Nature Reviews Genetics | AOP, published online 13 August 2013; doi:10.1038/nrg3558

GENE EXPRESSION

A cycle route to transcriptional noise

Substantial variability in the transcriptional activity of particular genes is frequently observed among genetically identical single cells in a cell population. This 'noise' is often attributed to a stochastic transcriptional bursting activity that is intrinsic to the genes being studied. However, a new report now shows that the cell cycle phase may make an important extrinsic contribution to noisy transcriptional activity.

To track gene expression in real time, Zopf *et al.* used *Saccharomyces cerevisiae* cells containing three reporter genes encoding fluorescent proteins of different colours: two were driven by identical inducible promoters and one was driven by a constitutive promoter. A microfluidic culture system was used to track fluorescent protein expression and cell size across single cells in the population. Computational analyses were then used to deduce the rates of transcription throughout the cell cycle.

When all promoters were driven constitutively, transcriptional output approximately doubled during S phase and remained so until M phase, probably reflecting the underlying gene copy number. Next, the authors studied the two inducible genes under various experimental conditions in which their output was restricted to infrequent transcriptional bursts. Additionally, the real-time protein fluorescence readings were supplemented by mRNA fluorescence *in situ* hybridization measurements as a more direct readout of transcriptional activity. Under these bursting conditions, the cell cycle phase had a stronger influence on transcriptional output, with a fourfold to >100-fold upregulation in transcription during S phase until M phase relative to G1 phase. Mathematical models that took this cell cycle dependence into account explained the observed data better than the models that were solely based on intrinsic stochastic activation. Furthermore, there was evidence of coordinated transcriptional timing between the two versions of the bursting reporter genes, supporting the view that shared factors that are extrinsic to the promoters are key determinants of transcriptional activity.

Finally, the authors used an alternative fluorescent reporter system in which the nuclear translocation of an activating transcription factor can be monitored in addition to the resultant expression of the encoded reporter gene. They found that the cell cycle has a strong influence on the kinetics of turning on an inactive gene.

It will be interesting to determine the contribution of the cell cycle to transcriptional noise across a broad range of genes in various species.

Darren J. Burgess

ORIGINAL RESEARCH PAPER Zopf, C. J. *et al.* Cell-cycle dependence of transcription dominates noise in gene expression. *PLoS Comput. Biol.* **9**, e1003161 (2013)