Role of PU.1 and C/EBPα in Remodelling the Interleukin (IL)-1β Enhancer-Promoter Interaction

Background:

IL-1β is a potent inflammatory cytokine promptly expressed in activated myeloid immune cells. Among various transcription factors, PU.1 and CCAAT/enhancer-binding protein alpha (C/EBPα) play a key role in the lineage commitment of myeloid cells. To date, however, the exact mechanisms by which these lineage-determining transcription factors employ to regulate the expression of myeloid-specific genes remains elusive; thus, this study explores the role of PU.1 and C/EBPα in remodelling the chromatin conformation that allows ample production of IL-1β.

Methods:

To examine the mechanism of these lineage-determining transcription factors, production of IL-1β and enhancer-promoter interactions were analyzed in non-myeloid B16-BL6 cells that were ectopically expressed with PU.1 and C/EBPα.

Results:

Overexpression of PU.1 and C/EBPα rendered B16-BL6 cells response to the bacterial component lipopolysaccharide (LPS) and expressed IL-1β. These cells also expressed a putative enhancer RNA, located ~10 kbs upstream of the IL-1β transcription start site, in response to LPS. Knocking out the enhancer region reduced IL-1β mRNA expression, suggesting that the genomic region is an enhancer. Based on the chromatin conformation capture-qPCR analysis, IL-1β enhancer-promoter interactions were established upon overexpression of PU.1 and C/EBPα, which was further enhanced by LPS.

Discussion & Conclusion:

These results suggest that PU.1 and C/EBPα are pioneering transcription factors that establish chromatin looping between IL-1β regulatory elements and induce the generation of enhancer RNA, resulting in the production of IL-1β in non-myeloid cells.

Interdisciplinary Reflection:

Our system that investigates how transcription factors can remodel the chromatin landscape will further expand our understanding of gene regulation.