2. Abstract

Histone methylation plays an important role in almost all cellular processes and its homeostasis is maintained by histone methyltransferases and histone demethylases. Misregulation of histone methylation levels is associated with gene expression misregulation and consequently also with various developmental defects and diseases. In this thesis we focus on the lysine demethylases KDM2A and KDM2B and on their demethylation deficient isoforms KDM2A-SF and KDM2B-SF. The lysine specific demethylases KDM2A and KDM2B have been predominantly studied for their demethylation function on CpG island-rich gene promoters. However, KDM2A-SF and KDM2B-SF have not been studied in detail. Therefore, the main goal of this thesis was to characterize KDM2A-SF more in detail and to focus on the role that KDM2A/B-SF might potentially play in canonical Wnt signaling pathway. We found that the *KDM2A-SF* mRNA arises through the action of an alternative intronic promoter and not by alternative splicing. We showed that the KDM2A-SF start codon is located in the exon that corresponds to KDM2A exon 14 and we thus determined the exact amino acid sequence of the KDM2A-SF protein. Furthermore, using an isoform specific knockdown assay we showed that KDM2A-SF, unlike KDM2A-LF, forms distinct nuclear foci on pericentromeric heterochromatin dependingly on the heterochromatin protein HP1α. These transcriptionally silent pericentromeric regions exhibit high levels of H3K36me2. Since H3K36me2 is the substrate of the KDM2A demethylase activity, we concluded that these regions are occupied by the demethylase deficient KDM2A-SF isoform. Further, we demonstrated that KDM2A-SF and KDM2B-SF repress canonical Wnt signaling despite lacking the demethylase domain. This thesis highlights the importance of distinguishing between different protein isoforms and their different functions, which can be sometimes even antagonistic.