposure and account for the possibility that treated cattle might produce toxic metabolites. Again, all survived without elevated uric acid levels or ill effects. As a final test, the authors treated ten endangered Asian vultures of two species with meloxicam; five received the maximum likely exposure. All ten were alive and healthy four months after the treatment.

These results make a strong case that the recovery of the Asian vulture depends on immediate action to replace diclofenac with meloxicam. The authors hope other researchers use this approach to evaluate the safety of veterinary drugs on vultures and other scavengers—preferably before the drugs reach the market. For more information, go to Darwin Initiative, http://www.darwin.gov.uk/projects/details/10013.html; Vulture Rescue, http://www.vulturedeclines.org; and BirdLife International, http://www.birdlife.org/action/science/species/asia_vulture_crisis/index.html.

Swan G, Naidoo V, Cuthbert R, Green RE, Pain DJ, et al. (2006) Removing the threat of diclofenac to critically endangered Asian vultures. DOI: 10.1371/journal.pbio.0040066
of this scanner (deriving from the stronger magnetic field plus a specially customized imaging sequence), the authors show that the same brain sector is activated whether the tactile sensation is illusory or real.

To identify brain-related activity associated with real and illusory perceptions, the researchers taped three electrodes to the inner side of participants’ left forearms, one just above the wrist, the others spaced equidistantly toward the elbow. Electrical stimulation could be applied to these points (P1, P2, and P3) while participants lay in the scanner. For the genuine rabbit experience, each point received three pulses in P1-P2-P3 succession. For the illusion, six pulses were applied to P1 (the last three substituting for pulses at the intervening P2 site), followed by three pulses to P3; this resulted in the same P1-P2-P3 tactile experience as when P2 was actually stimulated. For the control condition, P1 received three pulses, followed by three pulses to P3 and then to P1 (a sequence that does not produce the illusion of being stimulated at P2). After each sequence, participants indicated whether or not they felt any stimulation at P2.

Blankenburg et al. looked for brain regions that showed similar increases in neuronal activity during the real and illusory rabbit conditions, compared with the controls, and also looked for any regions that differed between the two conditions. Only one area showed similar and heightened activity during the genuine and illusory rabbit sequences, compared with controls: the precentral gyrus, where the first cortical area to represent touch is located (called S1). The increased activity within S1 fell in the exact sector corresponding to the P2 position on the forearm (even though it was not actually stimulated during the illusion). The researchers confirmed this correspondence by separate somatotopic mapping of the skin sites’ representation in each participant’s brain when each site was stimulated (with no illusion produced).

Altogether, these results suggest that the illusion of being touched at a particular place on the body engages exactly the same sector of the brain that would respond if that body part had actually been touched. This connection between conscious perception and somatotopic cortical processing for illusory percepts may shed light on conditions such as phantom limb pain following amputation, and other perceptual illusions associated with disease. The authors point out that recent fMRI studies have shown somewhat analogous effects in the visual system, with the primary visual cortex involved in some conscious visual illusions. It’s still unclear if this phenomenon will hold for all other perceptual systems as well, but future studies can now explore how the brain bridges the gap between actual stimulation and conscious experience.

Blankenburg F, Ruff CC, Deichmann R, Rees G, Driver J (2006) The cutaneous rabbit illusion affects human primary sensory cortex somatotopically. DOI: 10.1371/journal.pbio.0040069

Clues to Our Past: Mining the Human Genome for Signs of Recent Selection

Liza Gross | DOI: 10.1371/journal.pbio.0040094

Within the past 100,000 years, Homo sapiens left Africa in search of new opportunities, likely crossing paths with H. erectus in Asia and H. neanderthalensis in Europe. These early pioneers encountered unfamiliar climates, habitats, and food sources (not to mention alien human species). Then, after adjusting to a major climate change following the last ice age, they underwent a dramatic lifestyle switch, from hunting and gathering to agriculture—a change that brought crowded living conditions and new infections. All these radical changes likely precipitated significant genetic adaptations, with selection favoring genotypes most suited to the novel conditions. Indeed, recent studies have found evidence of strong selection on new gene variants reflecting adaptations to disease (conferring resistance to malaria) and dietary changes (lactose tolerance).

In a new study, Benjamin Voight, Sridhar Kudaravalli, Jonathan Pritchard, and their colleagues take a global approach to search for such signals across the genome and characterize the types of gene variants, or alleles, targeted by selection. Analyzing variants called single nucleotide polymorphisms (SNPs) in three populations—one sampled from Japan; one a combined sample of Japanese and Chinese individuals from Asia; and one from Europe—they found widespread signals of recent positive selection in all three populations. These signals highlight the types of biological processes that have been targeted by selection during the evolution of modern humans.

Voight et al. based their analysis on data recently collected by the HapMap Project, a repository of the SNPs that researchers use to identify genetic variants involved in human health and disease risk. Humans differ by just 0.1% at the nucleotide level, but these polymorphisms and the linked loci they are inherited with (called haplotypes) contain a wealth of clues to our evolutionary history.

The authors analyzed about 800,000 SNPs from 309 individuals, looking for genomic regions where strong selection has pushed new alleles to intermediate
How Females Keep Male Hoverfly Visual Neurons from Distraction

Jami Milton Dantzker | DOI: 10.1371/journal.pbio.0040081

Legendary athletes like running back Gale Sayers and center fielder Willie Mays earned fame and fortune by pursuing a target traveling at high speeds against a moving, chaotic background. But most animals rely on this evolutionarily honed skill for more fundamental needs. Peregrine falcons snatch prey while flying at speeds approaching 100 miles per hour. Males from several fly species chase females during dazzling courtship dances with impressive aerial maneuvers.

How the brain accomplishes visual pursuit has been a longstanding question, which becomes even more fascinating when one considers how the tiny nervous system of the male fly executes the visual precision and flight control necessary during courtship chase behavior.

The visual system of the male fly lends an attractive model for investigating this question, partly because females don’t chase males during courtship, allowing scientists to link the male-specific neurons to behaviorally relevant functions. In a new study, Karin Nordström, Paul Barnett, and David O’Carroll present surprising insight into the neural basis of visual pursuit in male hoverflies (Eristalis tenax), and identify a novel class of neurons associated with the task.

While hoverflies responded to pixel-sized dots moving against a cluttered, moving background, the authors measured neural activity in the hoverfly visual system (called the lobula complex). Even though the distracting background stimulus sometimes moved at the same velocity as the target, the authors focused on SNP clusters with extreme iHS scores rather than on individual SNPs.

The authors saw extreme values clustered within distinct genomic regions, including a region containing the lactase gene and other known targets of strong selection. Additionally, they looked for the strongest signs of selection, they found many regions classified as selection candidates by the HapMap Project in their results.

Most of the detected signals occurred recently, based on the lengths of the haplotypes. And since most of the selection signals are found in different populations, they likely occurred after the populations segregated, during the agricultural transition. Many of the selected genes play a role in fertility and reproduction (relating to sperm motility and egg fertilization) and morphology (relating to skin pigmentation and skeletal development). Others are involved in food metabolism, reflecting regional changes in diet.

With this genome-wide map of selected targets, future studies can explore what types of selective pressures these genes likely responded to and fill in the gaps in our recent evolutionary history. Although the nature and target of these selection signals are not yet clear, the authors argue that many might have medical implications and that such “selection maps” should become an integral part of annotating the human genome sequence. To facilitate this application, they have created files of SNPs that can be used to tag the strongest selection signals and a Web tool (http://pritch.bsd.uchicago.edu/data.html) for querying any HapMap SNP for evidence of selection. And by providing a more sensitive method of detecting selection, the authors’ new test statistic should prove a valuable tool for uncovering the significant events in our history that lay hidden in the sequence of our DNA.

Voight BF, Kudaravalli S, Wen X, Pritchard JK (2006) A map of recent positive selection in the human genome. DOI: 10.1371/journal.pbio.0040072
as the target, one class of neurons showed highly specialized tuning properties for the targets. The authors refer to these neurons as “small target motion detectors” (STMD). For a sense of the neurons’ performance, imagine driving a golf ball high up into a partly cloudy sky and trying to keep your eye on it while it soars through the air. The hoverfly neurons might be able to track the golf ball even if the sky was moving at the same speed as the ball.

To get this intriguing data, Nordström et al. secured 74 wild-caught male hoverflies in front of a monitor and presented the flies with a range of target and background stimuli that varied in contrast, movement, direction, and speed. The authors recorded intracellular electrical activity from several hundred individual neurons. Of these, 206 neurons shared the striking sensitivity to small moving targets, and the authors classified them as STMD neurons.

To further characterize the STMD neurons’ response properties, the authors varied the speed of the background motion. They expected the moving background to suppress target response based on the “feedback hypothesis,” which predicts that target neuron response would be dampened by the surrounding inhibitory circuitry. Unexpectedly, most STMD neurons maintained their sensitivity to the targets despite the distracting background motion. The authors also empirically confirmed the absence of inhibition in one class of STMD neurons.

To further understand the basis of the tuning properties of these STMD neurons, Nordström et al. explored the contribution of relative contrast between the target and background on the neurons’ response profile. This class of STMD neurons, they found, displayed a striking sensitivity to contrast. The neurons even responded when the luminance of the background and target was similar, though the response was attenuated. This result suggests that even a slight difference in contrast is enough to evoke a response, and that when a female hoverfly moves against foliage with similar luminance properties as her body, the male’s STMD neurons might be able to track her.

From the perspective of object recognition, the robust rejection of background clutter in favor of the target suggests that STMD neurons may be true feature detectors faithfully tuned to their preferred stimulus. Although predicted to exist, neurons that display such remarkable selectivity have not been particularly forthcoming. A compelling future direction of this work will be to uncover how the neural circuits of the insect compound eye and visual system mediate such exquisite feature detection. Eventually, the authors hope to link their physiological studies of visual neurons to the complex social behaviors of hoverflies.

Nordström K, Barnett PD, O’Carroll DC (2006) Insect detection of small targets moving in visual clutter. DOI: 10.1371/journal.pbio.0040054

When you’re a single-celled organism at the bottom of the food chain, it pays to be resourceful. Diatoms, highly successful photosynthetic plankton responsible for 40% of the net primary production in the oceans, undergo seasonal population explosions called phytoplankton blooms that attract billions of krill, copepods, and other grazing predators. As a defense, wounded diatoms release aldehyde compounds that minimize future diatom casualties by compromising the hatching success of grazers. But these diatom-derived aldehydes can also kill diatoms.

In a new study, Assaf Vardi, Chris Bowler, and their colleagues investigated the possibility that the contrasting effects of aldehydes reflect their role as “infochemicals” that trigger different responses attuned to changing conditions in the diatoms’ habitat. The authors found that different concentrations of aldehydes produce different diatom responses. At low doses, aldehydes induce resistance to the compound’s toxic effects. High aldehyde concentrations, on the other hand, trigger cell death, which may lead to termination of a bloom. Thus, diatom-derived aldehydes regulate the population dynamics of both diatoms and their predators.

To investigate aldehyde effects on diatom cell fate and population dynamics, the authors studied how two cultured diatom species responded to a highly reactive aldehyde called decadienal. *Thalassiosira weissflogii* is a ubiquitous, cosmopolitan species; *Phaeodactylum tricornutum* is a standard model for understanding diatom biology.

**Diatoms Rely on Sophisticated Signaling Systems for Population Control**

*Liza Gross* | DOI: 10.1371/journal.pbio.0040089

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**Zooming into the bloom: cell-to-cell signaling in the sea. (Illustration: Nivi Alroy)**

DOI: 10.1371/journal.pbio.0040089.g001
Reactive compounds like decadienal are likely to generate a variety of potentially harmful molecules called reactive oxygen species (ROS). But the authors detected increased levels of just one ROS, nitric oxide, an unstable compound involved in a wide range of physiological processes. Monitoring nitric oxide levels with a nitric oxide-sensitive fluorescent dye and time-lapse imaging revealed that both diatom species experienced similar bursts of nitric oxide production about five minutes after decadienal treatment.

Treated cells succumbed to decadienal in a time- and dose-dependent manner, with significant increases in fatalities above a specific threshold. Below this threshold, cells survived, but underwent cell cycle arrest. To clarify nitric oxide’s role in cell death, the authors stimulated nitric oxide production without using decadienal by using molecules called nitric oxide donors. Next, they pretreated cells with a nitric oxide inhibitor before exposing them to decadienal. The number of dying cells increased along with the levels of nitric oxide in the first experiments, and incidence of decadienal-related cell death decreased with the inhibitor. These results clearly implicate nitric oxide in cell death.

How does the cell stimulate nitric oxide production? Since plant and animal cells use calcium to perceive a wide range of environmental signals, Vardi et al. reasoned that diatoms might, too. Using *P. tricornutum* cells that express a calcium-sensitive bioluminescent protein, they tracked changes in intracellular calcium levels in response to aldehydes. As predicted, intracellular calcium levels spiked following decadienal exposure. None of the nitric oxide donors stimulated intracellular calcium production, suggesting that nitric oxide functions downstream of calcium. And, indeed, the nitric oxide synthase that produces nitric oxide was shown to be calcium-activated: after perceiving ambient aldehyde levels, the cell undergoes transient calcium increases that result in nitric oxide production.

Interestingly, nitric oxide production levels varied among the diatoms. Some cells showed rapid increases in nitric oxide production while their neighbors showed delayed responses, suggesting that the signal to produce nitric oxide was propagating through the diatom population. Healthy cells sensed the level of stressed cells in their midst by detecting the wounded cells’ aldehyde-generated signal. Cells pretreated with a lower dose of decadienal before receiving a higher dose had far better survival and growth rates than cells treated with only a single high dose. These results suggest that lower decadienal doses may immunize cells, stimulating resistance to normally lethal aldehyde concentrations. This induced resistance may provide diatoms who escape grazing predators with a better chance of surviving the toxic aldehydes released by the dying diatoms.

Altogether, these results suggest that decadienal-like aldehydes not only affect the reproductive capacity of grazers but also act as infochemicals that monitor stress levels in diatom populations. During phytoplankton blooms, this stress surveillance system can induce resistance or death. The authors propose that this differential response, regulated by the sophisticated use of intracellular calcium and nitric oxide signals, may determine the fitness and succession of phytoplankton communities.

The finding that diatoms use chemical signaling for cell–cell communication provides new insights into the cellular mechanisms mediating biotic interactions at the population level and challenges traditional concepts of phytoplankton bloom dynamics. With thousands of different diatom species potentially producing a diverse array of aldehydes, these reactive compounds may prove to be even more versatile than shown here—and may be a key factor contributing to the ecological success of these organisms. Now researchers can begin to unravel the mechanisms that endow one group of molecules with the means to mediate such diverse responses.

Vardi A, Formiggini F, Casotti R, de Martino A, Ribalet F, et al. (2006) A stress surveillance system based on calcium and nitric oxide in marine diatoms. DOI: 10.1371/journal.pbio.0040060