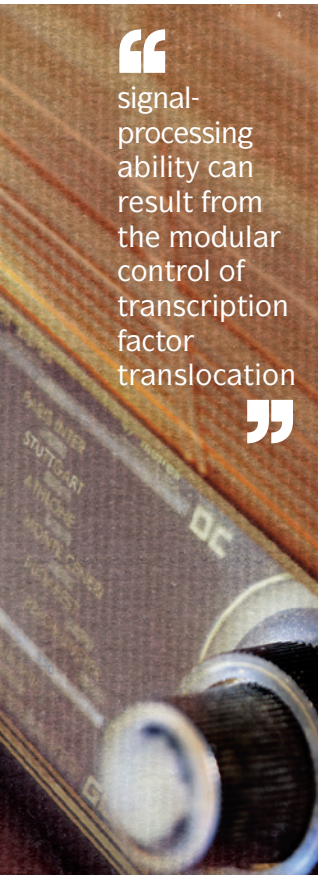
Nature Reviews Genetics | AOP, published online 5 February 2013; doi:10.1038/nrg3431



Macmillan

SIGNALLING

Transcription factors tune in

Individual transcription factors can often generate distinct gene expression outputs in response to different stimuli. A new study shows that this signal-processing ability can result from the modular control of transcription factor translocation.

Hao and colleagues studied the yeast transcription factor Msn2, which generates distinct gene expression outcomes in response to different stresses. In the absence of stress, Msn2 is phosphorylated by protein kinase A (PKA) and is located in the cytoplasm, but in response to stress it is dephosphorylated and translocated to the nucleus. The dynamics of Msn2 translocation vary depending on the type of stress, and this variability is thought to result from different oscillating patterns of PKA activity.

To study how Msn2 processes PKA inputs, the authors engineered a yeast strain in which PKA can be regulated by a cell-permeable inhibitor. Using a microfluidic platform, they delivered this inhibitor to generate oscillations of PKA inhibition with different amplitudes and pulse durations. Strikingly, the amount of nuclear translocation of Msn2 was highly dependent on the specific dynamics of this PKA inhibition input: high- and low-amplitude oscillations resulted in large and very small amounts of translocation, respectively, whereas a prolonged low-amplitude input resulted in translocation at half the maximum level.

How does this ‘tunability’ of Msn2 localization arise at the molecular level? Msn2 nuclear translocation is regulated by phosphorylation in two different modules of the protein: the nuclear localization signal (NLS) and the nuclear export signal (NES). The authors modelled and experimentally measured the dynamics of Msn2 localization, taking into account the separate processes of translocation to and export from the nucleus, and the fact that NLS sites are preferentially phosphorylated compared with those in the NES. This revealed distinct dynamics of Msn2 translocation in response to different oscillatory inputs. For example, Msn2 tracks the dynamics of a strong input but filters out low-amplitude signals. It is also able to integrate different signals.

Aspects of this signal processing were lost in specific NLS and NES phosphorylation site mutants. Furthermore, these mutants could no longer generate different dynamics of translocation in response to different naturally occurring stresses.

Given that dual regulation of nuclear localization is a feature shared with many mammalian transcription factors, this mechanism of tuning gene expression responses may be widespread.

Louisa Flintoft

ORIGINAL RESEARCH PAPER Hao, N. *et al.* Tunable signal processing through modular control of transcription factor translocation. *Science* **339**, 460–464 (2013)