Unexpected stability and complexity in transcriptional enhancers' interactions

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Contrary to what was thought, sequences of DNA called enhancers – which control a gene's output – find their targets long before they are activated during embryonic development, scientists at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, have found. Their study, published online today in *Nature*, also reveals that, surprisingly, the degree of complexity of enhancers' interactions in the 'simple' fruit fly *Drosophila* is comparable to what is seen in vertebrates.

"As an embryo develops, there are huge changes in transcription, much of which drives developmental progression: genes are changing from on to off, and off to on – but the contacts between enhancers and their target genes remain largely unchanged," says Eileen Furlong from EMBL, who led the work. "Enhancers regulate transcription, so it was really surprising that there are few changes in their interactions at a time when transcription is changing."

To activate a gene, an enhancer has to come into contact with the portion of DNA at the start of the gene – its promoter. For enhancers that are located far away from their targets, the cell achieves this by looping the DNA around to bring about that contact. Yad Ghavi-Helm, a postdoctoral fellow in Furlong's lab, found that, in developing fruit fly embryos, these DNA loops are formed, contact is established, and the cell's gene-reading machinery is recruited, hours before the gene is expressed. The results indicate that the whole system is primed in advance, ready to spring to action when needed.

When they looked at all the enhancers that are known in *Drosophila* and mapped what genes they establish contacts with, the EMBL scientists discovered that these genetic regulators act across long distances in the genome, and in complex ways. Such a prevalence of long-distance action and such complex interactions were previously known to be widespread among vertebrates, but these findings show that they evolved much earlier.

For Furlong, Ghavi-Helm and colleagues, the study opens up a plethora of further questions: At what point in an embryo's life do enhancer loops form? And how long after a gene has been switched off do the loops remain? If loop formation isn't the trigger for gene activation, what is? What's the exact role of the contacts they have found? And finally, a technically challenging question: unravelling if all an enhancer's interactions are happening at the same time in the same cell.

More information: Ghavi-Helm, Y., Klein, F.A., Pakozdi, T., Ciglar, L., Noordermeer, D., Huber, W. & Furlong, E.M. Enhancer loops appear stable during development and are associated with paused polymerase. Published online in *Nature*, 2 July 2014. DOI: 10.1038/nature13417

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