

3D nuclear positioning of IGF2 alleles and *trans* interactions with imprinted genes

Y. Lahbib-Mansais^{1,2,3}, M. Marti Marimon^{1,2,3}, V. Voillet^{1,2,3}, F Mompарт^{1,2,3}, J. Riquet^{1,2,3}, S. Foissac^{1,2,3}, D. Robelin^{1,2,3}, H. Acloque^{1,2,3}, Y. Billon⁴, N Villa-Vialaneix⁵, L. Liaubet^{1,2,3}, M. Bouissou-Matet Yerle^{1,2,3}

¹INRA, UMR 1388 Génétique, Physiologie et Systèmes d'Elevage, F-31326 Castanet-Tolosan, France

²Université de Toulouse INPT ENSAT, UMR 1388 Génétique, Physiologie et Systèmes d'Elevage, F-31326 Castanet-Tolosan, France

³Université de Toulouse INPT ENVT, UMR 1388 Génétique, Physiologie et Systèmes d'Elevage, F-31076 Toulouse, France

⁴INRA, UE 1372 Génétique, Expérimentation et Système Innovants, Surgères, F-17700, France

⁵INRA, UR 0875 Mathématiques et Informatique Appliquées de Toulouse, Castanet-Tolosan, F-31326, France

To explore the relationship between gene activity and nuclear position, genomic imprinting leading to parental-specific expression offers a good model. In one cell, it is possible to compare the nuclear environment of the two alleles for a given locus and search for a potential correlation between their nuclear position and expression status. Using 3D RNA-DNA FISH in porcine fetal liver cells, we focused on the imprinted region of *Insulin-like growth factor 2* (IGF2), a paternally expressed gene located on porcine chromosome 2. We investigated the interchromosomal interactions implicating IGF2. Through a 2D FISH screening, imprinted genes from the Imprinted Gene Network (Varrault et al 2006) were tested for interactions in liver cells. The locus DLK1/MEG3 showed the highest rate of colocalization with IGF2. By 3D RNA-DNA FISH combined to confocal microscopy, we demonstrated a preferential implication of the expressed paternal IGF2 allele in a *trans* association with DLK1/MEG3 region (chromosome 7). We showed that this colocalization occurs also in fetal muscle and demonstrated that it occurs preferentially between the expressed IGF2, DLK1 and MEG3 alleles. We are extending this analysis through an interdisciplinary approach to develop large “functional mapping” studies focused on the mechanisms involved in the transcriptional regulation of genes expressed in muscle during late fetal development of pig. From a transcriptomic analysis carried on fetal muscle of two extreme genetic lines to study maturity, we identified 2000 genes differentially expressed that characterize its establishment (Voillet et al 2014). We are now constructing by *in silico* processes, networks of co-regulated genes with IGF2 as starting point. We are also developing a Hi-C approach to construct interaction maps on a genome-wide scale. A set of key genes, belonging to these networks and interaction maps will be selected to study by 3D FISH their position in the nuclear space in cells of the two genotypes and to determine if co-regulated genes implicated in a same biological function whether or not co-localize in the nucleus. These data should allow us to define if these interactions are genotype and expression pattern dependent. This will open interesting questions to study the possible link between nuclear architecture and control of gene expression in muscle in an animal model for which extreme genotypes for maturity at birth are available.

Keywords:

trans interactions, imprinted genes, 3D nuclear organization