Epigenetic deregulation in AML

Acute myeloid leukemia (AML) is the most common acute leukemia diagnosed in adult patient, characterized by its high heterogeneity in terms of biology and clinical outcome. Despite progresses in the molecular characterization and prognosis refinement of this disease (Grimwade, *et al.,* 2016), the general approach to current therapy has not changed substantially in recent years. Our group is interested in epigenetic deregulations that are at the center of AML onset and offer potential avenues for targeted therapies. Epigenetic regulation can be achieved by multiple mechanisms including reversible post-translational modifications of histones ensured by specialized enzymes. Several genes with a key role in epigenetic regulation are found mutated in AML, leading to modification of gene expression patterns (Wouters and Delwel, 2016).

We have focused on the biological and clinical impact of deregulation of EZH2, the histone methyltransferase, which catalyzes the trimethylation of histone3 on lysine27 (H3K27me3), in leukemias. In T-acute lymphoid leukemias (ALLs), we identified micro-insertions in a unique site 5' of TAL1 that induces selective loss of repressive TAL1 by H3K27me3 silencing at the inserted allele (Navarro *et al*., 2015). In myeloid cells, we revealed a unique partnership between the promyelocytic zinc finger transcription factor, PLZF and EZH2 that revealed a non-canonical EZH2 activity (Koubi *et al*., 2018).

By performing H3K27me3 profiling in the cytogenetically normal (CN) AML entity, we uncovered a remarkable H3K27me3 enrichment at the chromosome 6 p22.2-22 region that encompasses 70 Kbp within the major *HIST1* cluster an characterized a subgroup of AML patients (Tiberi*, et al.*, 2015). This islet of the repressive H3K27me3 mark (named H3K27me3 HIST1^{high}) is found in what is normally a highly transcribed chromosomal region and suggests a located deregulation of EZH2. It is associated with the presence of an NPM1-mutated allele (NPM1mut) but not with known mutations in chromatin modifiers and predicts a good prognosis (Patent WO2015169906-A1). Following this, studies have shown that the H3K27me3 HIST1^{high} condition was associated with a mature gene expression profile and a peculiar pattern of lower histone gene expression in comparison to H3K27me3 HIST1^{low}. Thus, H3K27me3 *HIST1* status and histone mRNA levels define clinically and biologically different subgroups of CN-AML, suggesting their importance in AML development

The main objective of the project is to understand why some leukemic patients have this abnormal H3K27me3 deposition that influences leukemia onset. Using tools and cellular models developed by the host laboratory the student will decipher mechanisms behind this abnormal and local H3K27me3 deposition. Histone genes require a specific nuclear environment that gathers a distinct set of factors to produce mature mRNAs called the Histone Locus Bodies (HLBs). Considering the importance of HLB integrity in *HIST1* locus expression, the student will address the connection between, H3K27me3 and EZH2 activity, HLB (dis)organisation and leukemia. This program will advance in the current knowledge on the role of nuclear and chromatin architecture in gene regulation and cancer progression and may reveal an important role of H3K27me3/EZH2 deregulation and epigenetic control of transcription in leukemic cells.

References

Grimwade, D., *et al*., (2016). Blood *127*, 29-41.
Wouters, B.J., and Delwel, R. (2016). Blood *127*, 42-52.
Navarro, J.M., *et al.* (2015). Nat Commun *6*, 6094.
Koubi, M., *et al.* (2018). Nucleic Acids Res *46*, 3339-3350.
Tiberi, G., *et al.* (2015). Leukemia *29*, 1202-1206.