Ms.C. project: Interfering with the actions of enzymes involved in epigenetic regulation.

In recent years, the accessibility of chromosomes has been shown to be controlled by chemical modifications of the histones (Fig. 1). For each lysine in the histone tail, there is correlation between the degree of methylation and the compactness of the area of the chromosome (Mosammaparast & Shi, 2010). Mechanisms like these are called epigenetic gene regulation. Cancer is, among other things, characterized by abnormal expression of genes in a given cell type (Hanahan & Weinberg, 2011). Therefore, the enzymes involved in epigenetic regulation are obvious targets for new drugs targeting cancer (Højfeldt et al., 2013). The KDM5 family of histone demethylases can demethylate H3K4me3 markers and thus quench the expression of a gene, for example, for a gene encoding a tumor repressor. Specifically, the enzyme KDM5B is known to be overexpressed in a variety of forms of cancer (Li et al., 2014). Therefore, it has also been attempted to develop small molecule inhibitors that bind in the enzyme's active site. Drugs that are selective to the KDM5 family have been found and they have recently been reviewed (Kaniskan et al., 2018). However, no drugs that are selective between KDM5 family's four members have been found. This is due to high structural similarity between the active site in the KDM5 enzymes. Selectivity within the family is important as the four enzymes control widely different genes. An alternative way to achieve inhibition is to prevent KDM5B from interacting with chromatin. Rational development of substances that can prevent specific interaction between KDM5B and chromatin is based detailed knowledge of the 3-dimensional structure of full length KDM5B a structure that we have determined to low resolution.

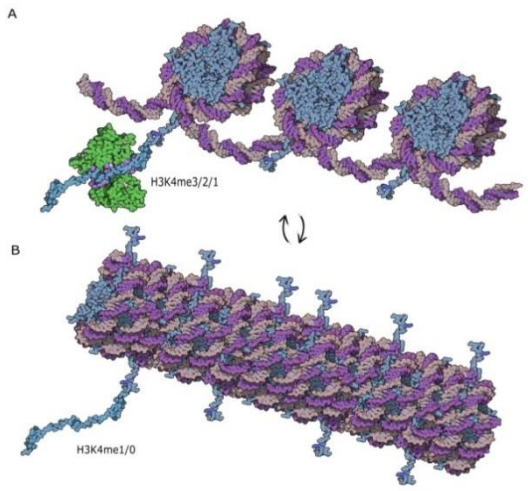

Fig. 1: The role of KDM5B in the regulation of genes. A. Genes available for transcription and thus expression of protein are characterized by the presence of 3 methyl groups on the fourth amino acid in the tail of histone 3 of the nucleosome. All of these methyl groups can be removed by KDM5B. B. After removal of these methyl groups, the gene becomes inaccessible for transcription (packaged). If the gene in question functions as a tumor repressor, inhibition of KDM5B will cause the tumor repressor to be expressed. This will counteract the development of cancer.

Within this area we have an opening for one Ms. C. Project. The actual content of the project will be dependent on exactly what we have accomplished at the time of the project and on interest of the student. Techniques that can be used include general molecular biology, expression of recombinant proteins, biophysical characterization, in vitro assays, crystallization, X-ray diffraction and electron microscopy again dependent on the interests of the student.

Contact: Michael Gajhede, mig@sund.ku.dk tlf. 35336407

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