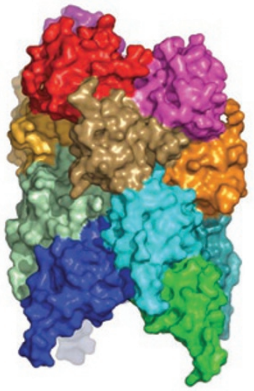
Helical signaling complex



MyD88, IRAK4 and IRAK2 are involved in mediating signaling downstream of the Toll-like receptor (TLR) family (TLR/IL-1R). Toll-like receptors have critical roles in immune system signaling and during early development. They contain a common intracellular Toll/IL-1R homology (TIR) domain and, upon activation, recruit adaptors such as MyD88 that also contain TIR domains. MyD88 responds to most TLRs and contains a death domain that interacts with death domains on IRAK2 and IRAK4, eventually resulting in the activation of transcription factors, including NF-κB. Wu and colleagues have now solved the structure of a complex consisting of death domains from MyD88, IRAK4 and IRAK2, and found that they unexpectedly form a left-handed helical assembly. The complex consists of six MyD88, four IRAK4 and four IRAK2 subunits. Although this is a complex of all death domains, there is specificity to these interactions and thus ordering of the superhelical assembly, endowed by specific features contributed by the different subunits. Indeed, there are specific interactions between layers of MyD88, IRAK4 and IRAK2 in the helical assembly. Given homology to *Drosophila melanogaster* components involved in body axis patterning during embryogenesis and in innate immunity, the authors were able to construct a model of the assembly that might be involved in *Drosophila* developmental and innate immunity signaling. Together, these findings indicate that an unexpected versatile, yet conserved, assembly process may be triggered by signal transduction in this system. (*Nature* **465**, 885–890, 2010) *SL*

Heirloom messenger

Caulobacter crescentus is a bacterium that undergoes asymmetric cell division. The replication-competent cell is attached to a surface via a polar stalk and is thus termed the 'stalk cell'. Upon DNA replication and cell division, two different daughter cells arise, a stalk cell and a swarmer cell, the latter of which has a flagellum in the distal pole and can swim away. In *Caulobacter* and other bacteria, cellular motility and adhesion are controlled by an intracellular messenger, cyclic diguanosine monophosphate (c-di-GMP). Cellular levels of c-di-GMP are regulated by the action of multiple enzymes that synthesize or degrade this molecule (diguanylate cyclases and phosphodiesterases, respectively). The activity of such enzymes can be spatially restricted: for instance, the diguanylate cyclase PleD is inactivated in the *Caulobacter* swarmer cell due to the localization of an inactivating phosphatase, PleC, to the pole opposite the stalk in the predivision stalk cell. Now work from Miller and colleagues reveals that c-di-GMP itself is distributed in a remarkably asymmetrical fashion in the *Caulobacter* progeny. By fusing c-di-GMP sensors to fluorescent proteins CFP and YFP, the authors were able to measure FRET values in live cells that could be converted into c-di-GMP levels. Time-lapse microscopy showed homogeneous levels of c-di-GMP in the predivision stalk cell. Upon formation of the septum, an increase in the c-di-GMP levels in the stalk daughter and a marked decrease in the swarmer cell resulted in 5-fold differences in the sister cells. Mutation of *pleC* and *pleD* genes or overexpression of another diguanylate cyclase demonstrated the role of these enzymes in generating this asymmetrical c-di-GMP distribution, whose disruption resulted in abnormal motility phenotypes in the daughter cells. Such a pattern of c-di-GMP distribution in daughter cells was observed in *Pseudomonas aeruginosa* (which has a single polar flagellum) but also in bacteria with flagella distributed all around the cell (*Salmonella enterica*) or nonflagellated bacteria (*Klebsiella pneumoniae*), indicating that c-di-GMP likely regulates other asymmetrical cellular properties besides motility. (*Science* **328**, 1295–1297, 2010) *IC*

Nrde inhibition

Small RNAs are involved in the silencing of gene expression in many species, and previously, a genetic screen for mutants affecting RNA interference (RNAi) in *Caenorhabditis elegans* nuclei was conducted. Now Kennedy and colleagues have followed up on one set of alleles that define *nrde-2*. Mutations in *nrde-2* affect the silencing of nuclear RNAs, with *nrde-2* worms failing to show the Muv phenotype that arises upon *lin-15b* RNAi. *nrde-2* alleles were also shown to act in the same pathway as *nrde-3*, previously defined as a nuclearly localized Argonaute homolog required for silencing of nuclear transcripts. Through further analysis, it was found that *nrde-2* functions downstream of *nrde-3*–siRNA interaction as well as downstream of recruitment of NRDE-3 to the target messenger RNA. The authors find that *nrde-2* alleles map to a conserved factor containing a domain of unknown function (DUF) and Ser-Arg repeats as well as half-a-tetratricopeptide–like domain. These domains are found in RNA-processing factors and NRDE-2 localizes to the nucleus, but it is currently unclear exactly how NRDE-2 functions. However, through a further screen, the authors do find that *nrde-2* genetically interacts with a subunit of the RNA polymerase, Rbp7. Although it is not yet clear that Rbp7 is involved in RNAi, both NRDE-2 and NRDE-3 interact with pre-mRNAs, hinting at a co-transcriptional function. In addition, chromatin immunoprecipitation (ChIP) analysis indicates an increase in the methylation of histone H3 Lys9 that is *nrde-2* dependent, indicating an effect on chromatin. Using a nuclear run-on assay in *C. elegans* nuclei, the authors show that transcriptional elongation at the *lin-15b* locus was affected during *lin-15b* RNAi and that this effect was dependent on NRDE-2. Further investigation will elucidate the mechanism of silencing in this system as well as whether *nrde-2* and *nrde-3* are directly involved, and it will be interesting to see whether the homologs of *nrde-2* in other species are involved in a similar process. (*Nature*, published online 13 June 2010, doi:10.1038/nature09095) *SL*

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