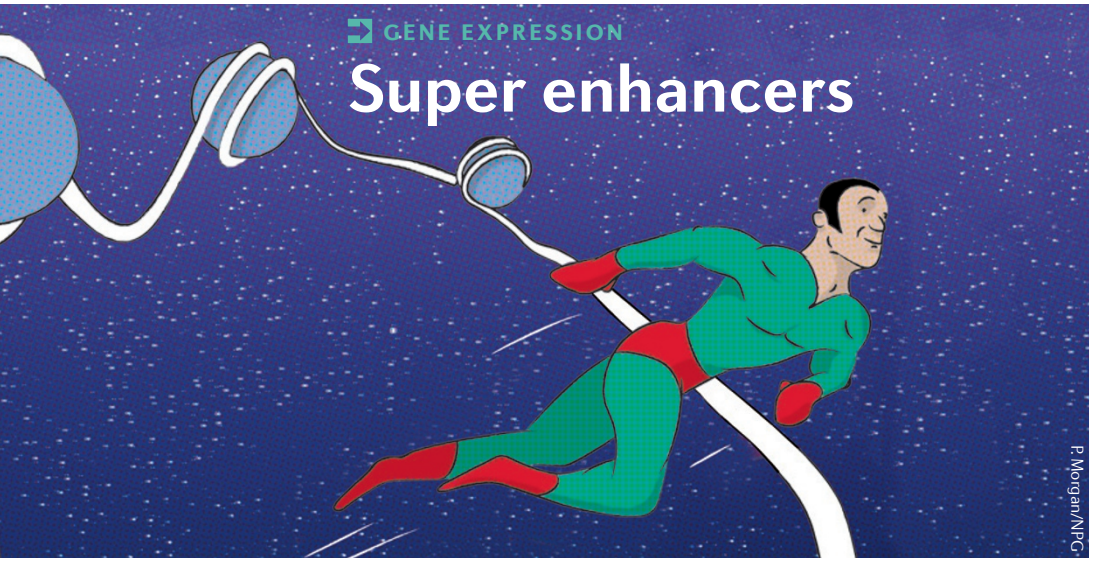
Nature Reviews Genetics | AOP, published online 23 April 2013; doi:10.1038/nrg3496



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Two recent studies from the same laboratory have shed light on the relationship among enhancers, gene expression and cell identity. In these two studies, the authors identified a subset of enhancers termed 'super enhancers', which have crucial functions in defining cell identity.

The transcription factors OCT4 (also known as POU5F1), SOX2 and Nanog are known to be involved in the maintenance of the pluripotent state in embryonic stem cells (ESCs). They bind enhancers along with Mediator to regulate key genes that are involved in ESC identity. Interestingly, ESCs are as sensitive to the loss of Mediator as they are to the loss of some of these transcription factors, and it is this that led Whyte *et al.* to investigate further the role of Mediator in ESCs.

Whyte *et al.* first carried out chromatin immunoprecipitation followed by sequencing (ChIP–seq) to look at binding patterns of OCT4, SOX2, Nanog and Mediator. Their investigation showed that the identified enhancers could be divided into two groups on the basis of Mediator levels: enhancers with lower levels of Mediator that spanned around a few hundred bases, and those with higher levels that were located in large clusters of enhancers up to 50 kb in size. These larger enhancers were also enriched for KLF4 and ESRRB, which are transcription factors that have roles in ESC identity. They termed these larger Mediator-rich enhancers super enhancers.

The authors then defined a set of super-enhancer-associated genes by searching for those adjacent to, or within, the same topological domain as the super enhancers. Gene ontology analysis showed that super-enhancer-associated genes all have important roles in ESC identity. Furthermore, they were generally expressed at higher levels than those associated with typical enhancers. The authors then knocked down OCT4 and Mediator and found that the effect on gene expression was larger for super-enhancer-associated genes than for those with regular enhancers. The knockdown also resulted in the loss of the ESC state and differentiation.

The authors showed that other cell types, such as T helper cells and mouse myotubes, also contain super enhancers that are characterized by high amounts of Mediator binding and large domains of binding of key transcription factors involved in maintenance of cell state. Super enhancers were consistently found to regulate genes key to cell identity. Thus, super enhancers are a key part of the cell identity network in a large variety of cell types.

The role of super enhancers in disease processes was investigated by Lovén *et al.* in the cancer multiple myeloma. They found that Mediator colocalized with the transcriptional activator BRD4, which binds to acetylated chromatin, again in large domains that are typical of super enhancers. These domains were associated with genes that are involved in multiple myeloma biology; crucially, this includes the gene that encodes the transcription factor MYC (also known as c-MYC). Targeted inhibition of BRD4 using the small molecule inhibitor JQ1 led to displacement of BRD4 from the super enhancers and specific disruption of transcriptional elongation at the super-enhancer-associated genes, including *MYC*. Super enhancers characterized by high-level BRD4 and Mediator binding were also identified in other cancer cell lines and were associated with well-known tumour-associated genes.

The authors studies suggest that cell-type-specific super enhancers are key in the maintenance of cell identity and have a crucial part in the network of maintenance of cell function. Their identification suggests ways to target cell identity specifically through the manipulation of transcription factors that are associated with these elements; this may be a powerful approach for cancer therapy.

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ORIGINAL RESEARCH PAPERS Whyte, W. A. *et al.* Master transcription factors and mediator establish super-enhancers at key cell identity genes. *Cell* **153**, 307–319 (2013) | Lovén, J. *et al.* Selective inhibition of tumor oncogenes by disruption of super-enhancers. *Cell* **153**, 320–334 (2013)