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Characterization of a New Mammalian Animal Model of Classic Galactosemia

Dr. Kent Lai

In humans, inherited deficiency of galactose-1-phosphate uridyltransferase (GALT) activity can lead to a potentially lethal disease called Classic Galactosemia. If galactose is not withdrawn from the diet of the affected infants in time, they will suffer from a range of acute toxicity syndrome and die. Consequently, all 50 states in the U.S. include this metabolic disorder in their newborn screening programs. Although a galactose restricted diet, which is the current standard of care, can prevent the neonatal lethality of this disorder, many well-treated patients continue to develop debilitating complications like mental retardation, growth restriction, premature ovarian insufficiency (POI), and other neurological deficits.

Despite decades of research, the pathogenic mechanisms of the acute toxicity syndrome and the long-term complications associated with this disorder remain largely unknown, thus further hampering the development of more effective therapies. One major obstacle in delineating the precise pathogenic mechanisms has been the lack of animal models that recapitulate the organ-specific dysfunctions in human patients. Armed with extraordinary insights, Professor Nancy Leslie and colleagues constructed the world's first GalT gene-knockout (KO) mouse model to address this deficiency. Paradoxically, initial, albeit by no means exhaustive, examination of these animals did not reveal any human disease phenotypes.

Recently, the Principal Investigator (PI)'s research aimed to develop a novel therapy for Classic Galactosemia has resulted in the need for a mammalian animal model for on-going studies. Despite the seemingly lack of patient disease phenotypes in the old GalT-knockout (KO) mouse model, the PI rationalized that it remained a model of choice because of its well-defined genetics, its mammalian nature, and the reported accumulation of galactose metabolites in these animals. Moreover, we cannot emphasize enough that the characterization of the old mouse model was never meant to be exhaustive, and it is too early to abandon the model after a couple of years of studies. Last but not the least; even if the KO animals did demonstrate some degrees of resistance to galactose toxicity, it does not automatically make them worthless research tools. On the contrary, if we can decipher the mechanisms utilized by these mice to resist/ minimize galactose insults, we could identify the molecular targets of galactose toxicity in human patients, and to design better therapeutic options.

When the PI contacted Professor Leslie and requested the sharing of the old GalT-KO mouse model, he was saddened to learn that the model no longer existed. However, this did not deter the PI's resolve to advance. In response, the PI used a similar technology to construct a new GalT-KO mouse model. Although these new GalT-KO mice, like the old GalT-KO mice, manifested some degrees of resistance to galactose toxicity, subtle phenotypic differences between the KO mice and their wild-type (i.e., normal) littermates do exist. In this application, we propose new studies to characterize these subtle differences at the molecular and biochemical levels, as well as to understand the basis of galactose resistance in these animals.