Review Article

Molecular Structure, Metabolic Pathways and Clinical Relevance of Arginase: A Review

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ABSTRACT

Arginase is an essential enzyme catalyzing the L-arginine hydrolysis to L-ornithine and urea, fundamental to the urea cycle in mammals. The isoforms, arginase I, mainly hepatic and cytosolic, critical for detoxifying ammonia and arginase II, mitochondrial and more widespread across tissues. This review investigates the significance of arginase, especially arginase I, in liver function, highlighting its role in converting toxic ammonia into urea. Understanding the enzyme's structure, including its binuclear manganese cluster and trimeric formation, is crucial for insights into its catalytic mechanism and possible therapeutic targets. Research on liver arginase spans decades, initially focusing on its biochemical properties and now exploring its regulatory mechanisms and clinical implications in diseases like cardiovascular disorders, diabetes and cancer. Arginase activity influences metabolic pathways, impacting nitric oxide production, insulin sensitivity and lipid metabolism. Dysregulation of arginase leads to hypertension, diabetes and hepatic steatosis, making it a promising target for therapeutic interventions. Technological advancements like X-ray crystallography, cryo-electron microscopy and computational modeling have elucidated the detailed structure of arginase, revealing its catalytic sites and potential for drug binding. These studies are pivotal for developing arginase inhibitors, which have shown promise in improving endothelial function and glucose metabolism in clinical settings. Overall, this review underscores the multifaceted role of liver arginase in metabolic processes and disease, advocating for continued research to fully harness its therapeutic potential.

Keywords: Arginase, Structural variants, Cardiovascular diseases, Protein Arginylation.

INTRODUCTION

Overview of Arginase

Arginase is a vital enzyme that catalyzes the L-arginine hydrolysis to L-ornithine and urea. This process occurs in mammals and involves 2 isoforms, arginase I and II, which differ only in their localization, regulation and tissue distribution. Arginase I, chiefly found in liver, play a key role in urea cycle, which detoxifies ammonia by converting it into urea (Figure 1). Operating in the cytosol, this isoform consists of a catalytic site with a binuclear manganese cluster.[1] Human arginase I, sharing 58% of its genetic sequence with arginase II, was identified over two decades ago with its gene located on chromosome 6q23.[2] Arginase II, discovered in 1996, is primarily mitochondrial but also found in the kidney, prostate and small intestine as well.[1]

The catabolism of L-arginine by arginase significantly impacts several metabolic pathways. Metabolism of L-ornithine into polyamines through Ornithine Decarboxylase (ODC), plays a crucial role in cell proliferation and membrane transport.[2] Alternatively, L-ornithine can be converted to L-proline, a collagen component, by Ornithine Aminotransferase (OAT).[3] The substrate in the reaction of Nitric Oxide Synthase (NOS) producing Nitric Oxide (NO) and other reactive

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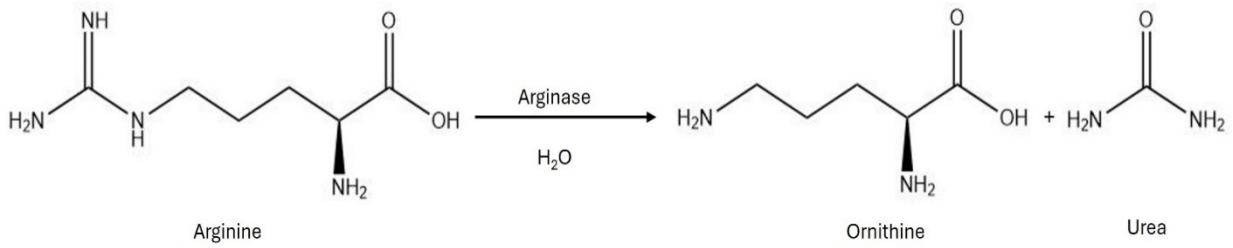

Figure 1: Arginase activity.

intermediates of nitrogen is also L-Arginine. Additionally, L-arginine can be regenerated from L-citrulline through enzymes, AAS (Argininosuccinate synthase) and ASL (Argininosuccinate lyase) (Figure 2). Therefore, understanding the structure and functions is crucial for comprehending its role in various physiological and pathological processes, offering potential therapeutic targets for diseases like cardiovascular disorders, cancer and metabolic syndromes.[4-6]

Importance of understanding Arginase structure in liver function

Arginase is pivotal in the liver's urea cycle, converting toxic ammonia into urea, which the kidneys excrete. Studying the enzyme's structure provides insights into its catalytic activity and interaction with other molecules, crucial for understanding its function and regulation within the liver.[7] This knowledge is significant for developing pharmacological interventions targeting liver and other metabolic disorders. Ammonia, a byproduct of protein metabolism, is converted to urea via the action of liver enzymes, including arginase. Understanding the structure of arginase is essential for gaining insights into its function and regulation within the liver. The arrangement of atoms and molecules three-dimensionally in the enzyme provides crucial information about its catalytic activity and interaction with other molecules. Moreover, studying the structure of arginase can offer valuable clues for the lead pharmacological interventions targeted at modulating its activity. The dysregulation of arginase function may have profound implications for overall health in general and metabolic disorders in particular.

Protein arginylation, a post-translational modification that adds arginine residues to target proteins, has emerged as a global biological regulator with far-reaching implications.[8] This process plays a crucial role in the actin cytoskeleton and muscle function regulation. Latest studies have identified an ever-growing list of proteins and polypeptides (obtained by proteolysis) as substrates for Arginyltransferase I (ATE1), including TDP43, β-amyloid and α-synuclein. Arginylation significantly

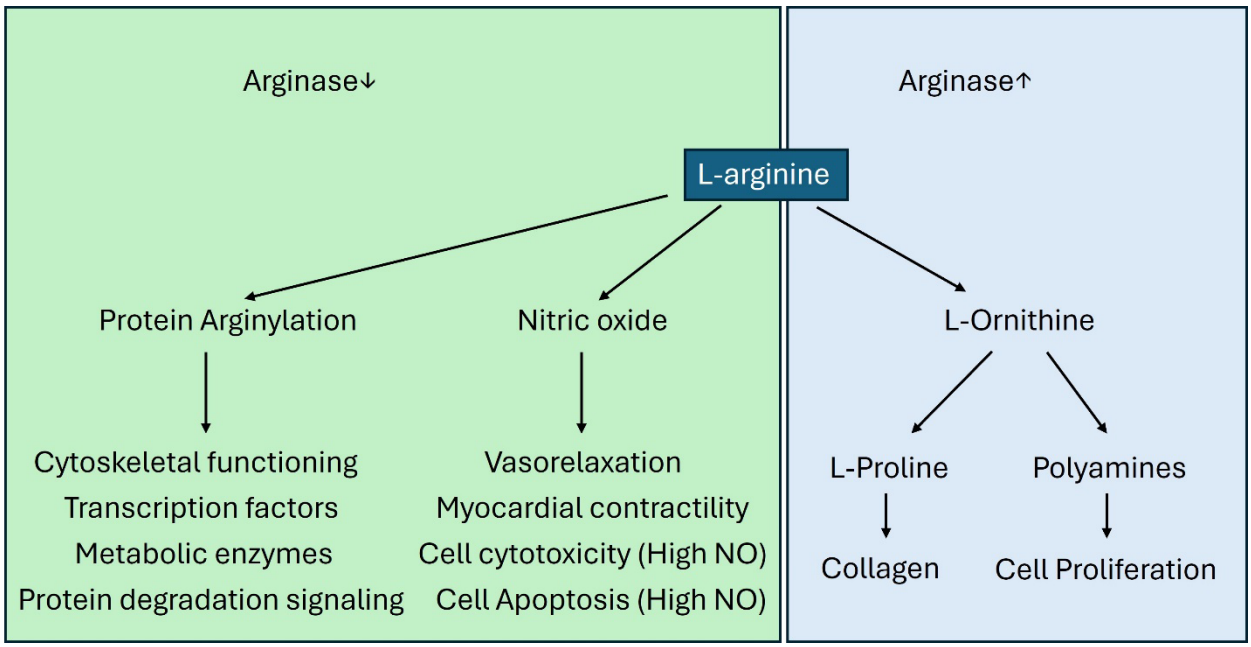

Figure 2: Effect of Arginase activity on various cellular functions.

involves in the proteins and polypeptides signaling, which are ubiquitinated and subsequently degraded by the proteasome. Additionally, arginylation is implicated in the autophagy and lysosomal degradation pathway as well[9] (Figure 2). Arginylation appears to be a unique mechanism for controlling contractility, suggesting that a comprehensive understanding of arginase structure and function may provide valuable insights into these broader physiological processes.[10] The ability to manipulate and control the availability of arginine through its regulation may have significant therapeutic implications, particularly in pharmacological interventions targeting conditions such as dental sensitivity, Parkinson's disease and antimicrobial agents.[10]

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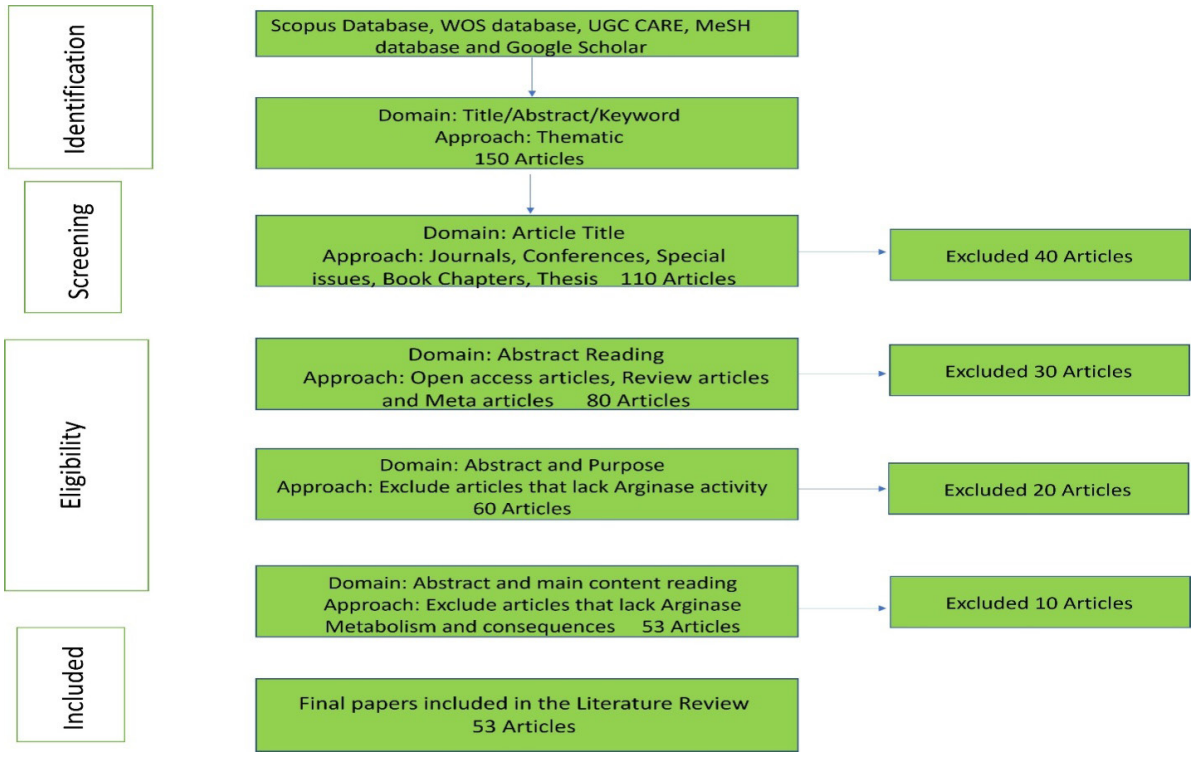

Background and Significance

Brief history of liver Arginase research

Liver arginase, an enzyme of urea cycle, has been the subject of extensive research over the past few decades. The history of liver arginase research dates back to the mid-20th century when its role in the urea cycle was first elucidated. Since then, numerous studies have been conducted to understand its physiological and pathological implications.[11]

The biochemical properties and role in urea production of liver arginase was extensively studies. Subsequent studies explored its regulation and expression in various physiological conditions, such as fasting, feeding and disease states. These investigations have provided a valuable understanding on the potential of liver arginase in metabolic homeostasis and promising target in metabolic disorders. More recent research has delved into the molecular mechanisms underlying the regulation of its expression which led to the identification of potential modulators of Arginase activity, which hold promise for the development of potential and novel therapeutic interventions.

Overall, the history of liver arginase research reflects a progressive understanding of its physiological significance. Despite the advancements made, there are still many unanswered questions and avenues for further exploration in this field. In recent years, studies have also focused on the liver arginase role in various pathological conditions, such as liver diseases, metabolic disorders and other systemic illnesses. The implications of liver arginase in these conditions have been a subject of great interest due to its potential as a diagnostic marker and therapeutic target.[2]

Ongoing research is investigating the potential of liver arginase inhibitors as a treatment for conditions such as non-alcoholic fatty liver disease and diabetes. The development and testing of these inhibitors represent a significant advancement in the field, offering new possibilities for clinical intervention.[6] Additionally, with the advent of advanced genetic and molecular techniques, researchers have gained a more comprehensive

understanding of the complex regulatory networks that control its expression.[1] This deeper insight has opened up new avenues for targeted therapeutic strategies and personalized medicine approaches.

Significance of liver arginase in metabolic processes

The enzymatic activity is vital for the removal of toxic ammonia from the body and the regulation of nitrogen balance and hence of high concern in the modulation of nitric oxide production. The activity of Arginase can influence the synthesis of NO' a key signaling molecule involved in vascular tone regulation and immune responses as it competes with competes with NO synthase for arginine.[12,13] Recent research has uncovered its intricate connections with energy metabolism, lipid regulation and glucose homeostasis.[14,15] Studies have highlighted the role of liver arginase in influencing insulin sensitivity and glucose metabolism, shedding light on its potential implications in diabetes and fatty liver of non-alcoholic origin.[16,17]

The interplay between liver arginase and lipid metabolism has raised interest in its correlation with the pathogenesis of hepatic steatosis and other lipid-related disorders. It has been depicted that liver arginase may participate in lipid metabolism regulation through mechanisms that extend beyond its traditional role in the urea cycle.[1] This multifaceted involvement underscores the complexity of liver arginase's impact on metabolic processes and highlights its potential for therapeutic intervention in a wide range of metabolic disorders.

The significance of liver arginase in metabolic processes is not limited to its enzymatic activity but also extends to its intricate crosstalk with other metabolic pathways. Furthermore, the evolving role of liver arginase in systemic metabolic regulation underscores its potential as a pivotal player in the complex network of metabolic homeostasis. The significance of liver arginase in metabolic processes extends beyond nitrogen metabolism and NO regulation. Studies have linked elevated arginase activity to impaired glucose metabolism, insulin resistance and hepatic steatosis.[18,19]

Clinical Relevance of Liver Arginase

Liver arginase in the arginine metabolism is indispensable for various physiological processes in the body. Arginine is known to be a part of the host defense system, as its metabolite, nitric oxide possesses anti-microbial activity, while another metabolite; ornithine helps in biosynthesis of polyamines, which influences the tissue repair and cell growth.[1,20]

Cardiovascular diseases

Arginase has been found in the vasculature and involve in the control of nitric oxide generation and the onset of vascular diseases, such as diabetes, atherosclerosis and hypertension[1,5] and overexpressed in these conditions leading to lowering of L-arginine bioavailability for NO synthase, which in turn promotes oxidative stress and endothelial dysfunction. The clinical significance of arginase has been further demonstrated by genetic studies that demonstrate distinct associations between cardiovascular disease risk factors and SNPs (Single Nucleotide Polymorphism) in the arginase 1 and 2 genes.[20] Arginase prevents the formation of nitric oxide through a number of possible mechanisms, such as competing with NO synthase thereby disabling the enzyme and producing superoxide, peroxynitrite and urea.[1,2,12,18] Therefore, a promising therapeutic target for the management of metabolic and cardiovascular diseases is the modification of arginase activity. Arginase inhibition has been shown to have therapeutic potential in clinical investigations. For instance, it has been demonstrated that giving the arginase inhibitor Nω-hydroxy-nor-L-arginine to hypertensive individuals improves endothelial function and lowers blood pressure. Moreover, arginase inhibition is linked to enhanced insulin sensitivity and glucose balance, indicating its potential use in the maintenance of diabetes.[5,12,18] As evidence of liver arginase's dysregulation's connection to the etiology of numerous metabolic and cardiovascular disorders grows, so does the enzyme's clinical significance. Arginase targeting is a potentially effective treatment approach and further studies are needed to determine the precise processes via which this enzyme influences the onset and course of disease.[18,20]

Diabetes

Numerous investigations have looked into the relationship between diabetes and liver arginase 1. The findings indicate that elevated liver arginase 1 levels are linked to poor glucose metabolism and insulin resistance. Furthermore, arginase 1 dysregulation contributes to the etiology of diabetes by inducing oxidative stress and inflammation.[21] It has been demonstrated that liver arginase 1 is involved in controlling gluconeogenesis, the process by which the liver makes glucose. The aberrant generation of glucose has been associated with dysregulated arginase 1 activity, highlighting its possible role in the onset of diabetes.[21,22] According to these results, liver arginase 1 has a prominent role in the development and course of diabetes, offering important

new information on the mechanisms underlying the condition. Knowing that liver arginase 1 and diabetes are correlated may open up new therapy options that target this enzyme to control and possibly even prevent diabetes and its effects. More investigation into this relationship could lead to the creation of innovative diabetic treatment plans.

Gout

There is limited research on the clinical correlation between liver arginase 1 and gout, a form of inflammatory-arthritis instigated by the deposition/buildup of uric acid crystals in extremities in general and in joints in particular.[1] However, some studies have suggested a potential link between liver arginase 1 and gout. The research have projected that the liver arginase 1 activity may influence the metabolism of purine, a compound that undergoes conversion to uric acid and contributes to uric acid production. This suggests that dysregulated liver arginase 1 is responsible for the accumulation of uric acid and potentially increases the risk of developing gout.[5,23] These findings recommend further investigations to fully comprehend the need of liver arginase 1 in the treatment of gout. Therefore, further probing in this area to unravel the mechanisms underlying these correlations is necessary and depicts the pharmaco-therapeutic implications.

Cancer

There is limited research on the clinical correlation between liver arginase 1 and cancer. However, some studies have suggested a potential link between liver arginase 1 and cancer progression and revealed that elevated expression of liver arginase 1 is related with metastasis in certain cancers, such as hepatocellular carcinoma and melanoma.[24,25] Furthermore, liver arginase 1 promotes tumor immune evasion by inhibiting the activity of T-lymphocytes and natural killer cells, which are important for tumor surveillance and elimination suggesting a possible involvement in cancer development and progression.[1,12]

Structural Features of Arginase-I

Understanding the structure of Arginase I is important for developing potential treatments for diseases related to urea cycle dysfunction. Research has revealed that human liver arginase is a trimeric enzyme, composed of 3 identical subunits (Figure 3). Each subunit contains a manganese cluster (binuclear) at its active site, which is essential for the catalytic activity of the enzyme. Additionally, the structure has been characterized at a high resolution, providing valuable insights into its enzymatic mechanism and potential binding sites for therapeutic inhibitors.[26] The trimeric structure has a role in its enzymatic function and regulation where, each subunit's interaction makes a proper assembly and makes the enzyme in active conformation.[27] Research efforts focusing on unraveling the regulatory mechanisms that modulate the activity which might provide valuable insights for designing novel treatments for urea cycle disorders. Further, each subunit's active site, housing the manganese cluster, serves as a site for the coordinated cleavage of L-arginine.[28] The high-resolution characterization of the structure has unveiled the precise spatial organization of amino acid residues, tossing light on the potential allosteric and regulatory sites governing its activity.

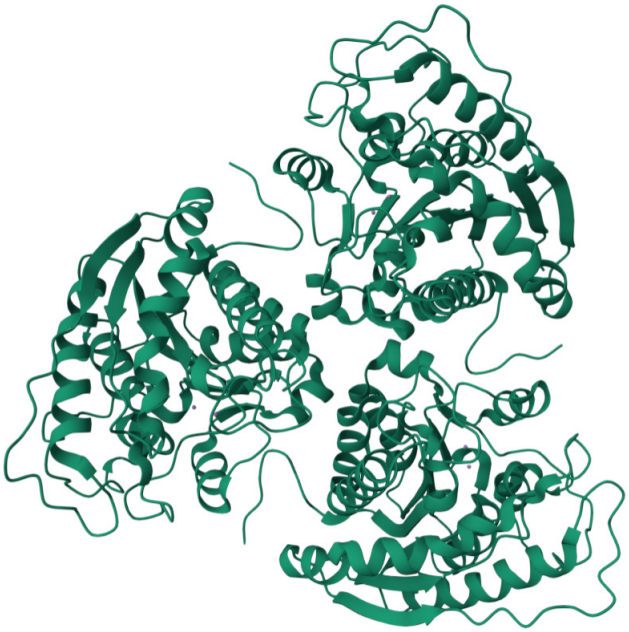

Figure 3: Trimeric structure of Liver Arginase-1 (1WVA.pdb).

Arginase 1 is a fascinating enzyme with a complex and intricate structure. The catalytic activity of this metalloenzyme is attributed to its unique structural domains and motifs. The structural features help in determining the function and specificity. The coordination and positioning of amino acid residues within the active site contribute to the enzyme's catalytic efficiency and substrate specificity.[26] The metalloenzyme nature involves the coordination of metal ions, typically manganese in the active site. Moreover, specific metal binding motifs in the enzyme structure is fundamental for maintaining its catalytic activity and stability.[29] Arginase 1 exhibits structural flexibility, allowing it to undergo conformational changes during

substrate binding and catalysis. This dynamic behavior is essential for efficient enzyme-substrate interactions and enzymatic turnover. Apart from catalytic domain, arginase 1 possesses regulatory domains that modulate its activity in response to various cellular signals and metabolic conditions.[30] Understanding the structural arrangement of these regulatory domains is crucial for deciphering the intricate regulatory mechanisms governing the enzyme's function.

Structural variations among Liver arginase

Structural variations in the enzyme involve differences in the sequence of amino acids, post-translational modifications and conformational states, all of which influence its enzymatic function, stability and interaction with other molecules. Understanding these structural variations can provide insights into its functional mechanisms and implications in various disorders.[31] At the primary structure level, Arginase I is defined by its specific sequence of amino acids, which are crucial for its catalytic capabilities and interactions with substrates and cofactors. Mutations within this sequence can significantly impact the enzyme's function, leading to hyperargininemia.[32] Around 408 variants are present in Clinvar and SNP databases, of which 9 variants are sought to be cause of hyperargininemia (Table 1). The 2º and 3º structures involve the enzyme's folding pattern, which forms a homotrimer-three identical subunits coming together to create a functional enzyme. The precise arrangement of amino acids around the manganese ions is critical for substrate binding and conversion. The quaternary structure is a trimer and is vital for its stability and functionality. Genetic variants and mutations, such as point mutations and natural polymorphisms, can alter amino acid residues in critical regions of arginase 1, affecting its stability, folding, or activity. These genetic differences can lead to variations in the enzyme activity among individuals, influencing their metabolic profiles and susceptibility to certain diseases.

The contributions of phosphorylation and glycosylation (post-translational modifications) to the structural variations cannot be neglected. Phosphorylation at specific residues can affect arginase activity and interactions with other cellular components, while glycosylation can influence its stability, solubility and interaction with other molecules. Conformational changes, including allosteric regulation, can occur upon binding to substrates or inhibitors, affecting the enzyme's activity. Variations that affect the active site or manganese binding can lead to substantial changes in catalytic efficiency. For example, mutations that alter the coordination of manganese ions can reduce the catalytic efficiency of the enzyme causing hyperargininemia.[2] This condition is characterized by elevated levels of arginine in the blood leading to associated neurological symptoms. Understanding the specific structural changes caused by these mutations aids in diagnosing and developing treatments for this disorder.

Table 1: List of Human arginase-1 protein structures in PDB databases.

Sl. No.	Position	Change in amino acid		Effect on Arginase
		Original	Changed	
1	11	Isoleucine	Threonine	Reduction of activity by 88%.
2	27	Glycine	Aspartic acid	Reduction of activity by 94.8%.
3	74	Glycine	Valine	Reduction of activity by 90.7%.
4	125	Alanine	Valine	Decrease in erythrocyte arginase activity.
5	134	Threonine	Isoleucine	Reduction of activity by 88%.
6	138	Glycine	Valine	Decrease in activity.
7	180	Arginine	Threonine	Decrease in erythrocyte arginase activity.
8	235	Glycine	Arginine	Decrease in erythrocyte arginase activity.
9	308	Arginine	Glutamine	Reduction of activity by 79.2%.

Techniques for Studying Liver Arginase Structure

To elucidate the detailed structure of liver arginase, researchers employ a range of biochemical and biophysical techniques. These methods help in the characterization of its primary, secondary, tertiary and quaternary structures, as well as its interactions with other molecules. Around 60 structural data entries of Human Arginase-1 can be obtained from PDB database (Table 2). This review explores the principal techniques used in the elucidation of liver arginase structure, including XRD, NMR, cryo-electron microscopy (cryo-EM) and various computational methods.

X-ray Crystallography

This is the powerful and most widely used technique for determining the 3-D structure of proteins at atomic resolution. For liver arginase, this method involves crystallizing the enzyme and then diffracting X-rays through the crystal. The resultant diffraction pattern is used to reconstruct the electron density map, which

Table 2: List of Human Arginase-1 Clinal Variants.

Sl. No.	Method	PDB ID	Resolution	Chain length (Aa)
1	X-ray crystallography	1WVA	1.94 Å	1-322
2	X-ray crystallography	1WVB	2.30 Å	1-322
3	X-ray crystallography	2AEB	1.29 Å	1-322
4	X-ray crystallography	2PHA	1.90 Å	1-322
5	X-ray crystallography	2PHO	1.95 Å	1-322
6	X-ray crystallography	2PLL	1.90 Å	1-322
7	X-ray crystallography	2ZAV	1.70 Å	1-322
8	X-ray crystallography	3DJ8	1.51 Å	1-322
9	X-ray crystallography	3E6K	2.10 Å	1-322
10	X-ray crystallography	3E6V	1.72 Å	1-322
11	X-ray crystallography	3F80	1.60 Å	1-322
12	X-ray crystallography	3GMZ	1.43 Å	1-322
13	X-ray crystallography	3GN0	1.70 Å	1-322
14	X-ray crystallography	3KV2	1.55 Å	1-322
15	X-ray crystallography	3LP4	1.90 Å	1-322
16	X-ray crystallography	3LP7	2.04 Å	1-322
17	X-ray crystallography	3MFV	1.90 Å	1-322
18	X-ray crystallography	3MFW	1.47 Å	1-322
19	X-ray crystallography	3MJL	1.90 Å	1-322
20	X-ray crystallography	3SJT	1.60 Å	1-322
21	X-ray crystallography	3SKK	1.70 Å	1-322
22	X-ray crystallography	3TF3	1.64 Å	1-322
23	X-ray crystallography	3TH7	2.10 Å	1-322
24	X-ray crystallography	3THE	1.97 Å	1-322
25	X-ray crystallography	3THH	1.85 Å	1-322
26	X-ray crystallography	3THJ	1.50 Å	1-322
27	X-ray crystallography	4FCI	1.82 Å	1-322
28	X-ray crystallography	4FCK	1.90 Å	1-322
29	X-ray crystallography	4GSM	1.70 Å	1-322
30	X-ray crystallography	4GSV	1.48 Å	1-322
31	X-ray crystallography	4GSZ	2.20 Å	1-322
32	X-ray crystallography	4GWC	1.90 Å	1-322
33	X-ray crystallography	4GWD	1.53 Å	1-322
34	X-ray crystallography	4HWW	1.30 Å	5-318
35	X-ray crystallography	4HXQ	1.45 Å	5-318
36	X-ray crystallography	4IE1	2.00 Å	5-318
37	X-ray crystallography	6Q92	1.50 Å	1-322
38	X-ray crystallography	6Q9P	1.66 Å	1-322
39	X-ray crystallography	6QAF	1.61 Å	1-322
40	X-ray crystallography	6V7C	1.80 Å	1-322
41	X-ray crystallography	6V7D	1.82 Å	1-322
42	X-ray crystallography	6V7E	1.99 Å	1-322
43	X-ray crystallography	6V7F	2.02 Å	1-322
44	X-ray crystallography	7K4G	1.80 Å	1-322
45	X-ray crystallography	7K4H	1.65 Å	1-322
46	X-ray crystallography	7K4I	1.98 Å	1-322
47	X-ray crystallography	7K4J	1.94 Å	1-322
48	X-ray crystallography	7K4K	2.27 Å	1-322
49	X-ray crystallography	7KLK	1.80 Å	1-322
50	X-ray crystallography	7KLL	2.22 Å	1-322
51	X-ray crystallography	7KLM	2.27 Å	1-322
52	Cryo-Electron Microscopy	7LEX	3.60 Å	1-322
53	Cryo-Electron Microscopy	7LEY	3.05 Å	1-322
54	Cryo-Electron Microscopy	7LEZ	4.15 Å	1-322
55	Cryo-Electron Microscopy	7LF0	3.68 Å	1-322
56	Cryo-Electron Microscopy	7LF1	4.04 Å	1-322
57	Cryo-Electron Microscopy	7LF2	3.72 Å	1-322
58	X-ray crystallography	8AUP	2.17 Å	1-322
59	X-ray crystallography	8E5M	1.84 Å	1-322
60	X-ray crystallography	8E5N	2.54 Å	1-322

discloses the positions of atoms within the protein. X-ray crystallography has been instrumental in elucidating the detailed structure, including the arrangement of its active site and the coordination of its binuclear manganese cluster (Figure 3). This technique provides insights into the enzyme's catalytic mechanism and also elucidates the key residues involved in substrate binding and catalysis.[33] Another significant study on human arginase 1 utilized high-resolution X-ray crystallography to determine the structures of enzyme-inhibitor complexes.[34-41]

Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR spectroscopy is another valuable technique for studying the structure of liver arginase, particularly in solution. Unlike X-ray crystallography, which requires crystallization, NMR can analyze proteins in their native, functional state.[42] NMR spectroscopy provides information on the protein structure by measuring the magnetic properties of atomic nuclei.[43-45] The dynamic aspects of the enzyme, such as conformational changes upon substrate binding or interactions with inhibitors, can be well understood with NMR. This technique is particularly useful for investigating regions of the protein that may be flexible or disordered in the crystal structure.

Cryo-Electron Microscopy (Cryo-EM)

Cryo-electron microscopy has cropped up as an effective tool for studying the structure of large macromolecular

complexes and membrane proteins.[46] Cryo-EM involves flash-freezing protein samples in vitriform ice and subsequent imaging in electron microscope. This technique has the advantage of requiring less sample preparation and avoiding the need for crystallization and suitable for studying the quaternary structure and interaction of the same with other proteins or cellular components. Recent advances in cryo-EM technology have significantly improved the resolution of this technique, making it a reliable technique to visualize the detailed architecture of liver arginase at near-atomic resolution.[47,48] A recent publication describes the discovery of potential inhibitory anti-hArg antibodies that complex with hArg1 (human Arginase 1), regulating the immune system and implicated in T-cell function and cancer. The structures of antibody-hArg1 complexes can be also be determined, providing a mechanism of inhibition, which includes allosteric actions. The antibodies form large complexes over 650 kDa in size and differ from the previously pursued small molecule inhibitors, offering an alternative strategy for inhibiting hArg1 activity.[49]

Computational Methods

Computational techniques, including MD (Molecular Dynamics) simulations and homology modeling, complement experimental approaches by providing detailed insights into the structural dynamics and function of liver arginase.[50] MD simulations allow researchers to model the movement and interactions of atoms within the protein over time, providing a dynamic picture of the enzyme's behavior in different conditions.[51,52] Homology modeling can also be suitable and reliable for prediction of the structure based on known structures of related proteins. These computational approaches can identify potential binding sites for substrates or inhibitors, predict the effects of mutations on enzyme function and guide the design of experiments to validate structural hypotheses. Recently, using MD simulations, the researchers examined the structural flexibility of the arginase enzyme, particularly the active site's plasticity, to understand how it interacts with inhibitors. They discovered the cavity opening model, which states that the binding of various ligands and posited that larger ligands could potentially enter the arginase cavity. The study introduces a novel 3-dimensional analysis of the pharmacophore method called "dynophores" which considers loop flexibility and ligand conformation changes. They tested their hypothesis experimentally and confirmed the potential for designing novel arginase inhibitors with diverse binding patterns.[53]

Other techniques, such as CD (Circular Dichroism) spectroscopy and Small-Angle X-ray Scattering (SAXS), also contribute to the study of liver arginase structure. CD spectroscopy provides information on the secondary structure content of the enzyme by measuring the absorption of circularly polarized light. SAXS, meanwhile, offers low-resolution structural information in solution, complementing the high-resolution techniques like X-ray crystallography and cryo-EM. Conformational changes, folding and stability of liver arginase under different conditions can be effectively studied using these methods. Computational methods enhance our understanding by modeling structural behavior and predicting functional impacts. Together, these techniques offer an inclusive thoughtfulness of liver arginase, facilitating advances in biochemistry, medicine and therapeutic development. Through these methods, researchers can unravel the complexities of liver arginase and this overlay a road for novel treatments for diseases related to its dysfunction.

CONCLUSION

This review highlights the significant features of liver arginase (Arginase I), in various metabolic and physiological processes. Understanding these differences is crucial for elucidating their specific roles both at tissues and physiological contexts. Its activity significantly impacts several metabolic pathways, including the formation of proline and polyamines which are essential for cell proliferation, membrane transport and collagen synthesis, respectively. The competition with NOS underscores the enzyme's involvement in cardiovascular health, immune responses and potentially various pathological conditions. The structural elucidation of arginase I, particularly through techniques such as XRD and cryo-EM, has provided profound insights into its catalytic mechanism and potential sites for therapeutic intervention. Structural variations and post-translational modifications further underscore the enzyme's dynamic regulation and functional adaptability. Clinical implications of its activity are significant, with dysregulation linked to various disorders/diseases, including cardiovascular diseases, diabetes, gout and cancer. The enzyme's role in modulating NO synthesis places it at the center of endothelial function and vascular health, while its involvement in insulin sensitivity connects it to metabolic disorders. Elevated levels of the enzyme are associated with tumor progression and immune evasion in certain cancers, making it a potential target for cancer therapy. The ongoing research into arginase inhibitors, such as

N ω-hydroxy-nor-L-arginine, demonstrates promising therapeutic potential for managing cardiovascular and metabolic disorders. These inhibitors have shown efficacy in improving endothelial function, reducing blood pressure and enhancing insulin sensitivity. The comprehensive understanding of arginase's structure and function is pivotal for developing targeted therapies for various diseases. Continued research into the enzyme's regulatory mechanisms, structural variations and interactions with other cellular components will further elucidate its roles in healthcare, paving the way for novel therapeutic strategies and personalized medicine approaches.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

As this a review article, there is no involvement of animals and human subjects and hence there is no need of ethics approval

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

CONTRIBUTION DETAILS

G. Rahul-Data acquisition, Literature search and Manuscript preparation.

S. Ravi Kiran-Concept, design and Manuscript editing.

J. Achyutha Devi-Concept, Manuscript editing and Manuscript review.

Ch. Venkataramana Devi-Concept, Manuscript editing and Manuscript review.

ABBREVIATIONS

hArg1: Human Arginase 1; **OAT:** Ornithine aminotransferase; **NOS:** Nitric oxide synthase; **NO:** Nitric oxide; **AAS:** Argininosuccinate synthase; **ASL:** Argininosuccinate lyase; **ATE I:** Arginyltransferase I; **XRD:** X-ray Diffraction; **NMR:** Nuclear Magnetic Resonance Spectroscopy; **Cryo-Em:** Cryo-Electron microscopy; **MD:** Molecular Dynamics; **CD:** Circular Dichroism; **SAXS:** Small-angle X-ray scattering.

SUMMARY

The present research emphasizes the vital role of liver arginase (Arginase I) in metabolic and physiological processes, notably its function in the urea cycle, where it catalyzes the hydrolysis of L-arginine into L-ornithine and urea, crucial for ammonia detoxification. Beyond its primary function, arginase affects various metabolic pathways and competes with nitric oxide synthase for L-arginine, influencing nitric oxide production and cardiovascular health. Structural studies done so far have unveiled arginase's catalytic mechanisms, highlighting its therapeutic potential. Dysregulation of arginase is linked to diseases like cardiovascular disorders, diabetes, and cancer, with ongoing research into arginase inhibitors showing promise for improving endothelial function, reducing blood pressure thus enhancing insulin sensitivity.

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