Diclofenac and acetaminophen dim the acute-phase response but amplify expression of the iron regulator hepcidin in liver cancer cells

Info

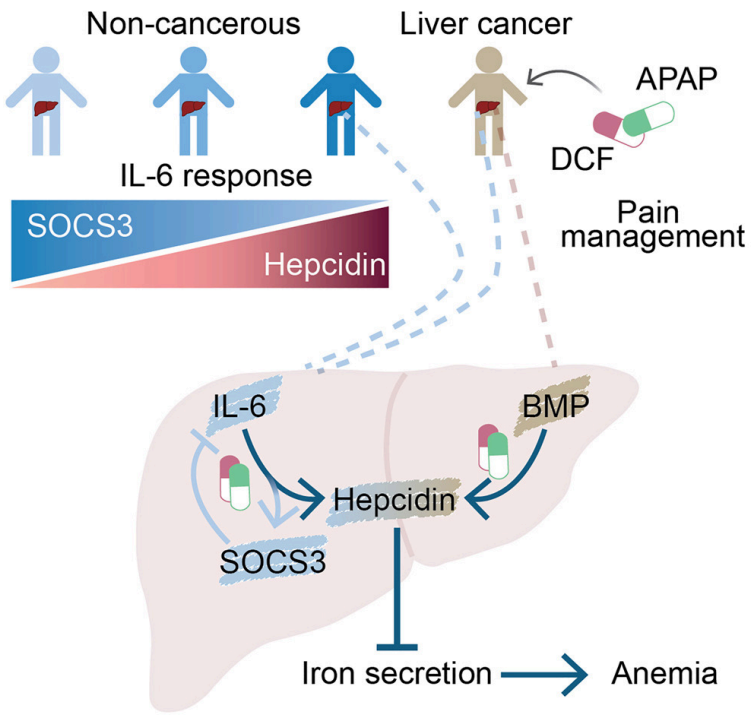
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Authors

Anja Zeilfelder Joep Vanlier Christina Mölders Philipp Kastl Barbara Helm Sebastian Burbano de Lara Till Möcklinghoff Nantia Leonidou Elisa Holstein Artyom Vlasov Alexander Held Silvana Wilken Katrin Hoffmann Gerda Schicht Andrea Scheffschick Markella Katerinopoulou Esther Giehl-Brown Christoph Kahlert Christoph Michalski Daniel Seehofer Georg Damm Martina U. Muckenthaler Marcel Schilling Jens Timmer Ursula Klingmüller



Abstract

Cancer patients frequently suffer from anemia and cancer-related pain, which can be treated by non-opioid analgesics such as diclofenac (DCF) and acetaminophen (APAP) attenuating inflammatory responses. The

pro-inflammatory cytokine interleukin (IL)-6 triggers the expression of acute-phase proteins, including the iron regulator hepcidin. Using proteomics and dynamic pathway modeling, we show that DCF and APAP directly impact IL-6 signaling by enhancing the induction of the feedback-inhibitor suppressor of cytokine signaling 3 (SOCS3), reducing signal transducer and activator of transcription (STAT)3 phosphorylation, and decreasing the expression of most acute-phase proteins except for hepcidin. In primary human hepatocytes (PHHs), the impact depends on the patient-specific extent of SOCS3 induction, which is anti-correlated with hepcidin expression. Whereas, in liver cancer cells, DCF and APAP stabilize the interaction of autocrine secreted bone morphogenic protein (BMP) with its receptor, resulting in strongly amplified hepcidin expression. Our studies suggest that co-inhibition of the BMP receptor counteracts excessive hepcidin production upon treatment with pain-relieving drugs and could prevent iron-deficiency-caused anemia in liver cancer. A record of this paper's transparent peer review process is included in the supplemental information.