Cancer Biology & Therapy 13:14, 1374–1375; December 2012; © 2012 Landes Bioscience

Loss of oatp1b3 function causes rotor syndrome

Implications for potential use of inhibitors in cancer

Elias Pratt, Tristan M. Sissung and William D. Figg*
Clinical Pharmacology Program; Center for Cancer Research; National Cancer Institute; Bethesda, MD USA

There has been increasing recognition that organic anion transporter proteins (OATPs) play an important role in the biology of various cancers. De novo expression of OATPs has been identified in breast, colon, pancreatic, gastric and prostate cancer cells, among others.[1] In patients with prostate cancer, polymorphisms encoding decreased functioning OATP1B3 were associated with a longer time to progression on androgen deprivation therapy and a longer overall survival which is likely caused by reduced tumoral testosterone uptake.[2-4] Because of these findings, therapeutic inhibition targeting OATP1B3 has been proposed. However, any enthusiasm for inhibiting OATP1Bs therapeutically has been tempered by reservations about potential consequences. For instance, inhibitors could interfere with several normal physiological processes mediated by OATP1B3 (i.e., bile acid reuptake, bilirubin uptake, etc.) or cause potential, as-yet unknown, drug interactions by barring hepatic uptake, subsequent metabolism and elimination.

A study recently published in the *Journal of Clinical Investigation* by van de Steeg et al.[5] elucidates that loss-of-function mutations in two highly homologous genes, SLCO1B1 and SLCO1B3 (encoding OATP1B1 and OATP1B3), cause benign unconjugated hyperbilirubinemia. These data provide insight into the potential physiological consequences of inhibiting OATP1Bs in patients.

The experiments described in the article arose from the observation that mice lacking genes for any functional OATP1A/1B proteins (*Slco1a/1b*$^{-/-}$) were jaundiced. Upon further examination, it was revealed that these mice had a profound conjugated hyperbilirubinemia. Because OATP1B1 and OATP1B3 normally localize to the basolateral membrane of hepatocytes, it was hypothesized that the jaundice and conjugated hyperbilirubinemia was due to their absence in the liver. To test this hypothesis, transgenic *Slco1a/1b*$^{-/-}$ mice that expressed liver specific, ApoE-dependent human OATP1B1 or OATP1B3 were created. In each case, the expression of either OATP1B1 or OATP1B3 restored normal phenotype to the mouse and reversed the conjugated hyperbilirubinemia.

Since the *Slco1a/1b*$^{-/-}$ mice exhibited a phenotype remarkably similar to the human condition Rotor syndrome, which typically presents as a benign conjugated hyperbilirubinemia, it was hypothesized that Rotor syndrome was caused by a deficiency of functional OATP1B1 and OATP1B3 proteins. After identifying 11 individuals from 8 families with Rotor syndrome, homozygosity mapping was performed in an unbiased fashion and identified a single region on chromosome 12 for which the individuals were homozygous.

The identified genomic region contained the genes for OATP1B1 and OATP1B3 as predicted, and further sequence analysis identified either deletions or sequence mutations that rendered both OATP1B1 and OATP1B3 non-functional. Staining of liver biopsy specimens from these individuals with anti-OATP1B1 and 1B3 antibodies confirmed the absence of the transporter proteins. Genetic analysis of family members

Keywords: OATP, prostate, cancer, therapy, Rotor syndrome, inhibition, DDI

Submitted: 08/22/12

Accepted: 08/29/12

http://dx.doi.org/10.4161/cbt.22010

*Correspondence to: William D. Figg; Email: figgw@helix.nih.gov

and a cohort of people from the general public who did not have Rotor syndrome revealed that only one functional copy of either OATP1B1 or OATP1B3 could prevent development of Rotor's, confirming the experiment with the transgenic *Slco1a/1b*$^{-/-}$.

The sum of these experiments makes it clear that the total loss of OATP1B1 and OATP1B3 in humans results in a benign, conjugated hyperbilirubinemia known as Rotor syndrome. This revelation should instill a cautious optimism in those who wish to pursue inhibition of OATP1B1 and OATP1B3 as a therapeutic aim. Complete loss of function of these proteins leads to an altogether benign condition in normal human physiology. In addition, OATP1B1 and OATP1B3 are normally expressed at a much higher level in the liver cells than in cancer cells, so it is likely that total inhibition of these transporter proteins in cancer cells could be achieved while still maintaining partial function in hepatocytes.[6]

As this article suggests, even partial function of OATP1B1 and OATP1B3 should be enough to prevent any negative sequelae; however, it is unclear if patients with Rotor syndrome, or undergoing therapy with OATP1B inhibitors, are more susceptible to significant drug interactions. For example, an investigational drug, AZX, which only moderately inhibits OATP1B1, was predicted to cause clinically significant DDIs, especially with certain statins.[7] As anti-cancer agents tend to have a narrow therapeutic window and are most often used to treat patients with a variety of comorbidities who are typically undergoing polypharmacy, we suggest that DDIs should be investigated as OATP1B inhibitors are developed. In conclusion, the study by van der Steeg suggests cautious optimism for the development of OATP1B inhibitors, but drug interactions may still be problematic.

Acknowledgments

This study was supported in part by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Bethesda, MD.

Disclaimer

The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products or organization imply endorsement by the US Government.

References

1. Obaidat A, Roth M, Hagenbuch B. The expression and function of organic anion transporting polypeptides in normal tissues and in cancer. Annu Rev Pharmacol Toxicol 2012; 52:135-51; PMID:21854228; http://dx.doi.org/10.1146/annurev-pharmtox-010510-100556.
2. Hamada A, Sissung T, Price DK, Danesi R, Chau CH, Sharifi N, et al. Effect of SLCO1B3 haplotype on testosterone transport and clinical outcome in caucasian patients with androgen-independent prostatic cancer. Clin Cancer Res 2008; 14:3312-8; PMID:18519758; http://dx.doi.org/10.1158/1078-0432.CCR-07-4118.
3. Sharifi N, Hamada A, Sissung T, Danesi R, Venzon D, Baum C, et al. A polymorphism in a transporter of testosterone is a determinant of androgen independence in prostate cancer. BJU Int 2008; 102:617-21; PMID:18537956; http://dx.doi.org/10.1111/j.1464-410X.2008.07629.x.
4. Yang M, Xie W, Mostaghel E, Nakabayashi M, Werner L, Sun T, et al. SLCO2B1 and SLCO1B3 may determine time to progression for patients receiving androgen deprivation therapy for prostate cancer. J Clin Oncol 2011; 29:2565-73; PMID:21606417; http://dx.doi.org/10.1200/JCO.2010.31.2405.
5. van de Steeg E, Stránecký V, Hartmannová H, Nosková L, Hrebícek M, Wagenaar E, et al. Complete OATP1B1 and OATP1B3 deficiency causes human Rotor syndrome by interrupting conjugated bilirubin reuptake into the liver. J Clin Invest 2012; 122:519-28; PMID:22232210; http://dx.doi.org/10.1172/JCI59526.
6. Pressler H, Sissung TM, Venzon D, Price DK, Figg WD. Expression of OATP family members in hormone-related cancers: potential markers of progression. PLoS One 2011; 6:e20372; PMID:21625523; http://dx.doi.org/10.1371/journal.pone.0020372.
7. Sharma P, Butters CJ, Smith V, Elsby R, Surry D. Prediction of the in vivo OATP1B1-mediated drug-drug interaction potential of an investigational drug against a range of statins. Eur J Pharm Sci 2012; 47:244-55; PMID:22538052; http://dx.doi.org/10.1016/j.ejps.2012.04.003.