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Fucosyltransferase 2: a genetic risk factor for primary sclerosing cholangitis and Crohn's disease--a comprehensive review.

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Abstract

Fucosyltransferase 2 (FUT2) mediates the inclusion of fucose in sugar moieties of glycoproteins and glycolipids. ABO blood group antigens and host-microbe interactions are influenced by FUT2 activity. About 20 % of the population has a "non-secretor" status caused by inactivating variants of FUT2 on both alleles. The non-sense mutation G428A and the missense mutation A385T are responsible for the vast majority of the non-secretor status in Caucasians, Africans, and Asians, respectively. Non-secretor individuals do not secrete fucose-positive antigens and lack fucosylation in epithelia. They also appear to be protected against a number of infectious diseases, such as Norovirus and Rotavirus infections. In recent years, genome-wide association studies (GWAS) identified inactivating variants at the FUT2 locus to be associated with primary sclerosing cholangitis (PSC), Crohn's disease (CD), and biochemical markers of biliary damage. These associations are intriguing given the important roles of fucosylated glycans in host-microbe interactions and membrane stability. Non-secretors have a reduced fecal content of Bifidobacteria. The intestinal bacterial composition of CD patients resembles the one of non-secretors, with an increase in Firmicutes and decreases in Proteobacteria and Actinobacteria. Non-secretor individuals lack fucosylated glycans at the surface of biliary epithelium and display a different bacterial composition of bile compared to secretors. Notably, an intact biliary epithelial glycocalix is relevant for a stable 'biliary HCO3 (-) umbrella' to protect against toxic effects of hydrophobic bile salt monomers. Here, the biology of FUT2 will be discussed as well as hypotheses to explain the role of FUT2 in the pathophysiology of PSC and Crohn's disease.

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