## Musical domains

Recombination to bring domains of distinct function together has been proposed to be a mechanism for diversifying and evolving new functionality for proteins during evolution. Lim and colleagues have now tested whether systematically recombining domains derived from 11 proteins in the mating pathway of budding yeast *Saccharomyces cerevisiae* leads to functional diversification. Using a reporter regulated by the mating pathway–responsive *FUS1* promoter, the authors found that such recombined proteins could both increase or decrease levels of activation. Such effects were not so overtly observed for mutations that involved whole domain duplication or for those in which the recombined domains were expressed in *trans*. The change monitored on a reporter was also observable at the level of a complex trait, mating efficiency, but did not have a pleiotropic effect on a distinct pathway that involved responses to changes in osmolarity. Interestingly, an effect was seen on growth, but decreased growth tended to be observed with expression of recombined proteins that increased mating efficiency. This is a first hint that the traits endowed by these recombined proteins might confer some type of selective advantage, although this requires future testing. Further examination revealed possible mechanisms underlying functional diversification. For example, combining the Ste50 sterile α motif (which binds Ste11) with the Ste20 kinase domain seems to result in constitutive Ste11 activation. This formally indicates that combining distinct localization or regulatory domains with catalytic regions might lead to recruitment of distinct catalytic domains into different biological pathways. In short, the study indicates that recombination of distinct domains can lead to new functions; whether these constitute adaptive changes remains to be tested. (*Science* **328**, 368–372, 2010) *SL*

## A transcriptional opeNER

The assembly of RNA polymerase II (RNAP II), transcriptional (co)activators and chromatin-modifying proteins at a promoter helps to open the DNA duplex so that RNA synthesis can initiate. During transcriptional elongation, if a structural DNA lesion such as that induced by UV is encountered, a process known as nucleotide excision repair (NER) removes the lesion so that RNA synthesis can resume. A subcomplex of RNAPII, transcription factor IIH (TFIIH), contains the NER proteins XPA and XPD; TFIIH has been linked to both transcription and repair. A recent report has examined whether other NER factors have a role in transcription that is independent of their repair function. By examining genes that are regulated by nuclear receptors, Egly and colleagues have now found that NER factors assemble on these promoters with RNAP II during transcriptional activation. Comparison of this assembly with one formed on the same promoter following UV irradiation showed that the two complexes could be distinguished by the presence of an exclusive factor—the repair complex contained the NER factor CSB, whereas the transcriptional complex possessed XPC. In addition, the two assemblies were distinguishable by their differential sensitivity to a transcription inhibitor. The basal transcription machinery binds promoters in the absence of NER factors, which subsequently assemble in an ordered fashion. If these NER proteins are not recruited, the DNA demethylation and histone modifications necessary for full transcriptional activation are impaired. It remains to be determined how these two complexes facilitate transcription and repair and whether the transcriptional NER complex remains associated with the elongating polymerase, perhaps swapping the CSB subunit for the XPC subunit when damage is encountered. (*Mol. Cell* **38**, 54–66, 2010) *AKE*

## Yo GABA GABA

$GABA_B$ receptors are expressed in nearly every neuron in the brain, and the binding of γ-aminobutyric acid to these G-protein–coupled receptors (GPCRs) leads to the opening of $GABA_B$-associated ion channels and the inhibition of neurotransmitter release. Native $GABA_B$ receptors are comprised of $GABA_{B1}$ and $GABA_{B2}$ subunits, but the broad functional diversity of these receptors is believed to be due to other, auxiliary subunits. Fakler, Bettler and colleagues recently used a proteomic approach to try to identify some of these auxiliary subunits. They determined that several members of the potassium channel tetramerization domain-containing (KCTD) family interact with $GABA_{B1}$ and $GABA_{B2}$. Additional experiments suggest that native $GABA_B$ receptors are homodimeric complexes, where each monomeric complex is comprised of one copy of $GABA_{B1}$, one copy of $GABA_{B2}$ and a tetramer of KCTD proteins that directly interacts with the C terminus of $GABA_{B2}$. The authors then examined whether KCTD proteins were able to alter the functional properties of $GABA_B$ receptors. They found that the presence of KCTD12 or KCTD12b led to large 'desensitization'—a drop in the flow of ions over time—of the $GABA_B$-associated ion channels. In addition, all four KCTD proteins changed the kinetics of $GABA_B$ receptor activation, and two of them altered the concentration dependence of the receptor to an agonist. Although additional work is needed to better understand the physiological functions of each of these auxiliary subunits *in vivo*, it is intriguing to see that such closely related proteins are able to have such different effects on the activity of this GPCR. (*Nature* advance online publication, doi:10.1038/nature08964, 18 April 2010) *JMF*

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