B CELLS

Genomic reorganization in germinal centres

B cells undergo profound phenotypic changes, accompanied by rapid and coordinated transcriptional reprogramming, as they transition from a resting state to a highly proliferative state in the germinal centre (GC). A new study published in *Immunity* shows that GC B cells undergo a multilayered three-dimensional (3D) reorganization of the genomic architecture, which enables coordinated changes in the expression of the GC B cell-specific transcriptional programme.

Using genome-wide, high-resolution chromosome conformation capture (Hi-C) analysis of human tonsillar naive and GC B cells, the authors observed increased promoter interactivity in GC B cells compared with naive B cells in regions enriched for genes linked with the GC B cell transcriptional programme. Promoter interactivity, which was highly correlated with increased active epigenetic marks, was associated with increased transcription of GC B cell-specific genes.

Chromosome conformation capture (3C) analysis also identified a substantial increase in

enhancer–promoter 5' to 3' looping at key GC genes, such as *BCL6*, in GC B cells compared with naive B cells. This gene looping was associated with increased CTCF and cohesin binding (which are linked to the formation of *cis*-interacting chromatin) and with increased gene expression. These data indicate that the GC transcriptional programme is coordinated through GC B cell-specific topological reorganization.

Further analysis showed that this multilayered chromatin reorganization in GC B cells was associated with the merger of 3D gene neighbourhoods into gene 'cities'. Previous studies have shown that groups of genes that share regulatory and epigenetic information are looped into physically partitioned 'neighbourhoods'. The authors identified numerous 3D gene neighbourhoods that were conserved between naive and GC B cells. Many adjacent neighbourhoods that shared active epigenetic marks merged in GC B cells to form *de novo* 3D cities in which newly connected genes that are important for GC B cell specification were coordinately regulated. These data suggest a

mechanism for more efficient coordination of the expression of GC B cell-defining genes.

Finally, *BCL6* was shown to have a key role in organizing the topology of the GC B cell genome by interacting extensively with other GC-expressed genes through an upstream locus control region (LCR). Deletion of this LCR in mice resulted in a specific defect in GC formation and function, indicating an essential role for this highly interactive *BCL6* LCR in the specification of the GC B cell phenotype.

Together, these results show that the profound transcriptional reprogramming in GC B cells is accompanied by a multilayered structural reorganization of GC-specific genes for coordinated expression.

Olive Leavy

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ORIGINAL ARTICLE Bunting, K. L. et al. Multi-tiered reorganization of the genome during B cell affinity maturation anchored by a germinal center-specific locus control region. *Immunity* <http://dx.doi.org/10.1016/j.immuni.2016.08.012> (2016)