Claudia Binda
Department of Genetics and Microbiology
Lysine-specific Histone Demethylase (LSD1): Oxidative Chemistry for Chromatin Remodelling
Prof Andrea Mattevi.

In the last years, we have studied a nuclear protein complex formed by the association of histone deacetylase 1, a co-repressor protein CoREST, and a protein formerly known as KIAA0601 or BHC110. Our group and the group of Y. Shi (Harvard University) have discovered that this protein is a lysine-specific histone demethylase (now called Lysine Specific Demethylase 1; LSD1) that specifically acts on Lys4 of histone H3.
Three years after this discovery, LSD1 remains at the forefront of chromatin research. Its demethylase activity on Lys4 of histone H3 supports its role in gene repression. Data from our and other laboratories indicate that the complex formed by LSD1 with histone deacetylases 1/2 functions as a "double-blade razor" that first eliminates the acetyl groups from acetylated Lys residues and then removes the methyl group from Lys4. By contrast, the biochemical mechanisms underlying LSD1 involvement in transcriptional activation are not firmly established and remain an open problem for future research.
Our structural studies of the CoREST/LSD1 complex highlight a specific binding site for the histone H3 N-terminal tail and a catalytic machinery that is closely related to that of other flavin-dependent amine oxidases. These insights are critical for the development of demethylation inhibitors. A challenge for future studies will be to extend these structural investigations to visualize nucleosome binding by LSD1-containing protein complexes through biophysical methods and biocrystallography. Furthermore, the exploration of putative non-histone substrates and potential signaling roles of hydrogen peroxide produced by the demethylation reaction could lead to new paradigms in chromatin biology.

References

1. Forneris, F., **Binda, C.**, Battaglioli, E., Mattevi, A. LSD1: Oxidative Chemistry for Multifaceted Functions in Chromatin Regulation. Trends Biochem. Sci. **33**, (2008) 181.