Telomeres avoid checkpoints

The ends of eukaryotic chromosomes look a lot like double-stranded DNA breaks (DSBs). But DSBs induce checkpoints that stall mitosis during DNA repair, whereas chromosomal ends do not. Unnecessary stalls are thwarted, say Rhett Michelson, Saul Rosenstein, and Ted Weinert (University of Arizona, Tucson, AZ), by telomeric sequences that activate “anticheckpoint” measures.

The authors created extra telomeres in yeast by inducing DSBs next to an internally inserted telomeric repeat. Unlike other DSBs, telomere-adjacent breaks induced only short-lived checkpoint delays. This temporary checkpoint delay probably occurs while telomeric proteins assemble at the new DNA ends—a process that only gets started once telomeric sequences are close to a DNA end. In normal cells, the telomeric proteins are already assembled, so checkpoints never get started.

One simple mechanistic explanation calls for a telomere-bound inhibitor that blocks the activity of Mec1, which initiates the checkpoint response from DSBs. Kinase activity of a mammalian Mec1 homologue, in fact, is known to be inhibited by overexpression of the TRF2 telomeric protein.

Anticheckpoints worked on DSBs as far as 600 bp from the telomeric repeats. Thus, says Weinert, “any problems in the DNA near the telomere may not benefit from checkpoint regulation.” This might explain why the DNA internal to telomeres is usually repetitive. “With repeats,” says Weinert, “breaks can be repaired off nearby intact sequences as a way to compensate for having no checkpoint.”

Reference: Michelson, R.J., et al. 2005. Genes Dev. 19:2546–2559.

Signaling with tortoise and hare

Findings from Onn Brandman (Stanford University, Stanford, CA) and colleagues suggest that switch-like signal transduction pathways attain speed and reliability by using two positive feedback loops: one fast and one slow.

Just one positive feedback loop is enough to create an all-or-none biological switch. Yet many systems, such as yeast polarization, rely on multiple loops. Removal of the faster loop (GTPase activation) delays polarization, whereas removal of the slower loop (GTPase localization) makes polarization unstable. Using mathematical models, Brandman et al. now show that speed and stability generally require loops of distinct kinetics.

“We can use equations,” says Brandman, “to see what would happen with every combination [of loop kinetics].” One or two fast loops provided a speedy “on” switch, but the system often turned off inappropriately in response to noise. Systems with one or two slow loops, in contrast, remained reliably activated, because short interruptions in a signal were restored before the loop could be shut off. Their slow kinetics, however, created delayed reaction times to the initial incoming signal.

Only the mixture of fast and slow provided both speed and stability. “You can have a switch that is rapidly inducible,” says Brandman. “And if there’s enough stimulus, the system will commit to that state.” Systems with kinetically dis-

Reference: Brandman, O., et al. 2005. Science. 310:496–498.