Nature Reviews Molecular Cell Biology | AOP, published online 31 March 2010; doi:10.1038/nrm2886

Journal club

MASTERS OF THE GENOME

As a young scientist at the National Institutes of Health, USA, in 1969, I read a publication by Britten and Davidson that proposed a theory which struck me as intriguing. They postulated the existence of a subgroup of genes in animal genomes that act as 'master genes' to implement the coordinated expression of subservient genes termed 'producer genes'. They considered that master genes might be a group of RNAs that directly regulate the transcription of other genes. Although subsequently ignored in the literature, we thought we might be onto the trail of such molecules in 1972 when we found a group of non-histone proteins that we termed 'acceptor proteins', which bound to nuclear receptors and increased their interaction with DNA and their transcription potential (Spelsberg *et al.*). We dropped the project because we couldn't purify these proteins. In recent decades, microRNAs, which act in part to dampen the effects of their parent genes, were discovered, but they did not fulfil the criteria for the master genes postulated by Britten and Davidson.

> co-activators fit the mold predicted for master genes

My memory of this 1969 paper was refreshed when we cloned a gene encoding a co-activator for nuclear receptors, steroid receptor co-activator 1 (SRC1; also known as NCOA1), in 1995 (Onate *et al.*). This was the first cloning of an authentic acceptor protein. We renamed acceptor proteins 'co-activators' and presented the criteria for future use of this name. The subsequent decade brought a host of surprises — hundreds of co-activators (and co-repressors) were identified and cloned. Importantly, co-activators fit the mold predicted for master genes because they have the ability to bind across unrelated families of transcription factors and coordinately regulate the expression of the multiple genes required for complex physiological goals. This unique capacity puts the co-regulators above the structural producer genes as higher order regulators of animal cell functions. Co-activators are the targets of the many environmental signalling pathways that post-translationally instruct these molecules, allowing them to simultaneously function at unrelated genes and in diverse manners in cells.

Co-activators are now also implicated in the recognized etiologies of many human diseases, highlighting the need to continue to study these master genes forty years on from when they were originally proposed.

Bert W. O'Malley
Department of Molecular and Cellular Biology, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030, USA.
e-mail: berto@bcm.edu

The author declares no competing financial interests.

ORIGINAL RESEARCH PAPERS Britten R. J. & Davidson E. H. Gene regulation in higher cells: a theory. *Science* **165**, 349–357 (1969) | Spelsberg T. C. *et al.* Progesterone-binding components of chick oviduct. III. Chromatin acceptor sites. *J. Biol. Chem.* **246**, 4188–4197 (1971) | Onate S. A. *et al.* Sequence and characterization of a coactivator for the steroid hormone receptor superfamily. *Science* **270**, 1354–1357 (1995)
FURTHER READING Lonard, D.M. *et al.* Nuclear receptor coregulators and human disease. *Endocrine Rev.* **28**, 575–587 (2007)