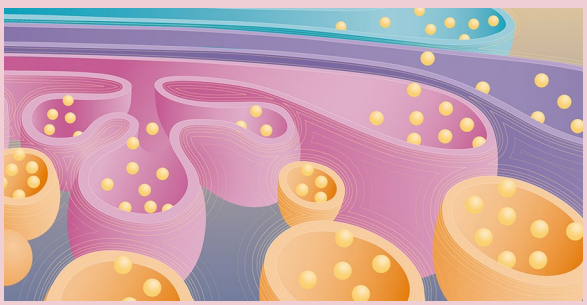
population Hi-C data, and TAD boundaries are dynamic features.

Finally, when individual alleles of locus pairs were analysed, little correlation was found between the behaviour of the two alleles in a given nucleus; again, in most cells (~70–99.5%), no interactions were found between pairs. Thus, when interactions do occur, they mostly occur independently at the two homologous chromosomes.

In summary, chromatin interactions are highly dependent on genomic distance and to a certain extent on gene content and presumably gene function; they occur in a minority of cells and are highly variable between cells and between alleles. This pattern indicates that genome-organization heterogeneity is cell-intrinsic, and raises the question of how gene expression programmes are maintained in the absence of the initiating cue against a backdrop of such stochasticity of interactions.

Eytan Zlotorynski

ORIGINAL ARTICLE Finn, E. H. et al. Extensive heterogeneity and intrinsic variation in spatial genome organization. *Cell* https://doi.org/10.1016/j.cell.2019.01.020 (2019)



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SREBP target genes is downregulated compared with normal skin.

This study indicates that mechanical cues from the ECM affect the activity of lipin 1 and ARF1 at the Golgi apparatus and thereby control SREBP processing and activity to regulate lipid synthesis. It will be important to further dissect how lipin 1 activity is regulated by the Golgi and whether other functions of the Golgi are mechanoresponsive.

Grant Otto

ORIGINAL ARTICLE Romani, P. et al. Extracellular matrix mechanical cues regulate lipid metabolism through Lipin-1 and SREBP. *Nat. Cell Biol.* https://doi.org/10.1038/s41556-018-0270-5 (2019)

Journal Club

DETOURING THE ROADBLOCKS IN GENE EXPRESSION

How the fertilized egg develops into a complex organism consisting of many different cell types is one of the great mysteries of biology. This is even more so if we consider how robust embryonic development is towards perturbations caused by fluctuations in environmental conditions and genetic differences. As a testament to the enormous stability of development, sequencing studies in human populations with reduced genetic diversity have suggested that even individuals with homozygous loss-of-function mutations often do not display obvious phenotypes (Narasimhan et al.), suggesting the existence of compensation mechanisms that ensure organismal fitness in the event of functional loss of individual genes. In a recent preprint (El-Brolosy et al.), Stainier and co-workers describe a fascinating new mechanism that may explain how mutations can be compensated for in zebrafish and mice.

CRISPR–Cas9 technology has made it much easier to create mutants. Notably, in many cases knockdowns of equivalent transcripts (for example, with the use of morpholinos (Kok et al.)) are associated with observable phenotypes, which are absent in mutants generated with these strategies. Such discrepancies are often attributed to off-target or toxic effects of the knockdown reagents. However, a recent study in zebrafish reported upregulation of certain genes in mutants, but not in morpholino-treated animals. These upregulated genes were functionally related to the mutated gene, suggesting activity of a compensatory mechanism in the mutant, but not in the knockdown fish (Rossi et al.). Following up on this observation, El-Brolosy et al. carried out a series of simple, but elegant experiments in zebrafish and mice. They found that in many mutants, the upregulated genes shared high levels of sequence similarity with the mutated gene. Interestingly, this compensatory feedback did not depend on decreased protein expression, since increasing protein levels by injecting wild-type mRNA for the mutated gene did not prevent related-gene upregulation. Instead, the authors found that genetic compensation is triggered by the generation of unstable mRNAs associated with mutated genes. Accordingly, genetic compensation was observed only in mutants in which unstable transcripts were produced, while it was absent from those in which no mRNA was made. This finding is strengthened by the observations that inhibiting the mRNA surveillance machinery, which detects and degrades abnormal transcripts, led to loss of transcriptional compensation, and that injection of uncapped — and hence unstable — mRNAs into wild-type embryos induced a transcriptional compensation response.

From a developmental perspective, the elegance of this mechanism, whereby the roadblock generates the detour, can hardly be overstated. Although many questions regarding the molecular mechanism of genetic compensation remain, one important conclusion from the work of El-Brolosy et al. is that generation of mutant alleles unable to produce mRNA may uncover mutant phenotypes that were so far masked by sequence-similarity-based transcriptional compensation, and hence, may be a key approach to improving understanding of the links between the genotype and phenotype.

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