Rifaximin induces a PXR-mediated antiproliferative effect and inhibits angiogenic factors release in Caco-2 cell line.

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Chronic inflammation is a known risk factor for carcinogenesis, and accumulated data indicate that up to 15% of human cancer incidence is associated with inflammation (Drexler and Yazdi, 2013). Activation of intestinal human pregnane X receptor (PXR) has recently been proposed as a promising strategy for the chemoprevention of inflammation-induced colon cancer. Several signalling molecules responsible for the initiation and perpetuation of chronic inflammation are also involved in the promotion of angiogenic process (Cianchi F et al., 2003). Rifaximin is a semi-synthetic antibiotic largely used for the treatment of travelers' diarrhea and hepatic encephalopathy (Mullen KD et al., 2014; de la Cabada Bauche J and Dupont HL, 2011). It is poorly absorbed on oral administration and as such has an optimum safety profile. Apart from its antibiotic potential, rifaximin has also been studied for its anti-inflammatory effects; several studies have highlighted the anti-inflammatory potential of rifaximin, which is mainly attributed to the inhibition of the NF-κB signaling and NO release via activation of intestinal human pregnane X (PXR) receptors (Cheng J et al., 2010; Mencarelli A et al., 2011). The present study was aimed at evaluating the effect of rifaximin on cell proliferation, in inhibiting angiogenesis in a model of human colorectal epithelium and investigating the role of PXR in its mechanism of action. Caco-2 cells were treated with rifaximin (0.1, 1.0 and 10.0 μM) in the presence or absence of ketoconazole (10 μM), a know antagonist of human PXR receptor, and assessed for cell proliferation, migration and expression of proliferating cell nuclear antigen (PCNA). The release of vascular endothelial growth factor (VEGF) and nitric oxide (NO), expression of Akt, mechanistic target of rapamycin (mTOR), p38 mitogen activated protein kinases (MAPK), nuclear factor κB (NF-κB) and metalloproteinase-2 and -9 (MMP-2 and -9) were also evaluated. Treatment with rifaximin 0.1, 1.0 and 10.0 μM caused significant and concentration-dependent reduction of cell proliferation (-25, -40 and -68%), cell migration (-18, -30 and -46%) and PCNA expression (-29, -53 and -76%) in the Caco-2 cells vs. untreated cells. Treatment downregulated VEGF secretion (-32, -45 and -72%), NO release (-40, -69 and -87%), VEGFR-2 expression (-33, -58 and -65%) and MMP-2 (-25, -62 and -87%) and MMP-9 expression (-38, -56 and -78%) vs. untreated cells. Rifaximin treatment also resulted in a concentration-dependent decrease in the phosphorylation of Akt (-50, -75 and -86%), mTOR (-38, -56 and -78%), p38MAPK (-24, -62 and -71%) and inhibition of HIF-1α (-65, -82 and -92%), p70S6K (-27, -55 and -85%) and NF-κB (-29, -55 and-61%). Ketoconazole (PXR antagonist) treatment inhibited these effects. These findings demonstrated that rifaximin causes PXR-mediated inhibition of angiogenic factors in Caco-2 cell line and may be a promising anticancer tool.

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