Drug Discovery Targeting Gut Bacterial β-Glucuronidases to ameliorate the irinotecan-induced toxicity

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Irinotecan inhibits cell proliferation and thus is used for the primary treatment of colorectal cancer. Metabolism of irinotecan involves incorporation of β-glucuronic acid to facilitate excretion. During transit of the glucuronidated product through the gastrointestinal tract, an induced up-regulation of gut microbial β-glucuronidase (GUS) activity may cause severe diarrhea and thus force many patients to stop treatment. We herein report the following findings. (1) Our structural and functional analysis pinpointed opportunistic gut bacterial GUSs as those that cause the aforementioned toxicity. (2) We completed the synthesis and evaluation of several iminocyclitols; especially uronic isofagomine derivatives act as general, potent inhibitors of bacterial GUSs, especially those of opportunistic and pathogenic bacteria (e.g., *Escherichia coli* and *Clostridium perfringens*). The best inhibitor, C6-nonyl UIFG, is 23,300-fold more selective for *E. coli* GUS than for human GUS (Ki = 0.0045 and 105 μM, respectively). Structural evidence indicated that the loss of coordinated water molecules, with the consequent increase in entropy, contributes to the high affinity and selectivity for bacterial GUSs. The inhibitors also effectively reduced irinotecan-induced diarrhea in mice without damaging intestinal epithelial cells.

Furthermore, my talk will also discuss the development of glucuronide-conjugated anti-cancer drugs.

References

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