POSTER 26: The promising role of the linker histone Hl.3 in H3K27me3H/ST/high leukaemia

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Acute myeloid leukaemia (AML) is a heterogeneous disease in terms of genetic and epigenetic alterations, clinical features and therapeutic outcomes.

Few years ago, the group discovered a new epigenetic biomarker named H3K27meHIST1 by performing an epigenetic profiling in normal cytogenetics (CN-AML) patients. This biomarker is an enrichment of H3K27me3 at part of the major histone cluster HJSTI locus, affecting 11 histone genes. Interestingly, patients with the presence of this biomarker (H3K27meHIST1) had a better prognosis and leukaemia free survival. As consequence of this epigenetic repression mark, low expression of some histone genes such as linker histone Hl.3 was observed. The linker histone Hl.3 is part of the DNA replication-dependent HI variants, which harbour chromatin function specificity. Indeed, a growing amount of evidences point the specificity of the HI variants in chromatin compaction, regulation of gene expression and other key aspects of genome biology.

To investigate the role of HI .3 in H3K27meHIST1 high leukaemia, we generated an OCI-AML3-derived cell model including an HI .3 KO line (knock-out obtained by classical CR1SPR/Cas9) and Hl.3-V5 OE (overexpression of a V5-tagged ofHl.3). We first performed differential gene expression analysis by RNA-seq in the cell lines. The results highlighted a deregulation in chromatin organization and nucleosome assembly genes as well as in cell cycle regulators as a consequence of Hl.3 absence. To specify Hl.3 role in cell cycle we synchronized the WT and KO cells at the G 1-S boundary using a double thymidine block. As suggested by RNA-Seq data analysis, we evidenced a deregulation in cell cycle when we knock-out Hl.3, with an accumulation of G0/G I phase and a decrease in S and G2/M phases. Further analysis will be carried out to better understand whether the absence of HI .3 is the result of either a delay or block in cell cycle progression. To determine whether H1.3 might be responsible for chromatin reorganisation at specific loci we carried out AT AC-seq in the WT and KO cells which be analysed in the light of current knowledge and together with our HI .3-V5 ChIP-Seq,that will determine specific Hl.3 genomic localisation.

In conclusion, we have identified a role for H1.3 in AML cell cycle progression that we are attempting to link to its genomic function. Overall, our work will pose the emerging role of histone linker variants in the phenotype of H3K27meHIST1 high leukaemia.