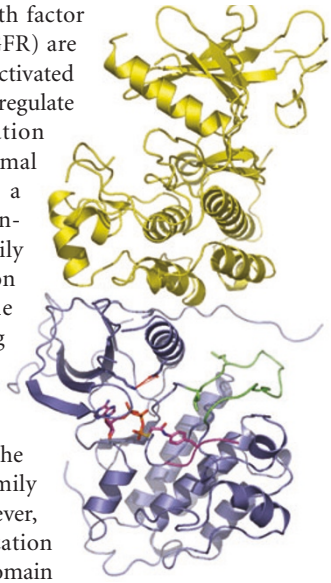
Cyclin up the EGF pathway



Members of the epidermal growth factor receptor family (for example, EGFR) are transmembrane tyrosine kinases activated by ligand-induced dimerization to regulate cell proliferation, differentiation and migration, and their abnormal activation is associated with a number of different human cancers. Dimerization of EGFR family members results in phosphorylation of tyrosine residues in the C-terminal tail segments; signaling molecules bind these segments and transmit the signal downstream. The structural basis for ligand-induced dimerization of the extracellular region of EGFR family members is well understood. However, the mechanism by which dimerization leads to activation of the catalytic domain of EGFR has remained elusive. Now, Kuriyan and co-workers show that the EGFR kinase domain on its own is intrinsically autoinhibited. It can be activated in one of two ways: by increasing its local concentration or by mutating a specific leucine residue in the activation loop. Further mutational studies and crystallography show that the autoinhibited form of the EGFR kinase domain resembles that of Src and cyclin-dependent kinases (CDKs). They find that EGFR activation occurs when an asymmetric dimer forms in which one kinase domain interacts with another in a way that is similar to the association of a cyclin with an activated CDK. This unexpected mechanism of activation provides insight into how current EGFR-blocking drugs interact with the receptor and could lead to the development of new anticancer drugs. (*Cell* **125**, 1137–1149, 2006) *BK*

RNAi and *cis* silencing

In *Schizosaccharomyces pombe*, the assembly and maintenance of heterochromatin at centromeric DNA repeats requires components of the RNA interference (RNAi) pathway. Specifically, the RNA-directed RNA polymerase complex (RDRC) and the RNA-induced transcriptional silencing (RITS) complex containing short interfering RNAs (siRNAs) complementary to the centromeric repeat interact with chromatin and each other to affect silencing and heterochromatin formation at the repeats. According to a model proposed by Moazed and colleagues, the siRNA in the RITS complex pairs with newly synthesized precursor messenger RNA. RITS recruits RDRC and histone-modifying enzymes, such as Clr4, to the targeted locus, leading to the production of more double-stranded (ds) RNA. Dicer then cleaves the newly made dsRNA into siRNA, which begins a new cycle of recruitment that contributes to the spreading of heterochromatin. In support of this mechanism, Moazed and colleagues now show that tethering RITS to a normally active reporter gene (*ura4*$^+$) artificially silences its expression. Silencing depends on a functional RNAi pathway, requires heterochromatin proteins, produces *ura4*$^+$ siRNAs and, in wild-type cells, is restricted to the locus where siRNAs are produced. Furthermore, silencing of either the RITS-tethered reporter gene or the reporter inserted within centromeric heterochromatin does not decrease its association with RNA polymerase II. Together, these data suggest that RNA silencing at heterochromatin is cotranscriptional and *cis*-restricted. (*Cell* **125**, 873–886, 2006) *AB*

New GTPase reaction is O-K$^+$

MnmE is a guanine-binding protein conserved between bacteria and eukaryotes. Unlike the well-known Ras proteins, MnmE does not seem to work with an effector molecule. Instead, the MnmE protein itself appears to participate directly in a catalytic reaction, the modification of the wobble uridine in transfer RNAs. Now, Scrima and Wittinghofer have used crystallography and biochemical experiments to show that the G domains of MnmE dimerize in a potassium-dependent manner and that a K^+ ion in the active site accelerates GTP hydrolysis, presumably by stabilizing the transition state. This is the first time that potassium has been identified as a GTPase-activating element. Remarkably, the K^+ ion seen in the MnmE G domain crystal structure is positioned just like the arginine finger in the Ras-RasGAP structure. The authors speculate that dimerization of the G domains in MnmE orients the tRNA-modification center appropriately for catalysis. (*EMBO J.*, advance online publication 8 June 2006, doi:10.1038/sj.emboj.7601171) *TSS*

Piwi's small RNA adventure

Small RNAs are involved in gene silencing at multiple levels. Argonaute homologs are involved in small RNA function, but the role of a subset of this family, the piwi proteins, has been enigmatic. Piwi proteins are conserved in a wide range of species, and mutations indicate they are essential for germ- and stem-cell development. In two related papers by the Hannon and Tuschl labs, the RNAs that associate with piwi proteins have been isolated, defining a whole new class of small RNAs, called piRNAs. The studies show that piRNAs appear at high levels in mouse testes as spermatocyte DNA condenses during meiosis. Indeed, Tuschl and colleagues estimate there are a million piRNA molecules per spermatocyte or spermatid. piRNAs specifically coimmunoprecipitate with the mouse piwi homologs (Miwi and Mili), but not with a distinct Argonaute family member, Ago2. piRNAs are surprisingly large (~30 nucleotides), and as only one strand could be detected, they may be single stranded. These features raise the question of whether piRNAs are processed by Dicer in the same way as the other small RNAs, though the presence of a 5′ uridine in piRNAs suggests some conservation. Thousands of distinct piRNA sequences were identified in these studies. piRNAs are highly clustered in the mouse, rat and human genomes, though there is little sequence conservation in divergent species. The function, targets and biogenesis of piRNAs remain to be determined, but the staggering depth of the small RNA family continues to surprise and challenge researchers. (*Nature*, advance online publication 4 Jun 2006, doi:10.1038/nature04916 and doi:10.1038/nature04917) *SL*

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