

## Carbon quantum dots may interfere with colorectal cancer treatment through affecting on glutamine metabolism

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### ABSTRACT

Cancer cells are metabolically different from normal cells, including the Warburg effect and uses glutamine to fill the Tricarboxylic Acid (TCA) cycle. It was demonstrated inhibiting glutamine metabolism prevents tumor growth. The mammalian Target of Rapamycin (mTOR) is one of the signaling pathways that involve glutamine metabolism in cancer. Carbon Quantum dots (CQ-dots) nanoparticles are associated with the mTOR signaling pathway. These findings indicate that irregular glutamine metabolism are related to the growth of Colorectal Cancer (CRC). Thus, the activating glutamine metabolism via the mTOR pathway in CQ-dots treatments has toxic effect on CRC therapy. So, more investigations need for therapeutic application of these nanocarriers.

**Keywords:** Colorectal cancer, mTOR, glutamine, carbon quantum dots, metabolism

### INTRODUCTION

Cancer cells have metabolically different from normal cells, including phenomena

such as the Warburg effect (conversion of glucose to lactate in the presence of oxygen) and glutamine dependence in cancer cells [1,2]. In normal cells, the

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acetyl-CoA (produced from glucose during metabolism) enters the Tricarboxylic Acid (TCA) cycle but cancer cells have the Warburg effect and use glutamine to fill the TCA cycle [3]. Metabolic products of glutamine are used in the production of ATP and the synthesis of macromolecules to increase tumor growth [4]. Although glutamine is known to be a non-essential amino acid but it has been reported to be a supplement needed to culture cancer cells [5]. Recent studies have shown that inhibiting glutamine metabolism reduces growth and prevents tumor progression [6,7]. One of the signaling pathways involved in glutamine metabolism in tumor cells is the mammalian Target of Rapamycin (mTOR), an important metabolism regulator and intracellular sensor in tumor cells. mTOR consists of two multiprotein complexes, mTORC1 and mTORC2. Akt signaling pathway activates mTORC1 by blocking tuberous sclerosis complex 2 (TSC2) and phosphorylation of Rheb GTPase-Activating Protein (GAPs) [8]. Akt has been related to increased reactive oxygen species (ROS) generation and oxygen consumption in cells with glucose starvation conditions [9], which indicated that the Akt/mTORC1 signaling pathway regulates the tumor cells oxidative balance [10]. mTORC1 signaling has been

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indicated to decompose glutamine to  $\alpha$ -ketoglutarate and glutamate, enhance the glutamine and glutamate dehydrogenase expression, increase the arginine metabolism and, promote the ornithine decarboxylase and argininosuccinate synthetase expression [11-13]. Carbon quantum dots (CQ-dots), one of the novel classes of carbon nanomaterials, are a hopeful tool in cancer detection and therapy. However, the influences of CQ-dots on cancer cell growth and metabolism are not well identified [14,15]. CQ-dots have sizes below 10 nm, and it was found through purification of single-walled carbon nanotubes with preparative electrophoresis for the first time since 2004 [15]. It uses in targeted therapy applications, drug delivery [16], and medical imaging because of its exclusive photophysical characteristics, low toxicity, and facile surface functionalization as well as its green synthesis due to high solubility in water [17]. The CQ-dots treatment demonstrated high metabolism and synthesis of amino acids, including glutamine [14]. CQ-dots involves the mTOR signaling pathway too. Ding *et.al* reported that in this pathway after CQ-dots are endocytosed, intracellular ROS are increased. Moderate ROS act as activator signaling molecules that stimulate

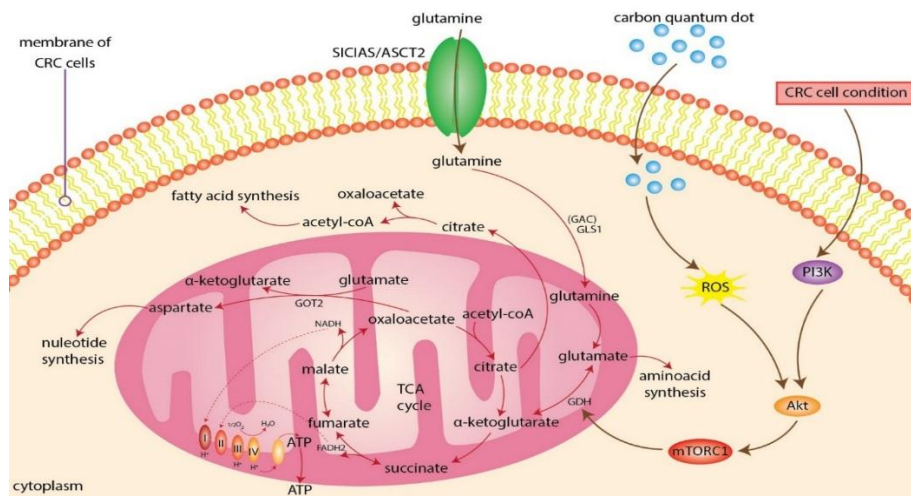
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Akt/mTOR signaling, leading to upregulated glutamine-related gene expression and fast glutamine metabolism, which increases Uveal Melanoma (UM) cell growth. High concentrations of CQ-dots stimulate excess ROS generation and result in UM cell death [14].

The findings show that irregular glutamine metabolism is significantly related to survival, metastasis, recurrence, and growth of Colorectal Cancer (CRC). As a result, blocking the transporters, enzymes, and signaling pathways involved in glutamine metabolism can be a way to prevent the progression of CRC [18]. As it is demonstrated that downregulation of

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glutamine transporter (alanine, serine, cysteine-preferring transporter 2, ASCT2/SLC1A5) could inhibit proliferation and lead to apoptosis in CRC cell lines [19]. In addition, Zhang *et al.* that in their study reported that the activity of mTOR signaling was much higher in CRC [20]. The phosphatidylinositol 3-kinase/Akt/mTOR (PI3K/Akt/mTOR) signaling axis plays a critical role in the resistance to apoptosis, proliferation, metastasis, and angiogenesis that is central to the maintenance and development of CRCs [21-24] (Figure 1).



**Figure 1.** The signaling pathway of glutamine activation via mTOR pathway by CQ-dots in therapy.

## CONCLUSION

It can be said due to activating glutamine metabolism via the mTOR pathway in CQ-dots, it has toxic effect in CRC therapy. So, more research is needed on the use of these nanocarriers as drug delivery systems.

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