

What have we learned about human metabolism from its inborn errors? Lessons from arginase deficiency and other disorders.

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Arginase, often perceived solely as the last of the now six enzymes of the urea cycle, exists in two forms and has a broad tissue distribution. A cytosolic form, AI, is highly expressed in the liver and is thought to be primarily involved in ureagenesis. A mitochondrial form, AII, has been thought to be more widely expressed and to be involved in the biosynthesis of polyamines, the amino acids ornithine, proline and glutamate and in the inflammatory process, among others. This presentation will discuss the background for these observations, the overlap and interdigitation between the clinical and laboratory observations and will address recent experiments that cast some doubt on the validity of these distinctions made previously.

Studies have now suggested that macrophages may express AI or AII in different experimental conditions, *in vivo* and *in vitro*. In contrast, most studies, at least in cell culture, suggest that AII may be most highly expressed in cancers of a number of different types. Inhibition of arginase activity has implicated this activity in maintaining ornithine levels for polyamine synthesis. *In situ* and quantitative PCR studies in mouse have demonstrated that AI, and not AII is the predominant isoform expressed during development and in the majority of organs.

Mouse knockout models for both AI and AII have been produced and are available to address the functions of both. Surprisingly, the AII knockout has no apparent phenotype except for some diminished fertility in homozygous males, consistent with the belief that AII, highly expressed in prostate, is important for sperm function in semen. The AI knockout animal has a more dramatic phenotype and dies at 10-12 days of life of hyperammonemia. The reason for the prolonged survival may be due to later-occurring hypo-ornithinemia, a contention not yet proven. Transgenic manipulation of the AI knockout animal and breeding the AI and AII knockouts into single animals may address the ability of AII to rescue animals from some of the metabolic consequences of AI deficiency, as appears to happen in man.