Targeting lysine-specific demethylase 1 (KDM1A/LSD1) impairs colorectal cancer progression by inducing cancer stem cells differentiation

LB-01.1-05

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Among all cancers, colorectal cancer (CRC) is the 3rd most common and the 2nd leading cause of death worldwide. New therapeutic strategies are required to target cancer stem cells (CSCs), a subset of tumor cells highly resistant to therapy and responsible for tumor relapse. CSCs display dynamic genetic and epigenetic alterations that allow quick adaptations to perturbations. Lysine-specific histone demethylase 1A (KDM1A), a FAD-dependent H3K4me1/2 and H3K9me1/2 demethylase, was found to be upregulated in several tumors and associated with a poor prognosis due to its ability to maintain CSCs staminal features. Here, we explored the potential role of KDM1A targeting in CRC by characterizing the effect of KDM1A silencing in differentiated and CRC stem cells (CRC-SCs). In CRC primary samples, KDM1A expression was associated with a worse prognosis, confirming its role as an independent negative prognostic factor of CRC. Consistently, our untargeted omics approach revealed the association of KDM1A silencing with CRC-SCs cytoskeletal and metabolism remodeling towards a differentiated phenotype (e.g., increased expressions of brush border’s protein villin, and ketogenic enzyme 3-hydroxy-3-methylglutaryl-coenzyme A synthase 2) resulting in loss of stem properties as well as cell migration and invasion. Validation by biological assays, such as methylcellulose colony formation assay, demonstrated a significantly decreased self-renewal potential in KDM1A-silenced CRC-SCs. Besides, proteomic analysis disclosed the activation of a collateral mitochondrial metabolic pathway independent from succinate-CoA ligase GDP-forming subunit beta 2, suggesting a key role of KDM1A in cell metabolism reshaping. Lastly, loss of KDM1A markedly reduced 53BP1 DNA repair foci, implying the involvement of KDM1A in the DNA damage response. Overall, our results indicate that KDM1A plays a key role in CRC progression and therefore it represents a promising epigenetic target to prevent tumor relapse.