SLC5A8: A Transporter with a Tumor-suppressive Function and Therapeutic Potenital

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SLC5A8 is a plasma membrane transporter belonging to the *SLC5* gene family which consists of Na^+-coupled transporters. SLC5A8 was first identified as a candidate tumor suppressor in human colon. Its expression is silenced in colorectal cancer by DNA methylation, and re-expression of the transporter in colon cancer cell lines leads to cell death. However, neither the functional identity of the transporter nor the mechanism by which the transporter functioned as a tumor suppressor was known. Short-chain fatty acids (SCFA) are generated in the colonic lumen by bacterial fermentation and these fatty acids are essential for the maintenance of normal colonic health and for protection against colorectal cancer. Since the transporter is expressed robustly in the colon and is a member of a Na^+-coupled transporter gene family, we hypothesized that it may function as a Na^+-coupled transporter for SCFA. This indeed turned out to be true. SLC5A8 is a Na^+-coupled electrogenic transporter for not only SCFA but also for a variety of other monocarboxylates such as lactate, pyruvate, β-hydroxybutyrate, and nicotinate. The transporter protein is expressed exclusively in the lumen-facing apical membrane of colonic epithelial cells. The normal physiologic function of the transporter in the colon is to mediate the concentrative entry of SCFA into colonocytes. Butyrate and propionate are inhibitors of histone deacetylases (HDACs) and thus are capable of influencing gene expression, and HDAC inhibitors are in clinical trials for cancer treatment. Therefore, it is very likely that the ability of SLC5A8 to transport butyrate/propionate into colonocytes with subsequent inhibition of HDACs underlies the tumor-suppressive function of the transporter in the colon. This is evidenced by the observations that colon tumor cells, engineered to express SLC5A8, undergo apoptosis but only when cultured in the presence of butyrate or propionate. This suggests that it is not the transporter protein itself but rather its transport function that is responsible for the tumor-suppressive role. SLC5A8 is also capable of transporting several monocarboxylate drugs, indicating that the transporter may potentially play a role in the intestinal absorption of therapeutic agents. The transport of butyrate by SLC5A8 shows unique features in terms of Na^+ coupling. The charge:butyrate transfer ratio is 3, indicating that the transport of butyrate involves the transfer of 4 Na^+. The presence of butyrate in the colonic lumen may therefore have marked stimulatory effects on Na^+ (and hence water) absorption in the colon. Thus, butyrate may be therapeutically effective as an anti-diarrheal agent and a useful additive to oral rehydration solutions used in the treatment of diarrheal diseases.

The silencing of SLC5A8 in colorectal cancer makes sense because this provides the tumor cells a mechanism to evade butyrate/propionate-induced HDAC inhibition and cell death. But, the transporter is silenced not only in colon cancer but also in a variety of other cancers. Interestingly, butyrate and propionate are not present in the blood at significant concentrations. What advantage does silencing of the transporter offer tumor cells in non-colonic tissues? Recently, we found that the ubiquitous metabolite pyruvate is an effective inhibitor of HDACs and its transport into tumor cells via SLC5A8 induces cell death at concentrations found in normal blood. Tumor cells are known to avidly convert pyruvate into lactate, but the reasons for this were not known. Our findings that pyruvate is a tumor suppressor provide an explanation for this phenomenon. In order to survive, cancer cells have a need to maintain intracellular concentrations of pyruvate at very low levels. They accomplish this goal by up-regulating LDH5 (to convert pyruvate into lactate) and by silencing SLC5A8 (to prevent the Na^+-coupled entry of pyruvate).