Metformin regulates cells epigenomic landscape leading to decreased proliferation and inflammation in hepatocytes

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Abstract

Metformin is the first-line oral therapy for type 2 diabetes. It has been approved for use in other diseases, like polycystic ovary syndrome, obesity, and promising clinical trials for cancer. However, metformin's mechanism remains to be entirely elucidated, with its potent anti-aging, anti-carcinogenic, and epigenetic-regulator effects commonly seen but not thoroughly explained. We propose a mechanism for metformin's beneficial effect on inflammation and proliferation, hyper and down expressing transcripts which act as potent epigenetic regulators. We analyzed high-throughput RNA-seq data of primary human hepatocytes with the standard laboratory pipeline. Then, we selected transcripts that acted as epigenomic regulators according to our functional enrichment analysis and queried their translated sequences for the presence of whole domains. From all differentially expressed transcripts (DETs), six were present in epigenetic regulation pathways, four upregulated and two downregulated, all being protein-coding transcripts with their active domains present. The four upregulated DETs belong to the histone lysine demethylase (KDM) subfamily and use a JumonjiC (JmjC) domain that converts a-ketoglutarate (a-KG) to succinate during the demethylation process. High levels of succinate inhibit a-KG conversion, and metformin is known to reduce intracellular succinate levels, leading to increased activity of KDMs. At the gene-level, our candidate KDMs were also up-regulated in hepatocellular carcinoma (HCC), which does not comply with metformin proposed effects of reducing inflammation and proliferation. Articles that linked KDMs super expression to proliferation did not analyze at the isoform-level, and a previous study showed that KDM isoforms that retain the JmjC domain show an anti-carcinogenic effect. Contrastingly, the ones which increase proliferation are short isoforms that lost the JmjC domain. Therefore, according to our data Metformin would upregulate the anti-carcinogenic KDMs. The two other DETs were downregulated isoforms of the Methionine Adenosyltransferase 2A (MAT2A). MAT2A is the leading synthesizer of S-adenosylmethionine (SAM), the main cellular donator of methyl groups. On Liver it is mostly expressed in extra-hepatic tissues, while its paralogue, MAT1A, is present in hepatocytes. A switch in MAT1A:MAT2A ratio in hepatocytes is positively correlated to liver diseases, such as HCC and fibrosis. Metformin downregulating MAT2A leads to more presence of MAT1A, which increases SAM, leading to more methyl groups available. Our findings point towards a robust epigenetic regulatory axis controlled by isoform-specific differential expression induced by metformin. This mechanism leads to new understanding of metformin's role in the hepatic microenvironment and new ways in which those pathways can be targeted in hepatic disorders.

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Link to Video: