Cell type specific chromatin architecture defines erythropoiesis and megakaryopoiesis.

Romina Petersen on behalf of the BLUEPRINT Consortium.

Department of Haematology, University of Cambridge and NHSBT, Cambridge, UK.

Oxygen delivery to tissues and haemostasis (blood clotting) are key evolutionary traits. These functions are carried out by two of the blood most abundant cell types, red cells and platelets respectively. Both types of anucleate cells originate in the bone marrow from erythroblasts (EB) and megakaryocytes (MK) respectively. Defects in these cells give rise to diseases affecting a large proportion of the world's population including anaemia, heart attack and stroke. Despite clearly distinct phenotypes EB and MK share transcriptional programs, controlled by a largely overlapping set of transcription factors and regulatory elements; therefor, our understanding of the molecular events leading to their commitment remains incomplete. Here, we integrated gene expression, chromatin accessibility, epigenetic states, promoter long-range DNA interactions (Promoter Capture HiC, PCHiC) and genome higher-order chromatin structures (HiC) data to map regulatory elements throughout the genome; to link these elements to the genes they regulate and to reconstruct these cells tridimensional regulatory landscape in order to identify the determinants of the unique functional identity of EB and MK. We established regulatory elements opening dynamics from the haematopoietic stem cell compartment (HSC) through a series of progressively lineage-restricted progenitors to EB and MK using ATAC-seq. We showed that promoter-enhancer interactions are the main discriminant between EB and MK common set of enhancers. We also showed that the 3D interactions landscape is dominated by cell type specific DNA long-range interactions and these form discrete networks within but also across higher order chromatin structures. We used a high throughput, quantitative, chromatin integrated and position independent reporter system to establish the relative contribution of thousands regulatory regions to gene expression. Moreover we showed that super-enhancers (SE) controlled MK functional identity associated genes and that MK SE are heavily enriched in platelet GWAS signals. Finally, we used CRISPR-Cas9 in IPSCs derived MK and functional assays in genotyped volunteers to validate the effect of SE on cellular phenotypes.