29ème congrès du CHO
11 au 14 octobre 2023
Giens, Var, France

Unraveling the effects of the leukemogenic Benzene metabolite,1,4-benzoquinone, on retrotransposition activation and global chromatin accessibility in hematopoietic cells

Han Xiao[1], Romain Aucagne[1,2], Mary Callanan[1,2], Laurent Delva[1], Fernando Rodrigues-Lima[3], Fabien Guidez[1]

1- Inserm UMR 1231, Team Epi2THM, LabEx LipSTIC Team, UFR des Sciences de Santé, Université de Bourgogne, Dijon
2- Unit for Innovation in Genetics and Epigenetics in Oncology, Dijon University Hospital, and Crispr-Functional Genomics (CRIGEN), CHU François-Mitterrand and Université de Bourgogne, Dijon
3- CNRS UMR 8251 - BFA, RMCX Team, Université Paris Cité, Paris

---

Understanding the mechanism of benzene toxicity in the hematopoietic system has slowly progressed during the years. It is now well established that benzene and its metabolites, particularly 1-4 benzoquinone, can influence gene expression and cell behavior, leading to tumorigenesis. Thus, DNA methylation is a major attribute of benzene effect and significant global hypomethylation of LINE-1 retrotransposons. However, little is known concerning the molecular mechanisms leading to this benzene-induced hypomethylation of LINE-1 and the possible retrotransposition activation in hematopoietic cells.

We and others have shown that the Promyelocytic Leukemia Zinc Finger (PLZF) protein is a factor involved in leukemogenesis and is also crucial for the development and homeostasis of hematopoietic stem cells (HSCs) and iNKT cells through posttranscriptional regulation of PLZF by acetylation. Additionally, PLZF has been identified as a key epigenetic regulator of DNA methylation patterns in HSCs, specifically targeting retrotransposon sequences in the HSC genome and silencing LINE-1 elements.

In this study, our aim was to investigate the impact of 1,4-benzoquinone at varying concentrations on LINE-1 DNA methylation and retrotransposition in hematopoietic cells. Furthermore, we explored the potential involvement of the PLZF protein in this process by testing its acetylation levels, DNA binding activity, and epigenetic functions. Moreover, we assessed global DNA methylation changes using dot

blot assays, specific DNA methylation of LINE-1 elements and examined variations in global chromatin accessibility through the application of Assay for Transposase-Accessible Chromatin with high-throughput sequencing (ATAC-seq).

Our results underline an inhibition of PLZF acetylation induced by 1,4-benzoquinone, leading to a loss of PLZF binding to its genomic targets and a decrease of DNA methylation. Thus, genomic hypomethylation of hematopoietic cells is associated with activation of LINE-1 element and increased retrotransposition.

By shedding light on the intricate mechanisms underlying benzene toxicity, our study aims to contribute to a deeper knowledge of hematological disorders induction by abnormal benzene exposure.