The greatest advance in the treatment of DLBCL in the past 2 decades has been the addition of rituximab to CHOP (or CHOP-like) chemotherapy, which has increased survival rates significantly in all subgroups with the disease.\(^1\) Patients with DLBCL and HCV infection appear to derive similar benefits. Whether R-CHOP has an adverse effect on the long-term natural history of HCV infection and its complications similar to that reported after allogeneic hematopoietic cell transplantation is unclear.\(^3\) It is clear that care must be used to monitor for acute and chronic hepatotoxicity associated with therapy, particularly in those with elevated transaminases at presentation or with underlying hepatic complications of HCV infection (including HCC). The role of antiviral therapy in aggressive lymphoma remains undefined and will require focused study.

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**REFERENCES**


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**HEMATOPOIESIS & STEM CELLS**

**ABC of D’s in the folate transporter**

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Consanguinity “loads the dice” for turning up matching pairs when it comes to Mendelian inheritance of autosomal recessive genes. Such is the case in a novel loss-of-function mutation involving PCFT in a female infant with megaloblastic anemia, seizures, and severe growth retardation described by Shin et al in this issue of *Blood.*

**Comment on Shin et al, page 5162**

**The Proton Coupled Folate Transporter**

In the topologic diagram used by Shin et al to depict the transmembrane proton-coupled folate receptor, the location of conserved aspartate residues is shown. Mutation of aspartate to tyrosine at position 156 in the proton-pcoupled folate transporter (PCFT) and its functional consequences in their patient. Then, using site-directed mutagenesis, they went on to describe that in the complex PCFT molecule that threads out and in through 12 transmembrane domains, 4 of...
the 6 conserved aspartate residues (designated “D” in amino acid notation) in the molecule (see figure) are permissive to change, but the other 2 (D109 and D156) are critical for function with resulting marked impairment or total loss of function when mutated. Why aspartate?

This amino acid is more highly conserved than others because of several attributes that include a short side chain, a high charge density, strong polar interactions, and molecular rigidity.3

Recently, the same laboratory were the first to identify that PCFT plays a critical role in folate absorption from the relatively acidic milieu of the upper small intestine and transports folate into the brain through the blood, choroid plexus, cerebrospinal fluid conduit.3

Unlike the reduced folate receptor, PCFT has a similar affinity for reduced folate and folic acid, at pH 5.5, ambient in the upper small intestine. A loss–of–function mutation affecting the pcft gene coding for this transmembrane protein was identified as the cause of hereditary folate malabsorption,3,4 an uncommon cause of folate deficiency of previously obscure etiology that presents within the first few months of life and leads to death during early infancy if not treated. Since then, several mutations affecting various other critical amino acid residues have been described in individuals with hereditary folate malabsorption (HFM) and these have been reviewed recently.5,6 Using a HELA cell subclone that lacks membrane folate transporters including PCFT, Shin and coworkers transiently transfected the cells with site-directed mutants of PCFT’s and monitored functionality using tritiated methotrexate as surrogate cargo for the transporter.1 The overall conclusions from these studies were that D156, located in the fourth transmembrane domain, is critical for PCFT protein stability. In addition, D109, in the first intracellular loop (between the second and third transmembrane domains) is absolutely essential for PCFT function, perhaps to maintain flexibility at what may be a critical hinge point in the molecule allowing for inward or outward flip–flop during the transport cycle.

Recommended treatment for HFM consists of parenteral injection of folate, preferably with folinic acid (5-formyl tetrahydrofolate), for correction of the anemia and central nervous system problems.5,7 As emphasized in the recent comprehensive review of this topic,5 the fact that folinic acid (leucovorin) has a much higher affinity than folic acid for the reduced folate carrier proves important in the management of HFM. In addition, as further pointed out by the same group, folic acid can bind irreversibly to the folate receptor alpha in the choroid plexus, also required for transport across this organ, putatively blocking transport of reduced folate forms including leucovorin that provide rescue to a folate-deprived brain.8

More than just a tour de force of molecular exploration, the present publication has, at core, a happy ending. All too often, by the time that the diagnosis of HFM is made, the patient has sustained irreversible damage to the nervous system. The efficacy of oral folate (as occurred in the patient who formed the basis of the current study) is curious and suggests either passive diffusion or hobbled participation by the reduced folate carrier located on the apical brush border membrane of the small intestine that functions poorly at low pH. Sufficiently high blood folate concentrations presumably then could be attained to clear the choroid plexus hurdle. In the currently described patient, after treatment first with oral folic acid and then only later with supplementary folic acid (1.6 mg/kg/d), the outcome was fortunately excellent. At age 18 months, she fell above the 95th percentile for weight, having attained normal developmental milestones—a satisfying, though seemingly fortuitous, example of translational success.

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ABC of D's in the folate transporter

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