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Review

Arginine: Challenges and opportunities of this two-faced molecule in cancer therapy

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ABSTRACT

Numerous antitumor therapies have been developed based on the differences in cells' metabolisms. Regarding the important role of arginine (Arg) in the regulation of multiple metabolic and signaling pathways, its deprivation has been proposed as a good strategy for tumor regression in tumors with defected Arg metabolic enzymes like argininosuccinate synthase 1 (ASS1). However, modulatory effect of Arg on various cancers is also a controversial issue. Therefore, this review article intends to address some of the challenges faced by Arg deprivation method as well as Arg administration for cancer therapy.

1. Introduction

Amino acids, aside from constituting the building blocks of proteins, are also involved in various physiological and pathological functions and different cellular events such as gene expression, cell signaling, and cell proliferation in both normal and cancer cells [1]. Furthermore, some of these substantial units are intermediates of metabolic pathways within the cells. So, the balance of amino acid level in the body is critically important for its impeccable physiological performance [2,3].

Reprogramming cellular metabolism is the key change that cancer cells have to make in response to their modified energy demands. In order to do so, tumor cells switch to an enhanced glycolysis pathway instead of oxidative phosphorylation (OXPHOS) in spite of having access to enough oxygen [4]. Another path cancer cells take to adapt to perform in an increased nutritional need situation, aside from increasing glucose uptake, is to start relying on other nutrients including amino acids. Therefore, targeting cancer metabolism is considered a promising strategy in cancer therapy nowadays. Amino acid deprivation is thus a fascinating field of focus regarding cancer treatment [5].

Glutamine (Gln), serine (Ser), asparagine (Asn) and arginine (Arg) are important amino acids for tumor growth among which Arg is considered to be multifunctional. This amino acid takes part in various cellular events and metabolism through its various metabolites [5,6]. Previous studies investigating the effects of Arg in cancer therapy have presented conflicting results. While some studies confirm that Arg enhances tumor growth [7,8], others introduce it as an appropriate candidate for cancer treatment [9–11]. Therefore, elucidating different aspects of the Arg metabolism in normal cells and cancerous one could be of great interest and benefit in therapy. This review article summarizes the metabolism and the role of Arg in normal and cancer cells with added emphasis on the challenges associated with this amino acid in cancer therapy.

2. Metabolism of the arginine

2.1. Endogenous arginine synthesis: its roles in the health and disease

Arg is a semi-essential amino acid for healthy individuals and under certain physiological conditions and diseases, it could turn essential [6]. Endogenous synthesis of Arg in humans and most other mammals occurs through intestinal-renal axis. In this process, citrulline derived from glutamine, glutamate, and proline in the small intestine is used to produce Arg in the kidney [12]. Also, it has been stated that Arg can be synthesized in the liver as well [13]. However, since Arg is further re-utilized in the urea cycle, there is no net synthesis of this molecule by hepatic cells [14] (Fig. 1).

Abbreviations: ADC, arginine decarboxylase; ADI, arginine deiminase; ADI-PEG20, ADI- polyethylene glycol 20; AIF, apoptosis-inducing factor; AMPK, AMP-activated protein kinase; Arg, arginine; ASL, argininosuccinate lyase; Asn, asparagine; ASS1, argininosuccinate synthase 1; CTLs, cytotoxic T cells; ECs, endothelial cells; ERK1/2, extracellular signal-regulated protein kinases 1 and 2; Gln, glutamine; HIF-1α, hypoxia inducible factor 1α; IL, interleukin; LC3, light chain 3; MDSCs, myeloid-derived suppressor cells; MHC, major histocompatibility complex; MMP2/9, matrix metalloproteinases 2,9; NF-κB, nuclear factor kappa B; NO, nitric oxide; NOS, nitric oxide synthase; OAT, ornithine aminotransferase; ODC, ornithine decarboxylase; OTC, ornithine transcarbamylase; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; Ser, serine; TAMs, tumor associated macrophages; TCA, tricarboxylic acid; TGF-β, transforming growth factor beta 1; VEGF, vascular endothelial growth factor

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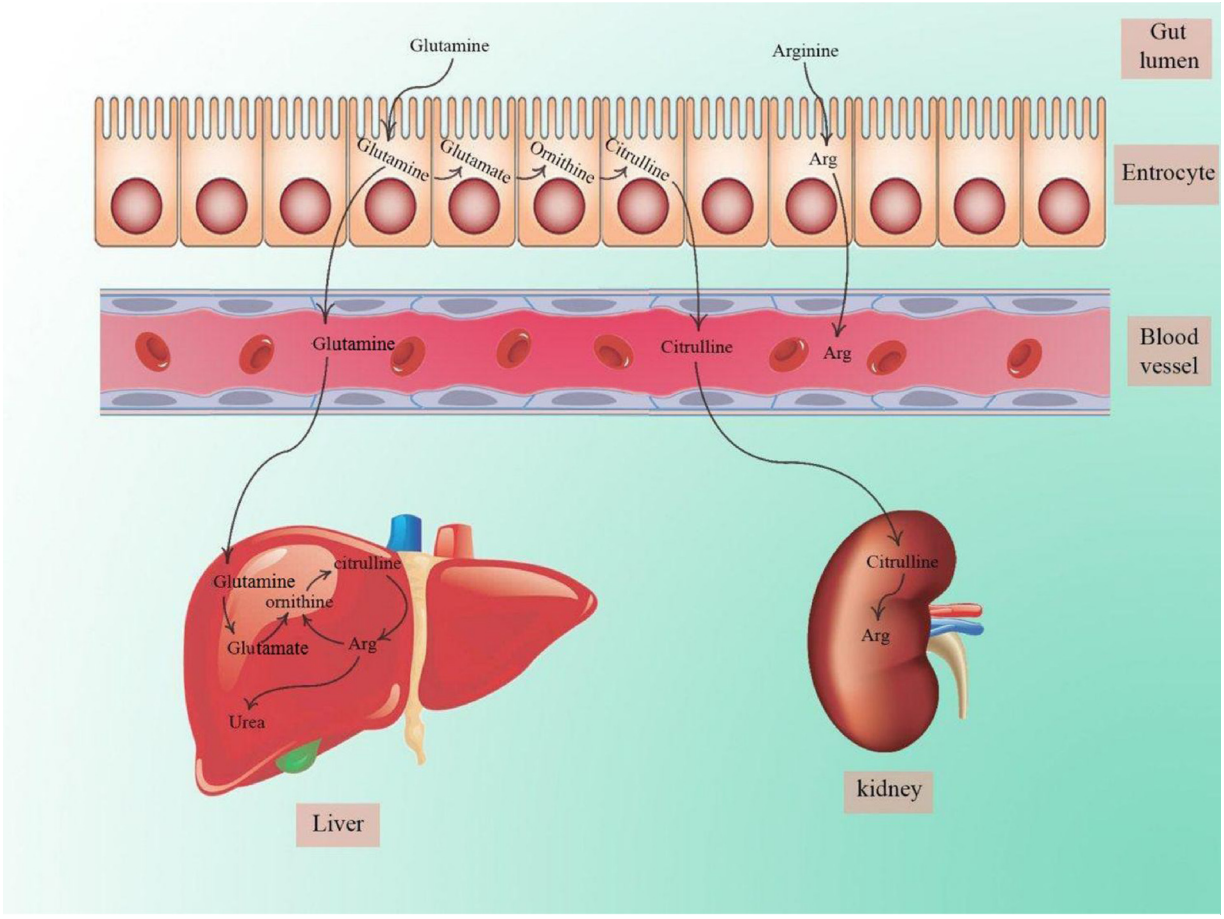

Fig. 1. Endogenous synthesis of Arg.
Endogenous synthesis of Arg in humans and most other mammals occurs in the intestinal-renal axis.

In a physiological state, Arg is the essential nutrient in spermatogenesis, preservation and growth of the embryo, fetal and fetus. Furthermore, it is also involved in ammonia intoxication, improvement of reproduction, immune system response, and cardiovascular, gastrointestinal, liver and renal systems functioning. Moreover, Arg enhances wound healing and also is effective in insulin sensitivity as well as tissue integrity [6].

However, despite Arg role in physiological state there are some contradictory results regarding its effect in cancer treatment. Accordingly, understanding the metabolic pathways and enzymes involved in the synthesis of Arg metabolites could be very enlightening when it comes to cancer therapy.

2.2. Degradation of arginine

The complex Arg metabolism is identified as a starting pertinent substrate for several metabolic pathways. These include synthesis of nitric oxide (NO), polyamines, proline, glutamate, agmatine, urea, nucleotides and creatine. Arg catabolism is mediated by various enzymes including the two most important ones, arginase and nitric oxide synthase (NOS). NO and citrulline are produced by NOS and the main products of arginase activity are ornithine and urea. Ornithine can be further metabolized into polyamines by ornithine decarboxylase (ODC) as well as proline and glutamate via ornithine aminotransferase (OAT). Furthermore, there is Arginine decarboxylase (ADC) which cleaves Arg into the agmatine. Each of these metabolites could exert a different effect on cancer cells which would be explained in the next section [15,16] (Fig. 2).

3. Arginine and cancer therapy

Altered metabolic phenotype has been known as a hallmark of tumor cells [17]. These cells have expanded nutrition needs as for various amino acids such as Arg to keep up with their intensive proliferation [3]. So, depriving malignant cells from these key nutritive elements is currently a practical approach towards the induction therapy especially in the case of certain cancers that are auxotrophic for specific non-essential amino acids [5].

Ascribing Achilles' heel to Arg is justified by the fact that tumor cells depend on this amino acid [18,19]. Arg is a versatile amino acid with some of its metabolizing enzymes being decreased or deleted in most cancer cells [20]. It can be reintroduced into the cells by argininosuccinate synthase 1 (ASS1) and argininosuccinate lyase (ASL) from citrulline [21]. ASS1 is a normally expressed rate-limiting enzyme in Arg metabolism)Fig. 3A(which is deficient in most cancer cells such as melanoma, hepatocellular carcinoma, and prostate carcinoma [22,23]. There are some transcription factors such as c-Myc and hypoxia inducible factor 1α (HIF-1α) involved in regulation and modification of ASS1 expression [24]. Moreover, it could also be activated or deactivated through demethylation and hypermethylation of its promoter in some tumors such as lymphoma, glioblastoma and myxofibrosarcoma [25]. Studies show that various types of cancer have various ASS1 expression levels (Fig. 3B/ Table 1). Accordingly, based on this enzyme status and activity, cancer cells can be either dependent on or independent of the exogenous Arg, where the former condition is called auxothrophy [22].

Since tumor cells are incapable of proliferation in the absence of Arg, removing this amino acid from their microenvironment has been