VWF springs into action

Following blood vessel injury, long strings of multimeric von Willebrand’s factor (VWF) act as a scaffold for platelets to help staunch bleeding. The VWF strings, 100-μm long or more, may be stored as a coiled, tubular spring inside obligately extended organelles, suggest Grégoire Michaux, Daniel Cutler (University College London, UK), and colleagues.

These organelles are the 1–5 μm-long Weibel-Palade bodies (WPBs). “If you look down a microscope they are such striking organelles—long and just very pretty,” says Cutler. “There had to be something underlying this.”

Cutler’s answer was striking. “The shape is determined by the function of the protein after exocytosis,” he says. The organelle needs to be long, he suggests, so that the spring can be stored in a straight line, allowing easy expansion upon release. “If it is coiled [inside the cell],” he says, “100-fold compaction is reasonable.”

The compaction is dependent on the pro-region of VWF. After cleavage in the Golgi, it stays glued to VWF until the two hit the bloodstream. When the pH changes from acidic (inside the organelle) to near-neutral (in the blood), the pro-region is released and VWF unfurls into the bloodstream.

When the UK team used drugs to neutralize the pH inside WPBs earlier, the tubular nature of VWF was lost, the organelles rounded up, and any VWF subsequently released from the cell formed short and sometimes tangled filaments. This correlation of form and later function prompted the model. Structural studies will be needed to confirm the details. JCB

Reference: Michaux, G., et al. 2005. Dev. Cell. 10:223–232.

Extended organelle form (left) is needed for later correct function.

Trip to the pore

A quick visit to the nuclear pore is not an oddity but occurs for most if not all regulated genes, say Manfred Schmid, Ulrich Laemml, and colleagues (University of Geneva, Switzerland). At least in yeast, the visit may be needed to boost activation of transcription.

Promoters (green) grab onto nuclear pores (red) only when activated (bottom).

The Geneva group had earlier found factors linking transcription activation to the nuclear pore. They now use a nuclease fused to a nuclear pore protein, which clips any DNA that comes to the nuclear pore for a visit.

The regions preferentially cleaved by the nuclease were just upstream of ~40% of genes on chromosome VI. Constitutively expressed genes use different promoter elements and may not need the activation conferred by the visit. But back-of-the-envelope calculations suggest that there are enough pores for all activated genes to get in a quick visit, even if they do so for every round of transcription.

Laemml suggests that “the pore is an active participant in forming a complex between enhancer and promoter.” Constrained enhancers could no longer influence more distant promoters.

In higher eukaryotes, Laemml thinks that so-called transcription factories may act as promoter attachment and assembly sites, and thus as the intranuclear equivalent of nuclear pores. In yeast, the Geneva group is mutating a newly isolated gene that should confirm whether the visit to the pore is an essential event. JCB

Reference: Schmid, M., et al. 2005. Mol. Cell. 21:379–391.

Metabolic waste smooths consumption

If metabolism were an unregulated engine it would overheat in times of plenty and shut down in times of starvation. Instead it attempts to smooth its activity. The first step in this smoothing process is to measure metabolic rate. Cells do so, say Dachun Yao, Michael Brownlee (Albert Einstein College of Medicine, Bronx, NY), and colleagues, by using the glycolysis degradation product methylglyoxal to modify the structure and action of transcription factors. Overactivation of this sensing pathway by hyperglycemia may explain some diabetic symptoms.

Brownlee’s group earlier found high methylglyoxal in endothelial cells bathed in high glucose. Methylglyoxal is a precursor of advanced glycation end-product (AGE) formation, a kind of covalent fouling-up of the cellular machinery. But the current finding is more specific. Methylglyoxal attaches to the transcriptional corepressor mSin3A; this brings in a transcriptional corepressor mSin3A; this brings in a

Endorsement by William A. Wells

wellsw@rockefeller.edu

Reference: Yao, D., et al. 2005. Mol. Cell. 124:275–286.