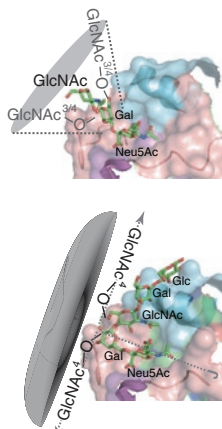


Of birds and men

Influenza A virus causes disease in people, but it was originally an avian pathogen. The viral glycoprotein hemagglutinin (HA) binds to sialylated glycans expressed on host mucosal surfaces, initiating infection. The transition from bird to human hosts is associated with mutations in HA, which are thought to switch HA recognition of sialylated glycans from α 2-3 (a form of linkage more common in birds) to α 2-6 (abundant in the human upper respiratory tract). However, previous studies showed that the correlation between glycan recognition by HA and viral transmission was not quite consistent. Sasisekharan and colleagues have investigated this issue in detail. Analysis of tissue samples showed that glycan structures are actually quite diverse in the human upper respiratory tract, with long α 2-6 chains, both linear and branched. Re-examination of crystal structures of HA variants in complex with sialylated glycans revealed that HA makes contacts with a region of the glycan that can adopt different topologies: the α 2-3 forms and short α 2-6 molecules have a cone-like shape, whereas long α 2-6 forms occupy a wider space, similar to an open umbrella. To explore whether glycan topology, rather than linkage type, is a determinant for HA binding, the authors analyzed data from previous glycan microarray studies, finding that, indeed, HA's binding properties to cone- and/or umbrella-shaped glycans have a predictive value for host specificity, with the ability to bind the umbrella glycan topology correlating with adaptation to humans. This was further tested by glycan binding studies with recombinant HAs and two strains of the H5N1 subtype, which causes bird flu and has infected people but is not able to spread from person to person. The results support the concept that efficient binding of HA to long α 2-6 sialylated glycans is a main determinant of human adaptation in influenza. These findings will have an impact on epidemiological surveillance as well as the development of an influenza vaccine. (*Nat. Biotechnol.* **26**, 107–113, 2008) *IC*



although this has not been shown directly, and it remains to be seen in what contexts Dnd1 functions. (*Cell* **131**, 1273–1286, 2007) *AKE*

MCM and maintenance

Maintaining genome stability is important during S phase and in response to DNA damage or blocks to DNA replication. One way to defend against genome instability is to activate S-phase checkpoints that recognize DNA damage, arrest the cell cycle and preserve essential replication structures. The minichromosome maintenance (MCM) complex is an essential replicative helicase that consists of six related subunits and is in a good position to monitor and maintain the integrity of the replication fork. To examine the role of MCM in maintaining genome integrity, Forsburg and co-workers used different *mcm* alleles in fission yeast to examine the consequence of inactivating MCM function during S phase in the absence or presence of forks stalled by hydroxyurea (HU). They found that loss of MCM function generated DNA breaks, cell-cycle arrest and loss of viability similar to that observed in mutants that undergo replication fork collapse. They also found that Mcm4 interacts with the checkpoint kinase Cds1 and undergoes Cds1-dependent phosphorylation in cells treated with HU. This suggests that MCM proteins act to maintain replication fork structure both during normal S phase and during S-phase arrest. The authors also observed an interaction between the MCM complex and the homologous recombination protein Rhp51 (Rad51) that may be required for proper chromosome segregation in mitosis. Together, these data suggest that MCM links replication fork stabilization with checkpoint arrest and recovery through direct interactions with checkpoint and recombination proteins, and that this role in S-phase genome stability is conserved from yeast to humans. (*Mol. Cell Biol.*, published online 7 January 2008, doi:10.1128/MCB.01717-07) *BK*

Folding a switch

Riboswitches are RNA elements that regulate gene expression through conformational changes induced by ligand binding. Secondary and tertiary riboswitch structure analyses have been carried out, but in recent work from Woodside, Block and colleagues, a more comprehensive view of folding is obtained using a single-molecule analysis of the *pbuE* adenine responsive riboswitch. The single-molecule setup examines unfolding and refolding of a nascent RNA encompassing the *pbuE* riboswitch, and thus the idea that riboswitches fold cotranscriptionally. Comparison of force-extension curves with and without adenine indicate that ligand-bound RNA requires higher forces to fully extend, indicating a stabilized structure upon metabolite binding. Because extensions can be related to the three helices, P1, P2 and P3, the nature of observed intermediates can be deduced. For example, events observed on a completely unfolded molecule upon force decrease are related to formation of P2, then P3 and finally P1. The P1 unfolded state is more highly occupied in the absence than in the presence of adenine, suggesting that progression out of this state toward the fully folded form is an observable switching step. A transient intermediate between the fully folded and P2-P3 folded state was deduced to represent the preorganized adenine binding pocket, indicating that tertiary-structure formation occurs before the secondary structure has entirely formed. As such, the experimental setup allows integrated observation of RNA folding and will probably allow insight into the cotranscriptional folding of other RNAs where sequential production of elements may influence structure. (*Science*, published online 3 January 2008, doi:10.1126/science.1151298) *SL*

Rising from the dead

To affect gene expression, microRNAs (miRNAs) bind directly to a short region of sequence complementarity in target mRNAs. Studies have shown that the 6–8-nucleotide 'seed' sequence at the 5' end of the miRNA is the most important determinant of recognition. However, computational analysis shows that sequences surrounding miRNA binding sites can also be evolutionarily conserved. Agami and colleagues asked whether these neighboring conserved sequences were recognized by RNA binding proteins, and whether they might influence miRNA-mediated repression. By cotransfecting various RNA binding domain (RBD) proteins into human germline cells with a miRNA-repressible reporter, they found that Dnd1 (dead end 1), a factor essential for germ-cell survival, reduced the amount of miRNA-dependent repression. Dnd1 acts through interaction with the mRNA, and not the miRNA, with a preference for uridine-rich ssRNA (URR). To show that Dnd1 has a physiological role, the authors found that two mRNAs regulated by miR-430, *nanos1* and *TDRD7*, are upregulated when endogenous Dnd1 is knocked down or when the URR in their 3' UTR is mutated. At this point, the evidence suggests that Dnd1, by binding to URR sequences near a miRNA target site, limits the accessibility of the miRNA,

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