Enzyme enhancing strategies: reshaping the treatment landscape of a galactose disorder?

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Classic galactosemia is an inherited metabolic disorder with thousands of patients affected in Europe (prevalence 1:16,000 to 1:50,000 live births in Western countries). It is caused by severe deficiency of galactose-1-phosphate:uridylyltransferase activity, pivotal to galactose metabolism. Substrate reduction using a galactose-restricted diet does not prevent brain and ovarian complications and poses a high burden to patients and families. To address the unmet treatment need, enhancing or restoring GALT activity seems promising. Our group studies chaperones and nucleic acid therapies.

Many of the pathogenic variants lead to conformational abnormalities that make GALT amenable to chaperones. The high prevalent variant in the Caucasian population, p.Gln188Arg, gives rise to a protein with lower stability and catalytic activity. In a prokaryotic model, the chemical chaperone arginine showed beneficial effect. A study with arginine administration to patients with the p.Gln188Arg/p.Gln188Arg variant, as well as *in vitro* studies, failed however to exhibit a positive effect. Other variants and other chaperones need to be explored yet.

Nucleic acid therapy is another approach to restore enzyme activity. In our *galt* knockout zebrafish model, lipid nanoparticle (LNP)-packaged *hGALT* mRNA was effectively translated and processed without signs of toxicity. One cell-stage and intravenous single-dose injections resulted in hGALT protein expression and enzyme activity at 5 days post fertilization. In adult fish, the used LNP primarily targeted the intestine and pancreas, with absent signal in the ovaries. Our next step is to facilitate direct delivery to the female gonads by using nanoparticles that specifically target ovarian follicle receptors.

The results encourage and challenge us, as each modality comes with advantages and limitations. For all of them, there are many unknowns that need to be tackled in our journey to reshape the treatment landscape.