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Review

# Ornithine and its role in metabolic diseases: An appraisal

Sivashanmugam Muthukumaran[a,c], J. Jaidev[a], V. Umashankar[a,*], K.N. Sulochana[b,*]

[a] Centre for Bioinformatics, Kamalnayan Bajaj Institute for Research in Vision and Ophthalmology, Vision Research Foundation, Chennai, India
[b] R.S. Mehta Jain Department of Biochemistry and Cell Biology, Kamalnayan Bajaj Institute for Research in Vision and Ophthalmology, Vision Research Foundation, Chennai, India
[c] School of Chemical and Biotechnology, SASTRA University, Thanjavur, India

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ABSTRACT

Ornithine is a non-essential amino acid produced as an intermediate molecule in urea cycle. It is a key substrate for the synthesis of proline, polyamines and citrulline. Ornithine also plays an important role in the regulation of several metabolic processes leading to diseases like hyperornithinemia, hyperammonemia, gyrate atrophy and cancer in humans. However, the mechanism of action behind the multifaceted roles of ornithine is yet to be unraveled completely. Several types of cancers are also characterized by excessive polyamine synthesis from ornithine by different rate limiting enzymes. Hence, in this review we aim to provide extensive insights on potential roles of ornithine in many of the disease related cellular processes and also on the structural features of ornithine interacting proteins, enabling development of therapeutic modalities.



**Contents**



* Corresponding authors.
*E-mail addresses:* vumashankar@gmail.com (U. V.), drkns@snmail.org (S. K.N.).

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## 1. Introduction

Ornithine is a non-essential amino acid, which plays a central role in the urea cycle [1]. It is produced by the enzymatic action of arginase on arginine, which results in the production of urea and generates ornithine [2,3]. In cytoplasm, the synthesized ornithine is transported, into the mitochondria by the membrane bound protein, ornithine transporter 1 (ORNT1) [4]. Ornithine was observed since, the works by Hans Krebs and Kurt Henseliet [1]. Its synthesis occurs in cytosol and it is observed to play critical role in mitochondrial metabolic processes [5]. Krebs and Bezinger proposed ornithine to act as a catalyst in the urea cycle [6,7]. This hypothesis contradicted the knowledge on catalyst and elucidated that ornithine yielded arginine in the presence of ammonia and Carbon-di-oxide [7]. Whereas, the resulting arginine on reaction with water yielded urea and ornithine. Latter, ornithine was proven to be an intermediate in urea cycle and also to act as a substrate for these rate limiting enzymes ornithine transcarbomylase **(OTC),** ornithine aminotransferase **(OAT)** and ornithine decarboxylase **(ODC)** producing citrulline, proline and polyamines, respectively (Fig. 1).

### 1.1. Properties of ornithine

Ornithine has a molecular weight of 132.16 Da, with a melting point of 140 °C and is fairly soluble in water. It has a log P value of −4.22 and pKa value is 1.94 (at 25 °C). It features 3 hydrogen bond donors and 4 hydrogen bond acceptors. Ornithine is also known to be involved in the production of excess growth hormone and to burn up excess fat in the body [8]. It also plays a critical role in the functioning of the liver and the working of the immune system.

### 1.2. Ornithine and it's metabolic role

Ornithine mainly acts as a substrate for the enzymes ornithine transcarbomylase **(OTC),** ornithine aminotransferase **(OAT)** and ornithine decarboxylase **(ODC)** producing citrulline, proline and polyamines, respectively (Fig. 1). Citrulline is a key component of urea cycle, as it interacts with aspartate to yield argino-succinate. Lack of citrulline occurs due to mutation and polymorphisms in OTC enzyme leading to hyper ammonic conditions [9–11]. Proline forms important component of collagen in its hydroxylated form [12]. Putrescine is generally derived from ornithine which in turn gets converted into spermidine and spermine successively by the action of ODC [13]. These polyamines are mainly involved in regulating the translation *via* hypusination of the putative translation factor eIF52A due to cell proliferation, hence, play an important role in modulating the progression of cancer as demonstrated in many of the studies [14–17]. For instance, Table 1 clearly depicts that the increase in ornithine levels over a wide range of samples as an indication of pathological conditions. Cellular level studies on L1210 leukemic, H35hepatoma, N18neuroblastoma, and W256 carcinosarcoma and 3T3 fibroblast have also reported excessive Ornithine levels as potential indicator of these conditions [22]. All these data clearly indicates a positive correlation of increased ornithine levels to diseased conditions, hence, reinforcing the need of potential therapeutic modalities essential for modulating ornithine levels.

## 2. Structural and genomic features of ornithine interacting proteins in the context of drug discovery

As discussed earlier, ornithine aminotransferase (OAT), ornithine decarboxylase (ODC), Ornithine transcarbomylase (OTC) and

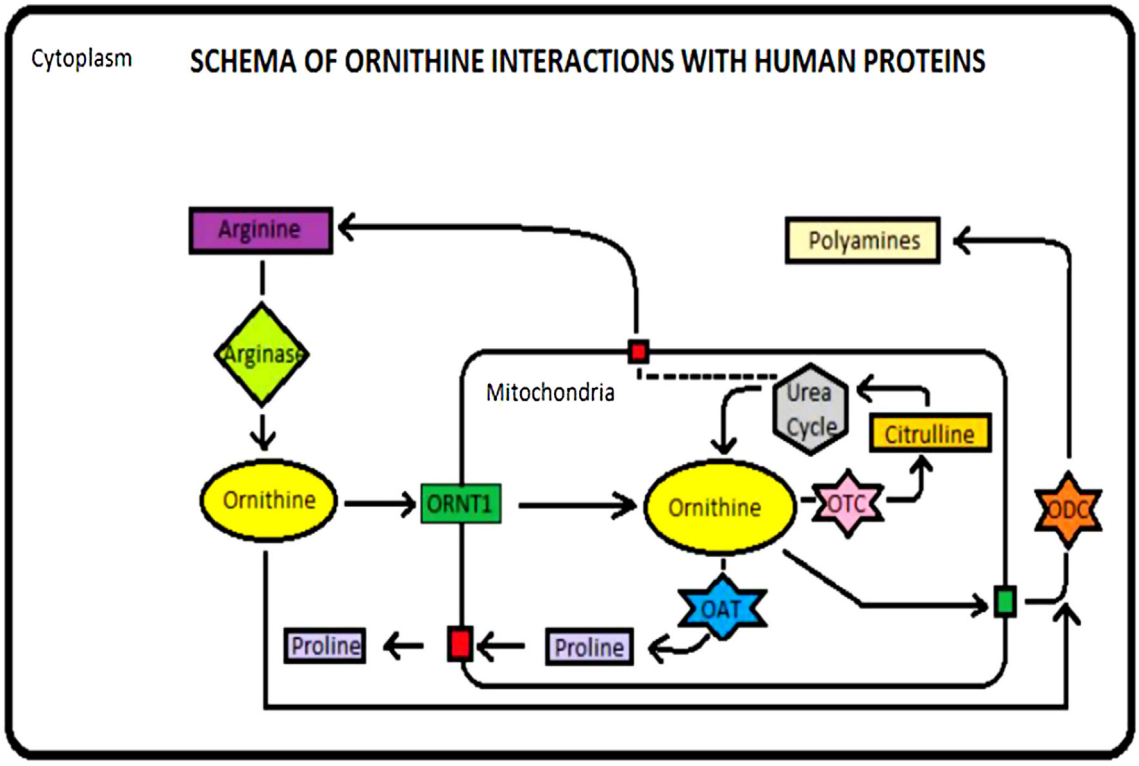


**Fig 1.** Schematic representation of ornithine and its interacting proteins: OAT, ODC, OTC, ORNT1 in the context of cellular localization.