Fecal microbial SN-38G metabolotypes in colorectal cancer patients are associated with irinotecan-induced delayed diarrhea

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Gut microbial β-glucuronidases (GUss) reactivation of the excreted, inactive metabolite SN-38G of irinotecan, a first-line chemotherapy drug in advanced colorectal cancer (CRC), caused severe late diarrhea in over 80% of CRC patients, of which 30%-40% was severe diarrhea. However, so far, the mechanistic understanding of the role of microbial GUss in differential responses of CRC patients to irinotecan is still poor. Herein, we first characterized the inter-individual variability in microbial SN-38G-hydrolyzing activity of CRC patients and assessed its impact on gastrointestinal toxicity of irinotecan using fecal microbiota transplantation. Ninety CRC patients fell into 3 distinct metabolotypes with 25 poor (PM), 38 moderate, and 27 extensive (EM) metabolizers on basis of SN-38G-hydrolyzing activity determined from ex vivo incubation with fecal microbiota. Notably, this metabolic activity exhibited a significant positive correlation with the TNM stages (stage IV vs I, p < 0.05) and was higher in male patients with right-side CRC than those with left-side CRC (p = 0.01). Shotgun metagenomic analysis of fecal microbiota revealed a clear separation of gut microbial composition between EMs and PMs. The EMs exhibited higher alpha-diversity than PMs at species level (p < 0.01). Specifically, Enterocloster bolteae, and Erysipelatoclostridium ramosum were more abundant in PMs, while 7 species were significantly enriched in EMs, among which 4 species (Blautia obeum, uncultured Blautia sp., uncultured Ruminococcus sp., and Lachnospiraceae bacterium) are GUS-expressing bacteria. Pseudo-germ-free mice colonized with fecal microbiota samples from 4 representative EM patients (EMMs) displayed higher fecal SN-38G-hydrolyzing activity than those receiving fecal microbiota transplantation from 4 PMs (PMMs) (p < 0.05). Correspondingly, animals of all EMM groups showed higher intestinal SN-38 accumulation and severer responses to irinotecan challenge (50mg/kg, i.p.) than all PMM groups, including lower survival rate, higher incidence of diarrhea and severer intestinal tissue damage. The 16s rRNA-based gene sequencing revealed no significant difference between EMM and PMM groups in alpha-diversity. Three phyla (Actinobacteriota, Proteobacteria and Verrucomicrobiota) were more abundant in PMM, while Campilobacterota showed higher relative abundance in EMM. Sangenon G, the Diel-alder adduct that isolated from Mori Cortex (sang-bai-pi) and strongly inhibited GUss activity in pooled human fecal microbiota, also potently suppressed SN-38G deconjugation by fecal microbiota from representative EMs (IC50 1.76-14.06 μM) and consequently, effectively prevented irinotecan-induced adverse effects in pseudo germ-free mice receiving FMT from EMs. Taken together, these findings demonstrate the causative role of gut microbial GUss in irinotecan-induced gastrointestinal toxicity in CRC patients and highlight the potential application of SN-38G metabotyping and GUS inhibition for targeted intervention in irinotecan therapy.

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