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Optimalisation of conventional therapies in inflammatory bowel disease

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Summary of this thesis

Optimalisation of conventional therapies in IBD, 'Old wine in new bottles'

The conventional thiopurines, azathioprine (AZA) and mercaptopurine (MP) are first-line immunosuppressive treatment in IBD. AZA and MP were both pharmacologically inactive prodrugs, converted by 3 major competing enzymatic pathways to produce, among others, the metabolites 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine ribonucleotides (6-MMPR). In daily clinical practice a disappointing number of patients discontinued thiopurine therapy, mainly due to adverse event or ineffectiveness. We assessed that high 6-MMPR concentrations and 6-MMPR/6-TGN ratio appears to be associated with hepatotoxicity as well as therapeutic inefficacy. Moreover, a routinely established skewed (6-MMPR/6-TGN>20) metabolism was a major risk factor for early thiopurine failure in IBD patients. In addition, different strategies were described to optimize thiopurine therapy in this thesis. We assessed that allopurinol-thiopurine combination therapy is effective at maintaining steroid-free remission and reducing hepatotoxicity with an excellent long-term safety profile. Moreover, we assessed the effect of allopurinol and low-dose thiopurine combination therapy on the activity of three pivotal thiopurine metabolizing enzymes. Switching to tioguanine is also an option to optimize thiopurine therapy in IBD patients with a skewed thiopurine metabolism who developed hepatotoxicity during thiopurine therapy. Tioguanine was well tolerated and hepatotoxicity improved in most patients. Another strategy to optimize therapy is improving therapeutic drug monitoring (TDM). It has been shown *in vitro* that the immunosuppressive mechanism of thiopurine treatment is primarily based on inducing T cell apoptosis via inhibition of Rac1. In this thesis we assessed that both, Rac1 expression as well as concentrations of Rac1-GTP may be pharmacodynamic biomarkers of thiopurine efficacy.