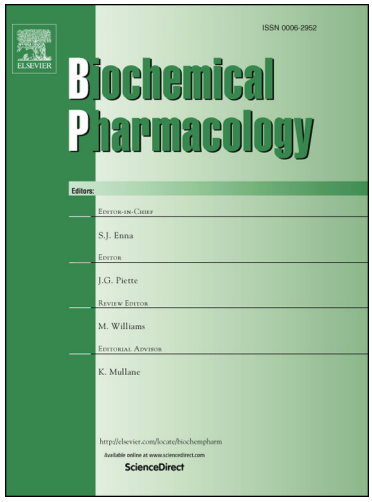
Accepted Manuscript



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PII: S0006-2952(16)30130-7
DOI: http://dx.doi.org/10.1016/j.bcp.2016.06.004
Reference: BCP 12564

To appear in: *Biochemical Pharmacology*

Received Date: 2 April 2016
Accepted Date: 7 June 2016

Please cite this article as: J. Yao, J. Xie, B. Xie, Y. Li, L. Jiang, X. Sui, X. Zhou, H. Pan, W. Han, Therapeutic effect of hydroxychloroquine on colorectal carcinogenesis in experimental murine colitis, *Biochemical Pharmacology* (2016), doi: http://dx.doi.org/10.1016/j.bcp.2016.06.004

Therapeutic effect of hydroxychloroquine on colorectal carcinogenesis in experimental murine colitis

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Running title: Therapeutic effect of HCQ on CAC

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Keywords: hydroxychloroquine; colitis-associated colorectal cancer; macrophages; toll-like receptor 4; reactive oxygen species.

ABSTRACT

Chronic inflammation in the intestine is a strong risk factor for colitis-associated colorectal cancer (CAC). Hydroxychloroquine (HCQ) is widely used as an anti-inflammatory drug in the treatment of immune-mediated inflammatory disorders and various tumors. However, little is known regarding the effects of HCQ on colitis-associated tumorigenesis. In this study, mice treated with HCQ showed a significant reduction in early-stage colitis following azoxymethane (AOM)/dextran sodium sulfate (DSS) administration, as well as a remarkable inhibition of colonic tumorigenesis and tumor growth at late stages of CAC. Mechanistically, the therapeutic effects of HCQ were attributed to inhibition of inflammatory responses and production of mutagenic reactive oxygen species (ROS) in immune cells and subsequent promotion of apoptosis and cell cycle arrest in tumor cells. Furthermore, we found that HCQ inhibited the production of inflammatory cytokines and ROS in response to toll-like receptor 4 (TLR4) activation in macrophages. Our data presented herein may help guide the clinical use of HCQ as a prevention and treatment strategy for CAC.

1. Introduction

Inflammation is a strong risk factor for many cancers. Colitis-associated colorectal cancer (CAC), which is associated with inflammatory bowel disease (IBD), including ulcerative colitis