J Mol Med (2015) 93:1287–1296
DOI 10.1007/s00109-015-1354-3

JMolMed CrossMark

REVIEW

Arginase-1 deficiency

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Received: 3 July 2015 / Revised: 14 September 2015 / Accepted: 1 October 2015 / Published online: 14 October 2015
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Abstract Arginase-1 (ARG1) deficiency is a rare autosomal recessive disorder that affects the liver-based urea cycle, leading to impaired ureagenesis. This genetic disorder is caused by 40+ mutations found fairly uniformly spread throughout the *ARG1* gene, resulting in partial or complete loss of enzyme function, which catalyzes the hydrolysis of arginine to ornithine and urea. ARG1-deficient patients exhibit hyperargininemia with spastic paraparesis, progressive neurological and intellectual impairment, persistent growth retardation, and infrequent episodes of hyperammonemia, a clinical pattern that differs strikingly from other urea cycle disorders. This review briefly highlights the current understanding of the etiology and pathophysiology of ARG1 deficiency derived from clinical case reports and therapeutic strategies stretching over several decades and reports on several exciting new developments regarding the pathophysiology of the disorder using ARG1 global and inducible knockout mouse models. Gene transfer studies in these mice are revealing potential therapeutic options that can be exploited in the future. However, caution is advised in extrapolating results since the lethal disease phenotype in mice is much more severe than in humans indicating that the mouse models may not precisely recapitulate human disease etiology. Finally, some of the functions and implications of ARG1 in non-urea cycle activities are considered. Lingering questions and future areas to be addressed relating to the clinical manifestations of ARG1 deficiency in liver and brain are also presented. Hopefully, this review will spark invigorated research efforts that lead to treatments with better clinical outcomes.

Keywords Urea cycle · Arginine · Hepatocyte · Mouse models · Rare genetic disorder

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Arginase-1 and the urea cycle

The urea cycle disorders (UCDs) represent a group of inborn errors of hepatic metabolism that affect the detoxification of ammonia. Deficiency in any of the six principal enzymes associated with the urea cycle results in perturbation of ureagenesis, leading to incomplete removal of ammonia and eventual hyperammonemia of varying degrees. The liver is the main site of urea cycle activity where the proximal three enzymes are in the mitochondria [N-acetyl-glutamate synthase (NAGS), carbamoyl phosphate synthetase 1 (CPS1), and ornithine transcarbamylase (OTC)], while the distal three are cytosolic [argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), and arginase] [1].

Arginase was discovered in mammalian liver tissue in 1904 [2]. Being the sixth and final enzyme of the cycle, arginase catalyzes the hydrolysis of arginine to ornithine and urea, where the latter is transported in the blood to the kidneys and excreted in the urine, while ornithine is recycled to continue the cycle for further rounds of urea production (Fig. 1). There are two major isoforms of arginase, which are encoded by separate genes in mammals: arginase-1 (ARG1) and arginase-2 (ARG2) that share approximately 60 % amino acid

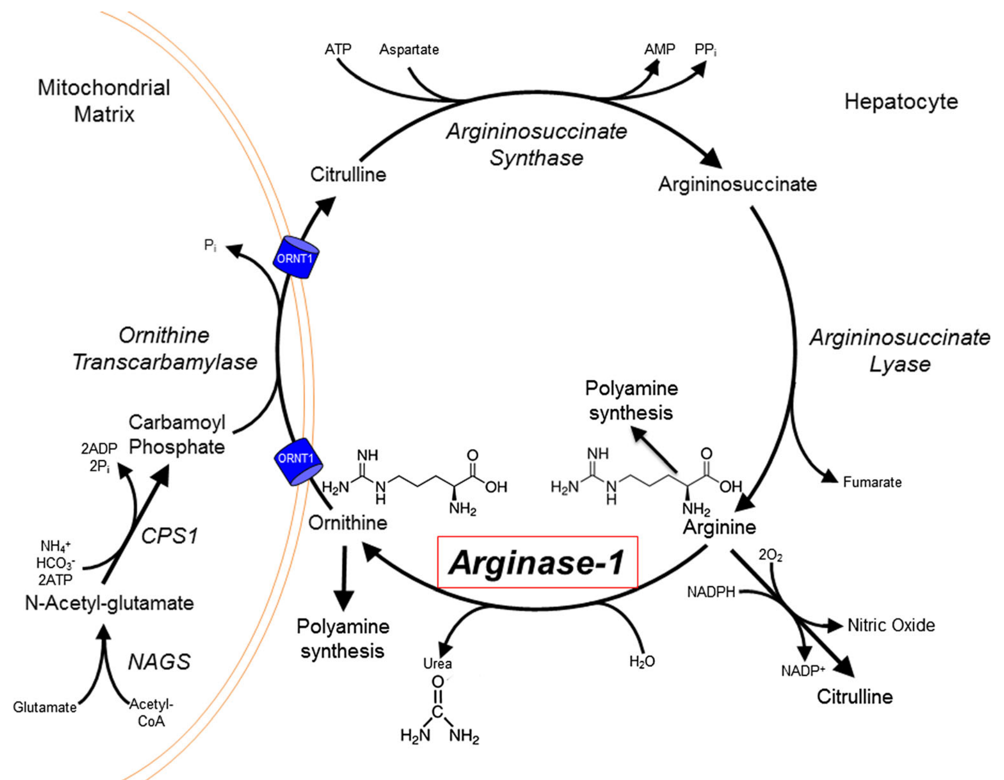

Fig. 1 Central role of arginase-1 to urea cycle function in liver hepatocytes. Note that the nitric oxide synthesis pathway primarily takes place in other tissues and cells of the body. *NAGS* N-acetyl-glutamate synthase, *CPS1* carbamoyl phosphate synthetase

sequence homology [3]. They are similar in enzymatic properties but differ in tissue distribution, subcellular localization, and metabolic functions. ARG1, expressed in highest amounts in the liver cytosol, serves its primary function in the urea cycle as mentioned above [3] but is also found in lesser amounts in human erythrocytes and in the vasculature and immune cells (M2-like macrophages), to mention a few [4, 5]. ARG1 via its metabolic activity also yields ornithine, which serves as precursor to polyamines, proline, and other products. ARG2, on the other hand, is in the mitochondrial compartment of extrahepatic tissues such as kidney and prostate, with lower levels in brain, macrophages, gastrointestinal tract, and lactating mammary glands [6–9]. Besides regulating arginine homeostasis, ARG2 also plays pivotal roles in the biosynthesis of polyamines, proline, creatine, citrulline, γ-aminobutyric acid (GABA), glutamate, and nitric oxide [3, 8, 10].

The first crystal structure of arginase to be solved derived from rat liver [11]. X-ray crystallographic analysis at 2.1 Å resolution revealed that Arg1 exists as a 105-kDa homotrimeric metalloprotein, which requires bivalent metal ions, in particular manganese (Mn^{2+}) for maximal catalytic activity and structural stabilization. Each subunit contains a highly conserved binuclear Mn^{2+}cluster with metal-coordinating histidine and aspartic acid residues at the active site [12–14] (see Fig. 2). According to a proposed mechanism of arginase-catalyzed hydrolysis, the metal-activated mechanism is facilitated when the binuclear manganese cluster activates nucleophilic attack of a metal-bridging hydroxide ion at the substrate guanidinium group of arginine to yield ornithine and urea [14].

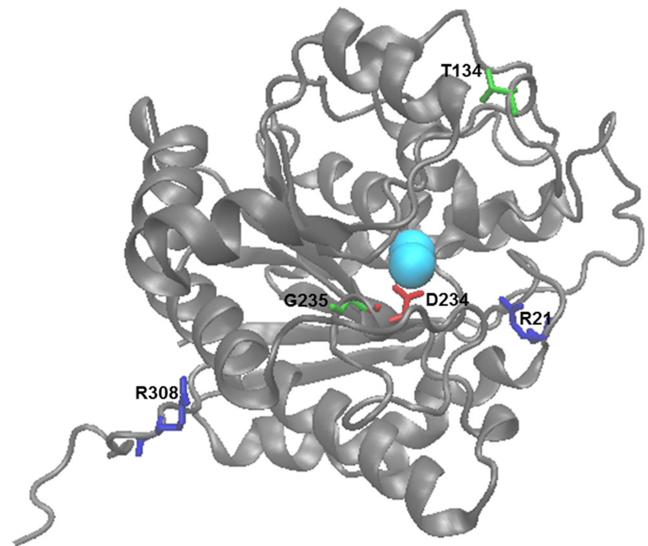

Fig. 2 ARG1 "mutations" superimposed on a crystal structure of native, unliganded human arginase at 1.90 Å resolution (PDB ID: 2PHA) [15]. ARG1 residues 5–318 are displayed in *gray cartoon mode* to represent secondary structural properties. Mn^{2+} is represented using cyan spheres. Residues associated with the most commonly occurring mutations are shown (R21, T134, D234, G235, and R308). Residues 1–4 and 319–322 were not resolved in this crystal structure

Arginase-1 deficiency: clinical characteristics

The first patients with ARG1 deficiency, two female siblings, were described in 1969. One presented at 22 months of age with epileptic seizures, abnormal gait at 2.5 years, and spastic diplegia at 3 years; the other had cerebral seizures at 3 months followed by periodic vomiting and hepatomegaly and later spasticity. Both had psychomotor retardation [16].

The clinical presentation of ARG1 deficiency is characterized by the development of spasticity predominantly in the lower limbs during early childhood [3, 17]. The clinical picture is strikingly uniform and has occasionally been mislabeled as cerebral palsy. Progressive loss of mental and motor skills, increasingly more severe spasticity, and pyramidal tract signs are the hallmarks of the disease [18]. The course and severity of spasticity distinguish ARG1 deficiency clinically from the other UCDs and from other disorders of amino acid metabolism [18].

The clinical manifestation of hyperammonemia in ARG1 deficiency is also different from the other UCDs. The initial presentation is usually not characterized by hyperammonemia. Rather, it is often only moderate, and neonatal presentations are rarely reported, although fatal hyperammonemic events [19, 20] and cases with early presentation [21–23] have been observed. Cyclic hyperammonemic episodes have been found related to the menstrual cycle [24, 25].

The development of progressive spastic paraplegia is the most obvious sign of the disease. Early symptoms of the disease include clumsiness, generalized developmental delays, failure to thrive, irritability, recurrent vomiting, feeding/protein aversion, and anorexia. Growth rate remains low leading to short stature. Ataxia, which is rare and usually only intermittent, is likely linked to hyperammonemia. Most of the patients show some degree of cognitive impairment and both loss of acquired skills and severe intellectual disability may occur [20, 26, 27].

Seizures occur in more than half of the patients and usually in the absence of hyperammonemia. They are mostly generalized tonic-clonic but can include simple focal epilepsy, complex focal epilepsy, generalized tonic, and generalized absence epilepsy and even generalized tonic-clonic status epilepticus [26]. The electroencephalograms are described as diffuse slowing, compatible with metabolic encephalopathy, and epileptic graphoelements [26], with no myopathy or neurogenic process in electromyography (EMG) and normal sensory and motor nerve conduction velocities [26].

Brain imaging may reveal cerebral atrophy, ranging from mild subcortical atrophy to severe cortical and subcortical atrophy, and less frequently cerebellar atrophy. Microcephaly observed in a few patients is likely a consequence of the cerebral atrophy. White matter changes with increased T2 signal have been observed in the periventricular and more peripheral white matter regions [26, 27].

Extraneurological symptoms of the disease are rare, affecting mostly the liver and the skeletal system. As in other UCDs, the liver can be involved with a spectrum ranging from mild hepatocellular injury with transient elevation of liver transaminases to mild dysfunction with coagulation abnormalities to acute liver failure [28, 29]. Histopathological and morphological findings include swollen hepatocytes, portal and sinusoidal fibrosis, macrovacuolar steatosis, increased cellular glycogen, and dilated endoplasmic reticulum [18, 26]. Intrahepatic cholestasis can lead to neonatal presentation with jaundice, hepatomegaly, and cirrhosis [30, 31]. Spinal deformities, such as scoliosis and lordosis, may occur as a consequence of the increasing spasticity [26].

Genetics of arginase-1 deficiency

The 11.1-kb arginase gene (*ARG1*)-encoding ARG1 sits on chromosome 6 (6q23) comprised of eight exons. There are at least 43 potentially disease-causing variations in *ARG1* with the majority (23) being missense (18)/nonsense (5) mutations and small deletions (9) [see Table 1]. The mutations are spread out fairly uniformly across the eight exons as well as at several exon-intron boundary splice sites, and the disorder is inherited in an autosomal recessive Mendelian manner [21–23, 32–49]. The incidence of ARG1 deficiency has been reported to range somewhere between approximately 1:300,000–1:2,000,000 live births, with the most complete study combining databases in the USA/Europe indicating an incidence of 1:950,000 [50]. Formerly regarded as the rarest UCD, the recent estimates [50] would place ARG1 deficiency as the third rarest of the six main UCDs (after NAGS and CPS1 deficiencies). Various case studies indicate that ARG1 deficiency is pan-ethnic with subjects being reported of Arabic (Palestinean, Saudi), Iranian, Korean, Puerto Rican, Chinese, French Canadian, Italian, Portuguese (mainland and Madeira Islands), Brazilian, Pakistani, Hispanic, Japanese, Turkish, Ashkenazi Jewish, and Caucasian descent [21–23, 32–49]. Approximately half of reported subjects are compound heterozygotes with the other half homozygous with a moderate number of cases arising from consanguineous relations.

Attempts to correlate genotype and phenotype have been carried out only to a limited extent [36] due to the rarity of the disorder. Thus, the scientific literature is mainly populated by isolated case reports and small scale studies on a distinct ethnic population [21–23, 32–48]. Patients present with symptoms at different ages in early infancy, some with very mild symptoms, others much more severe and with progression to variable degrees of mental retardation and spastic diplegia as mentioned above. In general, however, those patients with nonsense mutations have severe disease. While only a fraction

Table 1 ARG1 mutant alleles

1	*c.23 T>A* (exon 1)	*p.I8K*
2	*c.32 T>C* (exon 1)	*p.I11T*
3	*c.34G>T* (exon 1)	*p.G12**
4	*c.53G>A* (exon 1)	*p.G18E*
5	*c.57+1G>A* (splice site)	*p.?*
6	# *g.del10753GB_AL121575*	*p.0?*
7	*c.61C>T*(exon 2)	*p.R21**
8	*c.67delG* (exon 2)	*p.V24Wfs*8*
9	*c.77delA* (exon 2)	*p.G27Afs*5*
10	*c.80G>A* (exon 2)	*p.G27D*
11	*c.93delG* (exon 2)	*p.R32Efs*16*
12	*c.221G>T* (exon 3)	*p.G74V*
13	*c.223A>T* (exon 3)	*p.K75**
14	*c.232dupG* (exon 3)	*p.E78Gfs*40*
15	*c.262_265delAAGA* (exon 3)	*p.K88Rfs*45*
16	*c.292G>A* (exon 3)	*p.G98S*
17	# *c.305+1323 T>C*(intron)	# *p.0?*
18	*c.365G>A* (exon 4)	*p.W122**
19	*c.374C>T* (exon 4)	*p.A125V*
20	*c.383A>G* (exon 4)	*p.D128G*
21	*c.385_387delATC* (exon 4)	*p.I129del*
22	*c.401C>T* (exon 4)	*p.T134I*
23	*c.413G>T* (exon 4)	*p.G138V*
24	*c.422A>T* (exon 4)	*p.H141L*
25	*c.425G>A* (exon 4)	*p.G142E*
26	*c.466-1G>C* (splice site)	*p.?*
27	*c.466-2A>G* (splice site)	*p.?*
28	*c.523delG* (exon 5)	*p.V175Cfs*5*
29	*c.539G>C* (exon 5)	*p.R180T*
30	*c.560+5G>A* (by splice site)	*p.?*
31	*c.646_649delCTCA* (exon 6)	*p.L216Afs*4*
32	# *c.647_648ins32* (exon 6)	# *p.?*
33	*c.673delA* (exon 7)	*p.R225Gfs*5*
34	*c.695A>T* (exon 7)	*p.D232V*
35	*c.700G>C* (exon 7)	*p.D234H*
36	*c.703G>A* (exon 7)	*p.G235R*
37	*c.703G>C* (exon 7)	*p.G235R*
38	# *c.712_713dupGGACC* (exon 7)	# *p.?*
39	*c.842delC* (exon 8)	*p.L282Wfs*8*
40	*c.871C>T* (exon 8)	*p.R291**
41	*c.892G>C* (exon 8)	*p.A298P*
42	*c.913G>A* (exon 8)	*p.G305R*
43	*c.923G>A* (exon 8)	*p.R308Q*

Current human genome variation society nomenclature is used, which differs in some cases from the original designations in the literature [21–23, 32–49] describing the mutations. The DNA mutation column, in parentheses, is the location of the mutation within the gene

p.?, protein has not been analyzed but an effect is likely expected but difficult to predict; p.0?, probably no protein is produced

#, entry 6: a large deletion of 10,753 nucleotides from the first intron to past the poly(A) site; the exact reference positions are difficult to deduce from the reported publication

#, entry 17: an exon-splicing enhancer mutation that leads to a cryptic splicing of intronic sequence verified at the mRNA level and predicted to lead to a frameshift in the protein-coding sequence

#, entry 32: the 32-nucleotide insertion was not specified so the correct protein designation cannot be specified exactly but this mutation will definitely lead to a frameshift in the protein-coding sequence

#, entry 38: the predicted protein effect p.P238Rfs*77 differs from 254X designation in original publication

p.T290S variant not included as unlikely to be disease causing

of *ARG1* mutations have been systematically investigated biochemically in both patient erythrocyte enzyme assays and using in vitro overexpression systems, most have been predicted to modify enzyme function based on in silico methods. *ARG1* mutations may alter structure/function and/or stability of the enzyme by compromising active site residues, by introducing packing defects or by causing incorrect translation due to frameshifts [51]. Thus, these various mutations can affect the binuclear manganese cluster and influence the metal-activated hydroxide mechanism by distorting the active site or bridging residues, created steric clashes, and buried hydrophilic groups as well as by influencing the regions necessary for oligomerization (see Fig. 2 for sites of some residues that are most often mutated).

Modeling of arginase-1 deficiency in animals and new insights learned about arginase-1 deficiency disease pathogenesis

The *ARG1* gene was cloned in the 1980s, and the study of the genomic structure revealed a high degree of sequence homology between humans and rodents [52, 53]. Genetically manipulated mouse models have been employed to study the pathobiologic characteristics of ARG1 deficiency [54–62] (for summary, see Table 2). Thus, the first Arg1-deficient mouse model was generated by Iyer et al. [54] using standard gene knockout techniques to study the disease mechanisms. Exon 4 was replaced with a neomycin cassette, which would eliminate critical residues for enzymatic activity. This resulted in homozygous disruption of ARG1 expression with both mRNA and enzyme activities reduced to undetectable levels. The knockout (KO) mice were smaller at birth and continued to deviate in weight and other parameters from wildtype littermates until they died approximately 2 weeks postnatally, resulting in a much more severe phenotype than that observed in human patients. This model of arginase-deficient mice termed the "juvenile lethal model" [59] exhibited hyperargininemia, hypoornithinemia, and severe hyperammonemia [54]. The latter, which causes neurologic deficits, was thought to be the cause of death. Although a 2-fold upregulation in ARG2 activity was noted, it was still insufficient to compensate for lack of liver ARG1. A rescue strategy using intraperitoneal administration of ornithine was also unsuccessful [54].

Deignan et al. [55] later created *Arg1*/*Arg2* gene double KO mice, resulting in a model completely devoid of all arginase activity. The double KO mice shared the same phenotype as the single *Arg1* gene KO mice, with death invariably occurring by 14 days of age following severe hyperargininemia, hyperammonemia, and ornithine deficiency. There was no significant difference in plasma arginine and ornithine levels between the single and double KO mice. Taken together, their

Table 2 Comparison of the main phenotypic abnormalities in the four established ARG1 deficient mouse models as compared to their wild-type littermates

Mouse model	Knockout method	Phenotype	Life span	Refs
C57BL/6J *Arg1*$^{-/-}$	Deletion of exon 4 of *Arg1*	Hyperargininemia, hyperammonemia, hypoornithinemia, decreased body size at birth	10–14 days postnatal	[54]
C57BL/6J *Arg1*$^{-/-}$ /*Arg2*$^{-/-}$ *double KO*	Deletion of exon 4 of *Arg1*, and part of exon 4 and 5 of *Arg2*	Severe hyperargininemia, hyperammonemia, and hypoornithinemia	<14 days postnatal	[55, 56]
JAX strains B6.129-*Gt(ROSA)26Sor*$^{tm1(cre/ERT2)-Tyj}$/*J* x C57BL/6-*Arg1*^{tm1Pmu}/J (two intragastric tamoxifen administrations in neonates or five × 1 mg daily i.p. in adult mice)	Conditional deletion of exons 7 and 8 of *Arg1*	Hyperargininemia, hyperammonemia, ornithine unaffected, progressive weight loss	19 days after first tamoxifen administration regardless of starting age, humane end point set at >15 % loss of body weight	[57]
JAX strains B6.Cg-Tg(UBC-cre/ERT2)1Ejb/J × C57BL/6-*Arg1*^{tm1Pmu}/J (single oral dose of 4 mg tamoxifen)	Conditional deletion of exons 7 and 8 of *Arg1*	Hyperargininemia, hyperammonemia, hypoornithinemia, progressive weight loss	21.5 days after first tamoxifen administration, humane end point set at >30 % loss of body weight	[58]

findings indicated that ARG2 deficiency has no effect on the phenotype of ARG1 deficiency [55]. It was later reported that several guanidino compounds were elevated in plasma and brain tissues collected from the mouse model [56], similar to that observed in hyperargininemic patients [60]. Clearly, ammonia is not solely responsible for having undue adverse effects on the central nervous system in ARG1 deficiency. These guanidino compounds are also neurotoxins and are equally likely to cause the developing neurological sequelae in the disorder. Previous studies in the juvenile lethal model using helper-dependent adenoviral vectors expressing ARG1 showed only transient rescue by extending lifespan from 14 to 28 days [61], while adeno-associated vector (AAV) expression of ARG1 has allowed for metabolic correction lasting longer than 8 months, albeit with some lingering defects [59, 62]. Unlike the human disorder, where survival into adulthood is common, mice of the juvenile lethal model that die in the perinatal period were not amenable to further studies on somatic growth and neurological development/impairment.

To overcome this limitation, knockout technology and inducible expression systems were employed to circumvent the neonatal lethality. Using a Cre/loxP-directed conditional targeting strategy, two new ARG1-deficient mouse models that allowed spatial and temporal control of *Arg1* gene deletion were generated [57, 58]. Tamoxifen-mediated inducible *Arg1* KO was performed in mice of different ages (ranging from the neonatal period to adulthood) to replicate a later-onset juvenile ARG1 deficiency phenotype. Despite using different Cre reporter strains (ROSA26 vs ubiquitin C), the deletion of *Arg1* at various stages results in a phenotype similar to the original juvenile lethal global knockout model [57, 58]. However, different tamoxifen administration regimens attained different degrees of Cre-mediated recombination efficiency. Apparently, a regimen of five daily injections of 1 mg tamoxifen resulted in more substantial *Arg1* gene disruption than did a single oral dose of 4 mg tamoxifen, as demonstrated by a consistent near complete knockout of *Arg1* [57]. Thus, tamoxifen-induced excision of floxed exons 7 and 8 of *Arg1* resulted in significant loss of ARG1 at both mRNA and protein expression levels, especially in liver. The mice exhibited several hallmark presentations of ARG1 deficiency, such as impaired hepatic arginase activity and profound hyperargininemia accompanied by hyperammonemia, prior to the humane euthanization end point. The symptoms presented in these KO mice were consistent with perturbation of the urea cycle. Coincidently, both research groups provided evidence that the phenotypic abnormalities in the KO mice were independent of age of the animal and were most likely attributable to the biochemical derangements of the disorder [57, 58]. Thus, in concordance with previous observations using ARG1 deficient mice [54], these inducible KO mice also exhibited significant alterations in plasma metabolic profiles, including proline, citrulline, alanine, glycine, serine, isoleucine, and guanidino compounds. Interestingly, amino acids such as alanine, glycine, proline, and serine, which are involved in the incorporation of ammonia nitrogen, are conversely reduced, hence suggesting an alternative ammonia-scavenging pathway [57].

In addition, progressive decline in animal body weight was detected in both inducible knockout models [57, 58]. Despite tamoxifen being known to cause alterations in

gastric physiology [63], Sin et al. [57] showed that the substantial weight loss is unrelated to tamoxifen administration. According to the aminostatic hypothesis [64], it is possible that the abnormally high level of arginine triggers a satiety mechanism in the brain, resulting in a waning of appetite. Elevated levels of ammonia may also suppress food intake through the effect of insulin, a potent anorexigenic hormone [65]. Consequently, prolonged reduced food intake affects amino acid homeostasis, which may lead to undernutrition and eventually become life-threatening. However, the molecular mechanisms causing these weight differences remain to be elucidated.

There was some discrepancy between the two inducible models related to the expression of renal ARG2. As previously reported, a compensatory increase in ARG2 activity could be triggered to assuage symptoms of ARG1-deficient patients [19]. Although the exact mechanism is not clearly understood, it was hypothesized that the elevated expression of this second form of arginase could mitigate the severity of ARG1 deficiency via residual ureagenesis [19]. However, Sin et al. [57] found no evidence for renal ARG2 compensation, although Kasten et al. [58] reported a slight increment in renal expression, yet this failed to extend the lifespan of their KO mice. While ornithine was supplemented in an attempt to rescue the lethality of induced Arg1 deficiency, there was an absence of any phenotypic improvement despite showing elevated levels of ornithine in the blood [57, 66]. Other commonly used treatments for ARG1 deficiency, such as low-protein diet and administration of a nitrogen-scavenging drug, sodium phenylbutyrate, were also ineffective in alleviating the biochemical consequences in the induced KO mice [66]. These paradoxical observations indicate that compensatory responses in ARG1 deficiency are different between mice and humans.

Since there are so many uncertainties regarding the development of disease in ARG1 deficiency, it will be important to develop tissue-selective knockout mice. For instance, comparing liver-selective versus neuron-selective ARG1 knockout mice might aid in determining the steps of developing neurological symptoms; i.e., is it liver-derived circulating metabolites affecting the brain or metabolites derived within neurons that initiate neuropathogenesis?

Therapeutic strategies for arginase-1 deficiency

Reconstitution of enzyme function represents the only causal treatment but has not been successful in ARG1 deficiency. The attempt to replace the deficient enzyme by administration of packed red blood cells (which contain ARG1) led to a small immediate decrease of serum arginine but no significant clinical change [67, 68]. Erythrocyte exchange transfusion in addition to low-protein diet, an essential amino acid mixture, and sodium benzoate in one patient resulted in normalization of ammonia levels and serum arginine concentrations, but cerebrospinal fluid (CSF) concentrations of arginine remained unchanged [69]. Pegylated human recombinant ARG1, developed for treatment of liver cancer, has been tested in ARG1-deficient mice where it seems to normalize plasma and brain arginine levels but not in the liver and fails to rescue Arg1 KO mice from the lethal phenotype [70]. Liver transplantation in humans “cures” the disease in the liver but not in other organs including the brain, although it may normalize ammonia and arginine in blood [71, 72]. Extrahepatic ARG1 expression may be one explanation for incomplete phenotype reversal. An early attempt at “gene therapy” in three patients by intravenous injection of the Shope papilloma virus, which induces a viral-encoded arginase, was unsuccessful [73].

Management and treatment of ARG1, in general, is the same as for the other UCDs with the exception being that there is no supplementation with arginine or citrulline [74]. Diet plays the key role in the treatment of hyperargininemia since it has been shown that strict restriction of dietary protein in combination with the supplementation of an essential amino acid mixture that is free of arginine can ameliorate arginine levels in plasma and CSF. However, the response to dietary restriction is relatively poor and improvement of the clinical picture is unsatisfactory [18, 26, 75–77]. Reviewing the literature, Prasad et al. [20] found a clinical improvement in 50 %, stabilization in 25 %, and progression of the disease in 25 % of patients on treatment.

The use of nitrogen scavengers such as benzoate, phenylbutyrate, and phenylacetate, is an alternative pathway therapy for excretion of waste nitrogen via formation and excretion of hippuric acid and phenylacetylglutamine and can be used to lower plasma ammonia levels in ARG1 deficiency [3, 78, 79]. Since the removal of nitrogen via alternative pathways lowers the flux through the urea cycle and this cycle is the only synthetic pathway for arginine, nitrogen scavengers can also be used to lower the formation of arginine in ARG1 deficiency.

Treatment with the amino acid ornithine may help to replenish hepatocellular ornithine to prevent hyperammonemia [23], and it may also inhibit the formation of neurotoxic guanidino compounds through inhibition of the enzyme arginine:glycine amidinotransferase [32]. Lysine supplementation has been trialed to augment argininuria but also in the hope that lysine might compete with arginine for uptake in the brain, thus lowering brain arginine levels [67, 80, 81]. Symptomatic treatments to alleviate the consequences of spasticity progression, despite the aforementioned treatments, include injections with botulinum toxin and orthopedic surgery (i.e., tendon release procedures).

No gene therapy trials for delivery of an arginase repair construct have been attempted yet in humans. However, based on some of the promising results in the juvenile lethal and inducible ARG1-deficient mouse models using AAV delivery [59, 62, 66], it is likely only a matter of time before human trials will be initiated.

Non-urea cycle functions of arginase-1

ARG1 not only plays a vital role in urea cycle metabolism but is also known to affect a variety of other systems in ways that are not yet fully understood. Related to the cardiovascular system, there has been intense interest in L-arginine metabolic pathways since this amino acid is the substrate required for both the synthesis of vasorelaxant nitric oxide by endothelial nitric oxide synthase (eNOS) as well as for being the key substrate of ARG1 [82]. L-Arginine is found in endothelial cells at levels far exceeding the K_m for eNOS, indicating that substrate is not a limiting factor in vivo. Yet, infusion studies of L-arginine often enhance vasodilatation in an eNOS-dependent manner, a phenomenon referred to as the "arginine paradox" [83]. High arginase activity is associated with cardiovascular dysfunction potentially by limiting available substrate for eNOS and by excessive ornithine that can lead to vascular structural problems [84]. While the relationship of arginase with NOS activity is complex, inhibition of arginase has been shown in small-scale human studies to improve cardiovascular health in patients with coronary artery disease, type 2 diabetes, heart failure, hypertension, or following resuscitation after cardiac arrest [84]. It should be mentioned that some of the cardiovascular actions of arginase may be mediated by ARG2 and not by ARG1.

ARG1 is also known to play a large role in the immune system and cancer through the ability of the enzyme to alter macrophage and myeloid-derived suppressor cell (MDSC) states [85]. Macrophages are generally divided into two groups—M1 macrophages that are responsible for inflammation and immunity and M2 macrophages that promote resolution of inflammation, wound healing, and aid in tumor growth, with ARG1 expression being a hallmark marker of M2 macrophage expression. Ron receptor kinase activation induces ARG1 activity [86], leading to attenuation of the M1 phenotype. An increase in tumor-associated MDSCs is a key feature of the malignancy-mediated inflammatory response and a factor leading to T cell suppression in cancer [87]. ARG1-expressing MDSCs can deplete arginine in the tumor microenvironment leading to accumulation of ornithine for polyamine synthesis in cancer cells. Thus, via its ability to deplete arginine, ARG1-expressing cells can regulate the production of nitric oxide and modulate T lymphocyte function [88].

ARG1 is also implicated in airway hyperresponsiveness in asthma and airway inflammation [89]. Chronic asthma patients have a 4.4-fold increase in ARG1 expression compared to controls, while murine models of acute airway inflammation show an 11-fold increase in expression of the enzyme [90].Very high doses of L-arginine are beneficial in murine airway hyperresponsiveness models by reducing levels of TH2 cytokines, eotaxin, TGF-β1, and ovalbumin-specific IgE [91]. Additionally, inhibition of ARG1 expression through the use of a shRNA decreases IL13-induced airway hyperresponsiveness in mice [92].

Arginase plays a key role in maintaining levels of ornithine for use in polyamine synthesis [84]. Polyamines such as putrescine, spermidine, and spermine are derived from ornithine via ornithine decarboxylase (ODC). ARG1 KO mice have increased expression of vital polyamine enzymes ornithine aminotransferase (OAT) and spermidine/spermine-N1-acetyl-transferase (SSAT) in the liver; however, the levels of polyamines were highly variable and few significant trends were seen in the KO mouse tissues [93]. Conversely, overexpression of arginase in mouse macrophages leads to significant increases in putrescine and spermidine when cells are stimulated with either lipopolysaccharide or 8-Bromo-cAMP [94].

Concluding thoughts and future outlooks

Several lingering questions remain relating to the unique clinical manifestations of ARG1 deficiency among urea cycle disorders. In particular, is it excess arginine contributing to the main neurological features of the disease, or is it other toxic guanidino metabolites, diminished nitric oxide production, altered polyamine biosynthesis, or a combination of all these metabolic derangements in various regions of the brain and other tissues? The development of ARG1-deficient mouse models has revealed hyperargininemia in concert with diminished amounts of several other amino acids that affect feeding, leading to a wasting phenotype [57, 66]. It remains an enigma as to why the disorder is so much more severe in mice than in humans. Differences in extrahepatic ARG1 (and ARG2) expression patterns between humans and rodents are likely to explain these differences. Going forward, strategies that can rescue the severe phenotype of ARG1 KO mice should offer promise for similar therapeutic approaches in humans, although this remains to be seen. How much expression of liver ARG1 is necessary to restore adequate urea cycle function in ARG1 deficiency? Based on AAV delivery experiments in mice [66], it is likely that at least 15 % of normal levels are required, but this may not be enough to rescue the neurological sequelae. Adequate ARG1 expression may need to be present in precise metabolic zones of liver, in addition to proper expression in erythrocytes, immune cells [95], and various structures in the brain to adequately control pathophysiology.

Rapid advances have been achieved in modeling diseases in vitro using appropriately differentiated induced pluripotent

stem cells (iPSCs) from patients, combined with gene-editing tools to create "repaired" cells that are genetically identical to the patient cells except for the gene mutation site [96, 97]. Since ARG1 deficiency is so rare and obtaining adequate, unlimited supply of tissue (e.g., liver, blood, brain) from these patients is impossible, adopting these methodologies to study ARG1 deficiency is paramount. We have developed iPSC lines from three separate patients and have initiated the process to gene-edit the cells (unpublished observations). Thus, comparisons can be carried out at the cellular, transcriptomic, proteomic, and metabolomics levels of gene-edited versus parental-mutated iPSCs that have been differentiated to hepatocyte-like cells (and/or other cell types expressing ARG1, e.g., neuronal cells). This will enable insights into biochemical regulatory pathways, besides the urea cycle, that are disrupted/augmented, as well as detection of novel metabolites in ARG1 deficiency and may also lead to cellular phenotypes that would predict pathogenesis. Moreover, strategies to introduce gene-edited hepatocyte-like cells in a patient-specific manner may eventually be feasible, if engraftment strategies can be ameliorated. Hopefully, these types of studies will lead to new insights into this disorder and lead to new therapeutic options.

Acknowledgments CDF is a Tier 1 Canada Research Chair holder in Molecular, Cellular, and Physiological Medicine and kindly acknowledges the CRC program support.

Compliance with ethical standards

Disclosures A.S. is a paid consultant of Hyperion Therapeutics Inc. (Brisbane, CA, USA) and Medunik Canada (Blainville, QC, Canada). The other authors have no conflicts of interest to declare.

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