Spring 5-9-2016

Time course of transcription and chromatin states during batch culture in Chinese Hamster ovary cells

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TIME COURSE OF TRANSCRIPTION AND CHROMATIN STATES DURING BATCH CULTURE IN CHINESE HAMSTER OVARY CELLS

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Key Words: CHO, dynamic landscape, transcription, chromatin modifications, methylation

Chinese Hamster Ovary (CHO) cells are known to be easily adapted to different culture conditions and to be highly variable. Beside genetic alterations, epigenetic regulation, such as histone modifications, can play a role in determining altered cell and production characteristics. Epigenetic control is mainly achieved by DNA-methylation and modifications of histones. The main effect of these modifications is a change in chromatin structure, influencing the transcriptional machinery at the respective locus. So far, there is very little information available about changes in epigenetic regulation in cells in response to altered substrate availability and culture environment.

Here we examine the gene transcription pattern and the chromatin states throughout a batch culture, using RNA-seq every 24 hours as well as chromatin immunoprecipitation and sequencing (ChIP-seq) based on antibodies against 6 histone modifications every 12 hours. These histone modifications were the same as described in the International Human Epigenome Consortium (H3K4me3, H3K4me1, H3K27ac, H3K36me3, H3K27me3 and H3K9me3). In addition, DNA-methylation patterns at exponential and stationary growth phase were determined.

Both transcription and chromatin modifications during different growth phases are highly dynamic, characterized by a gradual and continuous adaptation to the changing substrate and waste concentrations in the culture. Direct impact of chromatin modifications on the function of co-regulated genes as well as the temporal association between transcription and chromatin state is observed, with special focus on modifications that link to gene expression. Apart from the results on epigenetic regulation, the complete data set has been a valuable resource to improve not only the annotation of the reference CHO genome with novel sets of coding and non-coding genes, but also with chromatin states. In addition, differential binding analysis in promotor regions for H3K27ac during changing environmental conditions shows the importance of epigenetic regulation for instance in apoptosis pathways. Such insights into short term epigenetic regulation could assist in optimisation of bioprocess strategies and control of cell death.