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In silico and in vivo analysis of the curative potential of curcumin in colitis- associated colorectal cancer

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Abstract

Background:

Curcumin, a natural polyphenol, has been used as a powerful anti-inflammatory and anti-oxidant medicine. However, Inductible nitric oxide synthase (NOS2) have been linked to the remodeling of tumor microenvironment. This study aims to investigate the chemopreventive and pharmacological modulation of curcumin on NOS2 and its correlation with prognosis and macrophage infiltration in colitis associated colon cancer in silico and confirmed in vivo.

Methods

We investigated NOS2 distribution and prognostic signature in colorectal cancer (CRC) patients using data from TCGA public datasets. The correlation of NOS2 expression with immune invasion was performed using cibersort. Molecular docking of curcumin with NOS2 was performed using Autodock Vina.

Colitis-associated colorectal cancer(C-CRC) was initiated in mice with two subcutaneous injections of 20 mg/kg dimethylhydrazine (DMH), a specific colon carcinogen, followed by 2% dextran sodium sulfate (DSS, orally). Curcumin (Cur, 60 mg/kg/day, orally) was administered from the 8th to 12th week. The colons recovered after mice sacrifice were subjected to biochemical, histological and immunohistochemistry analyzes.

Results

Based on TCGA database, NOS2 expression-significantly increased in several cancers, including CRC. NOS2 change alteration is related to the methylation of its promoter in CRC ($p< 0.001$). Correlation of NOS2 expression with tumor immune invasion showed that NOS2 alteration is associated with higher pro-inflammatory M1 macrophages infiltration ($p< 0.05$) and lower anti-inflammatory M2 macrophages ($p< 0.05$). Molecular docking confirmed NOS2 as a target of curcumin with a bound energy lower than 7 kcal/mol.

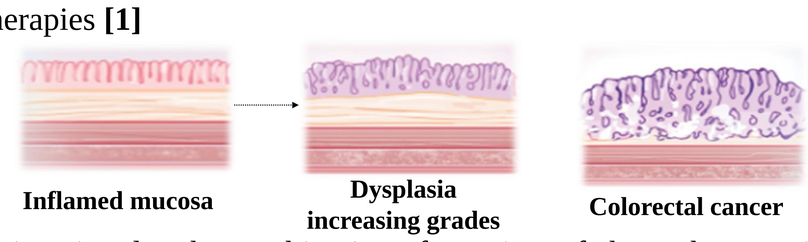
In vivo C-CRC showed colorectal adenomas with high-grade dysplasia, extensive cell proliferation, oxidative inflammation with severe M1 macrophage infiltration. Moreover, the ratio of nitrites (a marker of macrophages M1 polarization and iNOS activity) / arginase (a marker of macrophages M2 polarization) increased by about 2.4-fold ($p< 0.01$). Curcumin treatment significantly reduced-histological features of dysplasia and inflammation and-decreased the nitrites/arginase ratio by about 1.75-fold ($p< 0.05$), suggesting the shift of immune response to anti-inflammatory M2 phenotype.

Conclusion

These results demonstrated the efficacy of Cur in reducing inflammation and nitrosative stress during C-CRC through the blockade of NOS2 signaling, displaying the future prospects and investigation for curcumin as a therapeutic agent that are indeed promising.

Introduction

Colitis-associated cancer is the CRC subtype that is associated with inflammatory bowel disease (IBD) is difficult to treat, and has high mortality despite markedly improved response rates to current systemic therapies **[1]**



Current therapy options involve the combination of a variety of chemotherapeutic drugs, including the third generation **platinum-based drug oxaliplatin (Eloxatin)** which resulted in increased survival rates despite its sides effects

Macrophages as an essential component of the tumor-associated immune response are correlated with poor prognosis. At the same time, studies have highlighted the role of macrophages in chemoresistance through the secretion of factors modifying the response of cancer cells.

Curcumin, a natural polyphenolic antioxidant, has been shown to effectively inhibit tumor growth. Recent studies indicate that curcumin can modulate the tumor immune response microenvironment

Materials

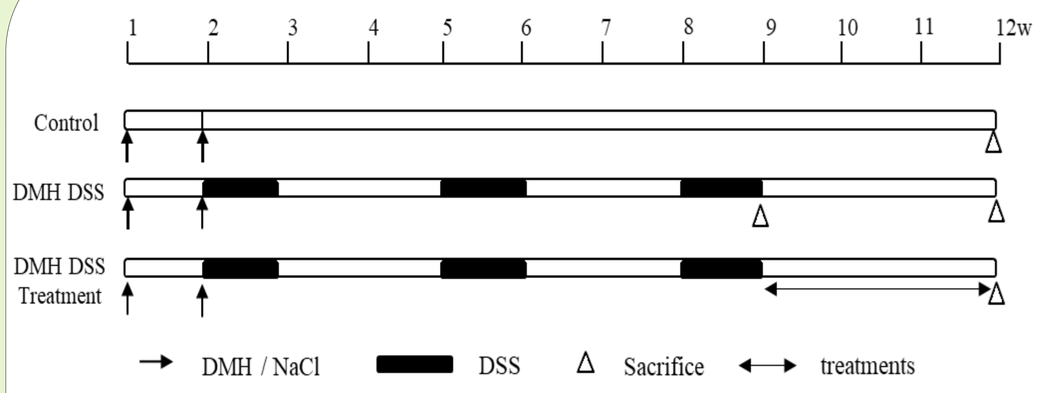
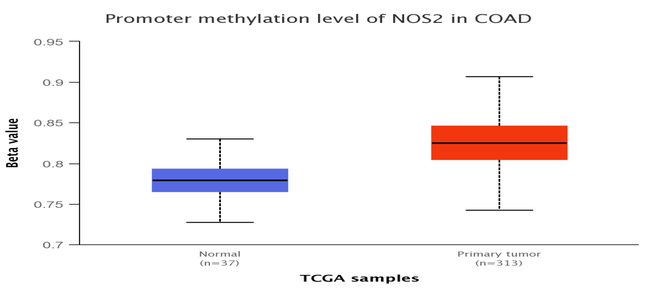


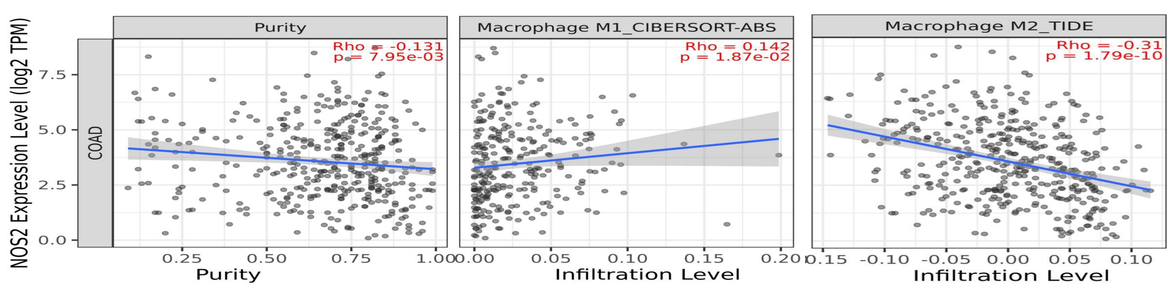
Fig. 3. Experimental design of DMH/DSS-induced inflammation associated mouse colon carcinogenesis.

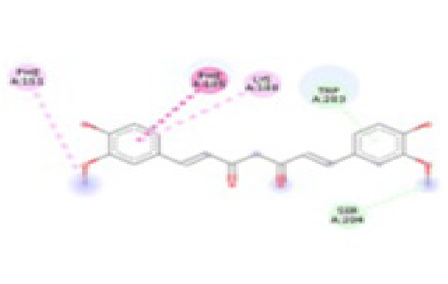
After sacrifice, mice liver samples were subjected to **histological and biochemical analysis**

Results

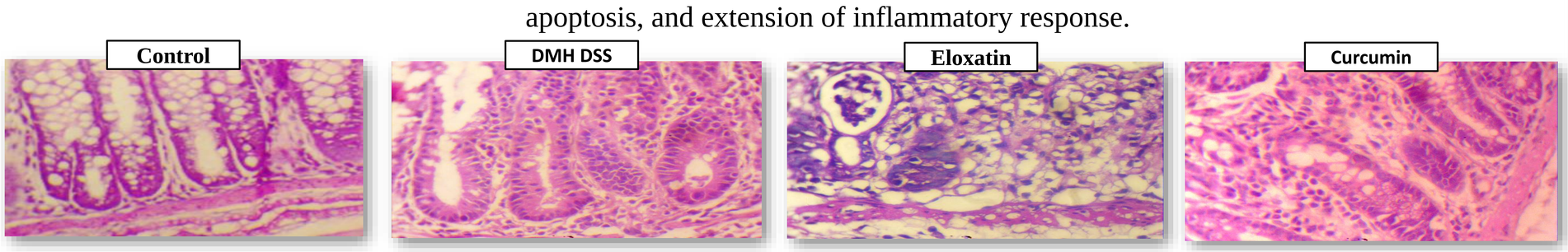
Bioinformatic analysis of NOS2 alteration and correlation to macrophages infiltration in human CRC, and its molecular docking with Curcumin

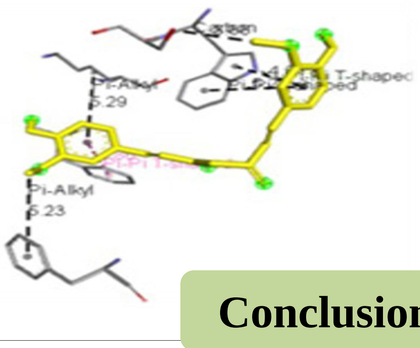




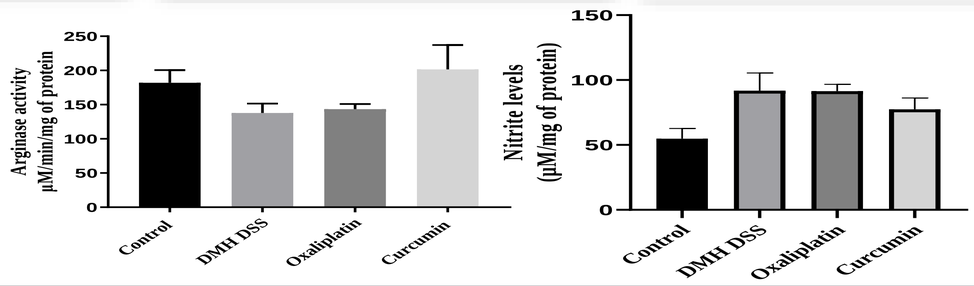


Formalin-fixed tissue was paraffin embedded, sectioned 5µm, and stained with H&E. Section was evaluated for cell cytology, apoptosis, and extension of inflammatory response.





Biochemical analysis of arginase activity and nitrite levels in DMH-DSS treated colon of mice



Conclusion

We provides further evidence that curcumin may be of use in therapeutic regimes directed against colorectal cancer and suggests that in combination with Eloxatin (oxaliplatin) may enhance chemotherapeutic efficacy.

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