



# Potential Role for the Metnase Transposase Fusion Gene in Colon Cancer through the Regulation of Key Genes

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## Abstract

The Metnase fusion gene consists of a SET histone methyltransferase domain and a transposase domain from Mariner transposase. This transposable element is involved in chromosome decatenation, enhances DNA repair, promotes foreign DNA integration, and assists topoisomerase II function. This study investigates the role of Metnase in colon cancer homeostasis and maintenance of the stemness phenotype in colon cancer stem cells (CSCs). Silencing of Metnase was performed in human cancer cell lines before and after treatment with cisplatin, and in colon CSCs. Subsequent changes in the expression of genes involved in repair mechanisms, DNA synthesis, topoisomerase II function, and metastasis as well as stemness transcription factors were studied with RT-qPCR experiments. Cellular viability and apoptosis were evaluated by flow cytometry. The results suggest that Metnase influences the expression of many genes involved in the above processes. Furthermore, Metnase levels appear to impact upon expression of NANOG, OCT3/4, and SOX2. Suppression of Metnase also led to an increase in apoptosis. Therefore, Metnase may possess an important role in DNA repair, topoisomerase II function, and the maintenance of stemness during colon cancer development.

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## Introduction

Metnase is a fusion gene with a SET histone methyltransferase domain and a Mariner transposase domain. Several of the main functions of HsMar1 transposase are shared with Metnase [1]. Metnase is a non-homologous end-joining (NHEJ) repair protein [2], and is involved in many cellular processes including mediation of foreign DNA integration, chromosome decatenation [3], and DNA repair [4] and replication [5]. Metnase further mediates resistance to topoisomerase II inhibitors through an interaction with topoisomerase (DNA) II alpha (TOP2A) [6]. These established roles in combination with recent experimental data suggest that Metnase may have a crucial role in cancer development and progression, which could be exploited during cancer treatment.

Colorectal cancer is the second leading cause of cancer in women, the third in men, and the fourth most common cause of cancer death overall [7]. The use of platinum-based chemotherapeutics is commonplace in treatment regimes. However, many patients either possess or develop resistance to these compounds [8]. Furthermore, cancer stem cells (CSCs) have the capacity for self-renewal and are resistance to chemotherapy and radiation treatment [9]. Therefore, improvements to current treatment strategies are required.

The present study examines the relationship between Metnase gene expression and colorectal cancer development. As transpos-

able genetic elements are implicated in genome rearrangement, they may regulate many transcription factors. These factors could in turn regulate genes that are involved in resistance, metastasis, or apoptosis. An evaluation of the complement of genes that are affected by Metnase as well as their correlation with basic cellular activities may enhance our understanding of how Metnase influences cancer development. Such knowledge could also contribute to improvements in cancer treatment programs.

This study examines the expression levels of several genes important in cellular development and DNA synthesis and repair before and after knockdown of Metnase by siRNA. These genes were DNA excision repair protein (ERCC1), dipeptidylpeptidase IV (CD26), Met proto-oncogene (cMET), TOP2A, topoisomerase (DNA) II beta (TOP2B), thymidylate synthase (TYMS) and DNA (cytosine-5-)-methyltransferase 1 (DNMT1). The effect of Metnase silencing was also investigated in a colorectal cancer cell line following treatment with cisplatin. While oxaliplatin is mainly used in clinical settings, here we wished to investigate the role of Metnase in a resistant cell line. According to experiments that were previously performed in the HCT-116 cell line, we have found that more resistance mechanisms develop following treatment with cisplatin. Finally, a potential relationship between Metnase and maintenance of the stemness phenotype of colon CSC was investigated by silencing Metnase and measuring levels