

# THE IMPACT OF INFLAMMATION ON CANCER DRUG METABOLISM AND TOXICITY

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Cancer associated inflammation is associated with worse cancer outcomes including response to chemotherapy and survival. This process is driven by increased plasma cytokine concentrations, including interleukin-6, derived either from the tumour or host immune cells. However, there has been little focus on the impact of cancer-associated inflammation on hepatic cytotoxic drug metabolism and toxicity from chemotherapy. The majority of anti-cancer drugs are metabolised by the hepatic cytochrome P450 system of enzymes, in particular 3A4 (CYP3A4). There is wide inter-patient variability in toxicity from chemotherapy and the ability to identify patients at increased risk of toxicity would significantly improve cancer management. Our research has shown that an acute phase plasma protein reaction in cancer patients and murine tumour models is associated with reduced CYP3A4 metabolism. In addition, in the animal models there is evidence of reduced hepatic expression of a range of drug transporters including Mdr2, Mrp2, Mrp3, Ntcp, Oatp2, Oatp-c and Bcrp. In combination, these changes lead to reduced plasma clearance and increased toxicity from cytotoxic drugs such as docetaxel that are substrates for CYP3A4. In a re-analysis of data from a large randomised study in patients with non-Hodgkin lymphoma (NHL), we have shown that patients with symptoms of inflammation have significantly worse treatment related toxicity. Preliminary data suggest that nutritional status correlates with elevated plasma markers of inflammation, creating the potential for nutritional interventions to improve drug metabolism. In murine models, anti-IL-6 antibodies produce partial reversal of *Cyp* repression. Further clarification of the molecular pathways by which inflammation leads to reduced hepatic drug metabolism will enable the development of conditioning strategies that will normalise drug metabolism prior to administration of chemotherapy, thereby reducing inter-patient variability in toxicity.

## References:

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