KMT9 Controls Stemness and Growth of Colorectal Cancer

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1. **簡述論文概要與重大發現:**

早期由於結直腸癌症狀不易被發現，大多數的人到了晚期才接受治療，尤其癌細胞擴散到身體遠處部位時，生存率大幅降低。然而作者發現了新型組蛋白賴氨酸甲基轉移酶 KMT9，先前的文獻紀載了 KMT9 單甲基化 H4K12me1，從而控制調節前列腺和肺癌細胞增殖的基因。值得注意的是，高水平的 KMT9 與前列腺癌和肺癌患者的低生存率有關。而作者在結直腸癌的小鼠模型中研究了 KMT9 在體外人和小鼠類器官系統以及體內結直腸癌中的功能。數據顯示 KMT9 是結直腸癌細胞增殖和幹性的重要調節因子，這使 KMT9 成為結直腸癌的潛在治療靶點。

2. **對論文內容的疑問:**

在研究中已證實 Kmt9$\alpha^{fl/fl}$ 加入 TAM 後會使 Kmt9α 在腸上皮細胞造成特異性缺失，使腫瘤的尺寸、數量、重量減少，然而在圖 1I 的數據中，為何 Kmt9α 的 mRNA 表達還有 50%?

3. **論文的缺點、評論:**

雖然本篇研究證實了體外和體內沒有 KMT9α 的情況下，炎症誘導的腫瘤以及散發性結直腸癌的生長顯著減少，是因為 KMT9α 能破壞參與增殖、細胞週期進程和細胞凋亡的基因的調節來損害腫瘤生長。然而 KMT9 的缺失在 AOM/DSS 治療後的炎症或再生過程中可能會發揮作用，這值得進一步研究。

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ABSTRACT

Colorectal cancer is among the leading causes of cancer-associated deaths worldwide. Treatment failure and tumor recurrence due to survival of therapy-resistant cancer stem/initiating cells represent major clinical issues to overcome. In this study, we identified lysine methyltransferase 9 (KMT9), an obligate heterodimer composed of KMT9α and KMT9β that monomethylates histone H4 at lysine 12 (H4K12me1), as an important regulator in colorectal tumorigenesis. KMT9α and KMT9β were overexpressed in colorectal cancer and colocalized with H4K12me1 at promoters of target genes involved in the regulation of proliferation. Ablation of KMT9α drastically reduced colorectal tumorigenesis in mice and prevented the growth of murine as well as human patient-derived tumor organoids. Moreover, loss of KMT9α impaired the maintenance and function of colorectal cancer stem/initiating cells and induced apoptosis specifically in this cellular compartment. Together, these data suggest that KMT9 is an important regulator of colorectal carcinogenesis, identifying KMT9 as a promising therapeutic target for the treatment of colorectal cancer.

Significance: The H4K12 methyltransferase KMT9 regulates tumor cell proliferation and stemness in colorectal cancer, indicating that targeting KMT9 could be a useful approach for preventing and treating this disease.

Introduction

Colorectal cancer, which includes hereditary, sporadic, and colitis-associated forms, is one of the leading causes of cancer-associated deaths worldwide (1). Four distinct consensus molecular colorectal cancer subtypes (CMS1–4) have been defined based on gene expression signatures, DNA methylation status, somatic copy number alterations, miRNA regulation changes, and presence of genetic aberrations in tumor suppressor genes [e.g., tumor protein p53 (*TP53*), adenomatous polyposis coli protein (*APC*)] or oncogenes [e.g., kristen rat sarcoma viral oncogenes (*KRAS*); refs. 2–6]. To date, systemic therapeutic options for colorectal cancer include chemotherapy (adjuvant and neoadjuvant) and to a lesser extent, therapeutic antibodies directed against growth factor receptors, for example, vascular endothelial growth factor receptor (VEGFR; ref. 7). Despite treatment, 30% to 40% of human patients relapse and suffer from tumor recurrence (8). This has been attributed to the acquirement of genetic aberrations during therapy and survival of cancer stem/initiating cells (CSC; ref. 9). CSCs and adult intestinal stem cells in the healthy gut have similar characteristics with respect to their self-renewal and differentiation capacity (10). For example, leucine-rich repeat containing g-protein–coupled receptor 5 (*LGR5*), a well-established target of the *WNT* signalling pathway, is expressed in benign intestinal stem cells and also defined as a CSC marker because *LGR5*-expressing (*LGR5*$^+$) tumor cells have a high clonogenic capacity (11–13). Currently, resistant CSC populations are poorly characterized and therapeutic strategies for targeting CSCs remain to be identified (14, 15). One important feature of CSCs is their dynamic ability to switch between proliferative or differentiated states by modulating gene expression, which suggests the existence of epigenetic regulation (16).

Histone methyltransferases (HMT) catalyze the transfer of a methyl group from S-adenosyl-methionine (SAM) to lysine or arginine residues of histones. Histone methylation regulates various biological processes including proliferation, cell cycle, and stemness (17). Aberrant expression of histone methytransferases contributes to global changes of the histone methylation landscape, which has been associated with colorectal cancer development, progression, and patient survival (18). Therefore, targeting epigenetic regulators such as HMTs has been proposed as therapeutic strategy for colorectal cancer (19–21).

Recently, we identified the novel histone lysine methyltransferase KMT9 (22). KMT9 functions as an obligatory heterodimer composed of KMT9α (also named N6AMT1) and KMT9β (also named TRMT112), and their interaction is required for SAM binding and methyltransferase activity (22). KMT9 monomethylates lysine 12 of histone H4 (H4K12me1), thereby controlling genes that regulate proliferation of prostate and lung cancer cells (22, 23). Of note, high levels of KMT9 have been associated with poor patient survival in

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Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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