Press Release

EMBL

DNA's twisted communication

The organisation of the genome is a key element for the control of gene expression

Heidelberg, 28 February 2013 – During embryo development, genes are dynamically, and very precisely, switched on and off to confer different properties to different cells and build a well-proportioned and healthy animal. *Fgf8* is one of the key genes in this process, controlling in particular the growth of the limbs and the formation of the different regions of the brain. Researchers at EMBL have elucidated how *Fgf8* in mammal embryos is, itself, controlled by a series of multiple, interdependent regulatory elements. Their findings, published today in Developmental Cell, shed new light on the importance of the genome structure for gene regulation.

Fgf8 is controlled by a large number of regulatory elements that are clustered in the same large region of the genome and are interspersed with other, unrelated genes. Both the sequences and the intricate genomic arrangement of these elements have remained very stable throughout evolution, thus proving their importance. By selectively changing the relative positioning of the regulatory elements, the researchers were able to modify their combined impact on *Fgf8*, and therefore drastically affect the embryo.

"We showed that the surprisingly complex organisation of this genomic region is a key aspect of the regulation of *Fgf8*," explains François Spitz, who led the study at EMBL. "*Fgf8* responds to the input of specific regulatory elements, and not to others, because it sits at a special place, not because it is a special gene. How the regulatory elements contribute to activate a gene is not determined by a specific recognition tag, but by where precisely the gene is in the genome."

Scientists are still looking into the molecular details of this regulatory mechanism. It is likely that the way DNA folds in 3D could, under certain circumstances, bring different sets of regulatory elements in contact with each other and with *Fgf8*, to trigger or prevent gene expression. These findings highlight a level of complexity of gene regulation that is often overlooked. Regulatory elements are not engaged in a one-to-one relationship with the specific gene that has the appropriate DNA sequence. The local genomic organisation, and 3D folding of DNA, might actually be more important factors that both modulate the action of regulation elements, and put them in contact with their target gene.

Visualisation (in blue) of the activity of the Fgf8 regulatory region in a mouse embryo.

More research will be necessary to understand in detail the impact of the 3D structure of DNA on the communication between the various elements of the genome, and on the regulation of gene expression. Further down the line, this could also further our understanding of how genomic rearrangements might disrupt these 3D regulatory networks and lead to diseases and malformations. ●

Source Article

An integrated holo-enhancer unit defines tissue- and gene specificity of the Fgf8 regulatory landscape - Mirna Marinic, Tugce Aktas, Sandra Ruf, and Francois Spitz – Advanced online publication in Developmental Cell on the 28 February 2013

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About EMBL

The European Molecular Biology Laboratory is a basic research institute funded by public research monies from 20 member states (Austria, Belgium, Croatia, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom) and associate member state Australia. Research at EMBL is conducted by approximately 85 independent groups covering the spectrum of molecular biology. The Laboratory has five units: the main Laboratory in Heidelberg, and Outstations in Hinxton (the European Bioinformatics Institute), Grenoble, Hamburg, and Monterotondo near Rome. The cornerstones of EMBL's mission are: to perform basic research in molecular biology; to train scientists, students and visitors at all levels; to offer vital services to scientists in the member states; to develop new instruments and methods in the life sciences and to actively engage in technology transfer activities. Around 190 students are enrolled in EMBL's International PhD programme. Additionally, the Laboratory offers a platform for dialogue with the general public through various science communication activities such as lecture series, visitor programmes and the dissemination of scientific achievements.

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