Irinotecan induces steroid and xenobiotic receptor (SXR) signaling to detoxification pathway in colon cancer cells

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Résumé en anglais
Background Resistance to chemotherapy remains one of the principle obstacles to the treatment of colon cancer. In order to identify the molecular mechanism of this resistance, we investigated the role of the steroid and xenobiotic receptor (SXR) in the induction of drug resistance. Indeed, this nuclear receptor plays an important role in response to xenobiotics through the upregulation of detoxification genes. Following drug treatments, SXR is activated and interacts with the retinoid X receptor (RXR) to induce expression of some genes involved in drug metabolism such as phase I enzyme (like CYP), phase II enzymes (like UGT) and transporters (e.g. MDR1). Results In this study, we have shown that endogenous SXR is activated in response to SN-38, the active metabolite of the anticancer drug irinotecan, in human colon cancer cell lines. We have found that endogenous SXR translocates into the nucleus and associates with RXR upon SN-38 treatment. Using ChIP, we have demonstrated that endogenous SXR, following its activation, binds to the native promoter of the CYP3A4 gene to induce its expression. RNA interference experiments confirmed SXR involvement in CYP3A4 overexpression and permitted us to identify CYP3A5 and MRP2 transporter as SXR target genes. As a consequence, cells overexpressing SXR were found to be less sensitive to irinotecan treatment. Conclusions Altogether, these results suggest that the SXR pathway is involved in colon cancer irinotecan resistance in colon cancer cell line via the upregulation of select detoxification genes.

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