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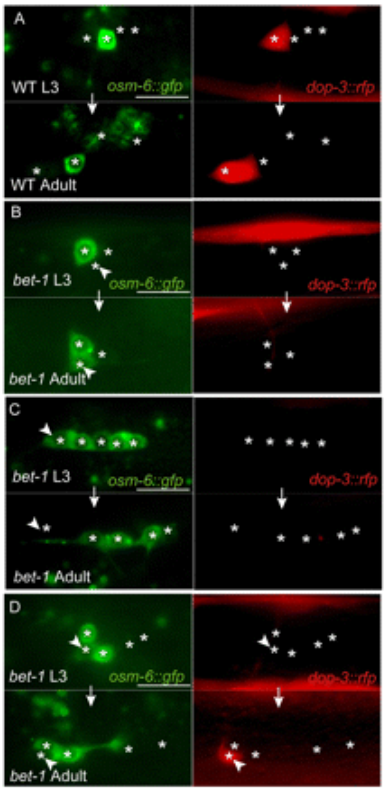
Epigenetic factors hold cell fate to the script

March 25, 2010 – DNA famously plays a central role in determining the body's form and function, typically through the transcription of genes, and the translation of these transcripts to proteins. Controlling this expression of genes, so that they are only "switched on" at the right times and in the right places, makes reliable and precise regulatory mechanisms a necessity. The results of such regulatory activities result in the establishment and maintenance of cells with specific functional identities, or fates. But how is this spatiotemporal transcriptional control achieved?



Comparison of wildtype (A) and *bet-1* mutants (B-D) reveals altered numbers of cells expressing cell type-specific markers genes.

Research scientist Yukimasa Shibata and others in the Laboratory for Cell Fate Decision (Hitoshi Sawa; Team Leader) were interested in possible roles for epigenetic mechanisms in the upkeep of cell fate in *C. elegans*, as a body of previous work had pointed to functions for such phenomena as DNA methylation and histone modifications in cell type-specific transcriptional regulation in various model systems. Now, in recent work published in the journal *Development*, they show that a pair of protein factors implicated in histone acetylation play crucial roles in setting up and stably maintaining cell fates. Acetylation is one of various modifications known to modify histone protein activity and configuration, and to affect the expression of genes in associated regions of DNA within chromatin complexes.

The team identified the first of their molecules of interest in a mutation screen, which gave the first hint that the histone-associated bromodomain factor BET-1 might play a role in cell fate stability. A mutant allele yielded phenotypes in which cell-fate maintenance is disrupted. The result of these aberrations was seen, for example, in the mistaken adoption of inappropriate cell fates by progeny of tail neural precursor cells lacking *bet-1* function, with the result that neuroblasts gave rise to hypodermal cells (in wildtype animals, these neuroblasts produce neural cells).

In the somatic germ and other neural lineages as well, loss of BET-1 resulted in the ectopic expression of cell type-specific markers and more than usual numbers of specific type of cells. In at least one case, they traced this effect to the regulation of the expression of a cell-fate determinant by BET-1, a general mechanism that they suspect may be common to other lineages as well.

Armed with evidence of the ability of *bet-1* mutation to cause cell fate transformations in the somatic germ and neural lineages, the Sawa team suspected that this might also be true in other cell populations. To test this possibility, they observed the expression of marker genes over time in the hopes of gleaning insights into the effects of loss of *bet-1* function on cell fate stability. Again, they found that differentiated cells switch between fates in mutants, but not in wildtype. Further tests using heath-shock treatment to conditionally rescue the phenotype suggested that BET-1 establishes and maintains stable cell fates.

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Pursuing the role of histone acetylation in cell fate establishment and maintenance even further, Shibata next looked at a family of acetyltransferases known as MYST HATs, and found that blocking their function produced phenotypes closely resembling those of the *bet-1* mutants. Distribution analyses showed that the localization of bet-1 within the nucleus depends on MYST factors, highlighting a possible functional relationship between the two.

These findings shed new light into roles for epigenetic processes in establishing and maintaining cellular identity, possibly through the regulation of the expression of cell fate determinant genes. As analogs of BET-1 and MYST proteins have been implicated in expression of developmental genes in other organisms, such as the fruit fly *Drosophila*, these factors may have a more generally conserved function in cell fate maintenance and the prevention of wayward differentiation.

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