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Review

Molecular mechanisms of anticancer effects of Glucosamine

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ABSTRACT

Glucosamine is an amino sugar that is produced naturally in human body. It is an essential carbohydrate component of many cellular glycoproteins, glycolipids, and glycosaminoglycans (GAGs). This popular over-the-counter supplement is also found in the exoskeleton of crustaceans. Glucosamine and its derivatives have a long history in medicine for inflammatory conditions specially to relieve arthritis. This dietary supplement has numerous biological and pharmacological properties, including anti-inflammatory, antioxidant, anti-aging, anti-fibrotic, neuroprotective and cardioprotective activities. Many studies have shown that glucosamine has anti-cancer activity through influence on biological pathways involved in cell death, apoptosis, cell proliferation, and angiogenesis. Accordingly, this comprehensive review summarizes anti-cancer molecular mechanisms of glucosamine in details.

1. Introduction

Cancer is a growing and major health problem around the world. According to the GLOBOCAN database, there will be estimated 21.7 million of new cancer cases in 2030. It is predicted that the number of cancer mortality will rise to 13 million in the next 15 years [1]. So, the considerable efforts have been made to develop novel cancer therapeutic agent with anti-proliferative activity. In recent years, there has been an increasing interest to use natural compounds for treatment of various diseases due to less adverse effects.

Glucosamine (GlcN) is an interesting natural compound due to inhibition of tumor growth both *in vivo* and *in vitro* conditions. Glucosamine is an amino sugar that is now widely used as a dietary supplement by patients who suffer from osteoarthritis [2]. It is also demonstrated that GlcN has no serious adverse effects and toxicity for human with the exception of mild gastrointestinal disorders [3]. In addition, this amino sugar is expected to exert an important role in cancer treatment. In 1953, Quastel and Cantero published the first report of anti-cancer activity of glucosamine. They found that daily injection of GlcN led to decrease cell mass and extensive hemorrhagic areas in the Sarcoma 37 tumors in mice. Although GlcN treatment did not result in complete tumors regression, the survival time of the treated mice was extended approximately doubled [4]. Moreover, it was observed that there was a relationship between glucosamine usage and lower risk of lung and colorectal cancers [5,6]. The results of a cohort study indicated that use of glucosamine combined with chondroitin was significantly associated with lower risk of colorectal cancer (CRC), while this association was not observed when glucosamine used alone [6].

It is also well known that GlcN possesses an anti-inflammatory effect and probably exerts its most of anti-cancer activity via inhibition of pro-inflammatory mediators synthesis [7]. It is believed that the anti-cancer properties of glucosamine, *N*-acetyl glucosamine (GlcNAc) and D-glucosamine hydrochloride are related to their functional groups such as hydroxyl, amide and acetylamine [8]. Several mechanisms have been proposed for the anti-cancer effects of this amino sugar (Table 1). However, the exact anti-cancer molecular mechanisms of glucosamine are still not clearly understood. In this review, we focus on different possible mechanisms of anti-cancer activity of glucosamine.

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Table 1
Various anti-cancer mechanisms of glucosamine against different cell lines.

Cell or Model	Anticancer Mechanism	Ref.
HeLa and COS7 cells	Autophagy induction via an mTOR-independent pathway	Shintani et al. [42]
C2C5 cells	Autophagy induction via PERK/eIF2a phosphorylation and polyglutamine-induced LC3 conversion	Kouroku et al. [151]
U87MG human glioma cancer cells	Autophagy induction through the stimulation of ER stress	Hwang et al. [53]
Human ALVA41 prostate cancer cells	Proteasomal inhibition through down regulation of proteasome activator PA28γ	Liu et al. [68]
A549 (lung), H292 (bronchial), and Hep2 (laryngeal)	Increasing COX-2 protein turnover in a proteasome-dependent Manner	Jang et al. [152]
Human lymphocyte	Antigenotoxic effects	Jamialahmadi et al. [102]
SW1353, ATTC HTB94, RAW264.7, ATTC TIB 71	Intracellular free radical scavenging	Mendis et al. [100]
YD-8 human oral cancer cell line	Induction of the caspase-dependent apoptosis and down-regulation of HIF-1a	Jung et al. [94]
YD-8 human oral cancer cell line	Down regulation of HIF-1α at the protein level	Jo et al. [153]
Human NSCLC[a] cell lines A549, H226B, H1299, and H460	IGF-IR/Akt–dependent anticancer effect	Song et al. [97]
MCF-7 and MDA-MB-231 breast cancer cells	Inhibition of PKC-Induced COX-2 and IL-8 Expression	Chou et al. [118]
DU145 human prostate carcinoma cells	Inhibition of STAT3 signaling	Chesnokov et al. [72]
DU145 cells	Inhibition of p70S6K	Oh et al. [85]
Lung cancer	Suppressing the phosphorylation of FOXO [45]	Zhanwu et al. [45]

[a] Human non-small cell lung cancer.

2. Main molecular mechanisms

2.1. Glucosamine alters the uracil and adenine nucleotide contents

Glucosamine is produced intracellular from glucose. UDP-glucosamine can be formed from UTP and glucosamine 1-phosphate in a reaction catalyzes by UDP-glucose pyrophosphorylase [9]. GlcN diverts uridine monophosphate from UTP into UDP-*N*-acetyl glucosamine. This reaction can result in a reduction of UTP and other pyrimidine nucleotides. [10]. The expansion of UDP-*N*-acetylhexosamine pool by GlcNAc could therefore create an imbalance in the pattern of sugar nucleotide which is the main mechanism of cytotoxic effect of GlcN [11]. The nucleotide depletion caused by glucosamine could inhibit the nucleotide salvage pathways, uptake of exogenous thymidine, and RNA synthesis [12,13]. It also promotes the cellular leakage of nucleotides and their metabolites [14]. Additionally, increased amounts of UDP-GlcNAc causes an increase in adenine catabolism and then decrease in ATP levels [10].

External glucose or glucosamine level affects on the UDP-*N*-acetyl glucosamine (UDP-GlcNAc) concentration in mammalian cells. UDP-GlcNAc and UDP-GalNAc are essential intermediates in the protein glycosylation which has an established function in cell differentiation. There are conflicting results that show UDP-GlcNAc accumulation in colon cancer cells blocks cell differentiation pathway [15]. Undifferentiated cancer cells are more aggressive than matured ones. Therefore, cancer treatment with glucosamine disagrees with “differentiation therapy” which induces differentiation in cancer cells and converts them to normal cells [16].

2.2. Glucosamine damages the structure and function of plasma and cell membrane compartment

Several reports showed that GlcN exhibits little toxicity toward normal tissues and cells but is toxic to many malignant tumors and cell lines [17–22]. Within the first 3 h after addition of D-glucosamine to cell culture, it starts to change the structure of the plasma and intracellular membranes [23,24] and prevents nucleoside uptake, increases nucleoside efflux to the extracellular space [25]. Moreover, D-glucosamine can move the glucosamine moiety from glycoproteins to glycolipids, prevent cell aggregation, and inhibit homotypic cell sorting [26–28]. Glucosamine also disrupts cellular membrane through prevention of cholesterol synthesis by inhibiting a step prior to the formation of acetyl CoA [29]. Therefore, glucosamine could be selectively toxic to many tumor cells in combination with other membrane active drugs [30]. These effects were observed preferentially in cancer cells but not in normal cells [31].

2.3. Glucosamine induces autophagic cell death

Autophagy is an intracellular system to degrade old proteins and recycle cellular components such as mitochondria or endoplasmic reticulum within the lysosomes. It has been supposed that autophagy has a crucial role in both tumor formation and cancer cell death [32,33]. Glucosamine treatment can cause endoplasmic reticulum (ER) stress and initiates the unfolded protein response (UPR) in ER [34,35]. Thereafter, unfolded proteins are translocated from ER to cytoplasm and their proteolysis occurs via ER-associated ubiquitin/proteasome degradation ERAD system [36]. On the other hand, following increase in unfolded and misfolded proteins, they aggregate in the ER and induce cell death through caspase-12 activation [37,38]. ER stress response also leads to expression of the transcription factor GADD153/CHOP which induce cell growth arrest and programmed cell death [39]. In a study by Su et al., it was suggested that ER stress is linked to autophagy. Extreme cellular stress triggers autophagy and leads to cell death by depletion of cellular contents. Dual effects of autophagy on cell survival or death depends on the cellular context, the stimuli power and duration [40].

Research studies suggested that GlcN-induced autophagy is mediated via mTOR-dependent [41] and −independent [42] pathways. mTOR plays important roles in a variety of cellular processes including cell growth, cell survival, motility, transcription and cell proliferation. mTOR achieves its diverse roles through participating in two protein complexes referred to as mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) which differ in subcellular localization and binding partners. The inhibition of mTORC1 by glucosamine results in autophagosome formation and autophagy initiation [43,44]. Glucosamine reduces the phosphorylation of Akt and FoxO3,1 [45], compatible with the well-known interaction between Akt and FoxO3 [46]. Hence activated FoxO negatively regulates mTOR signaling [47] that is required to induce autophagy. Conclusively, GlcN increases autophagy *in vitro* and *in vivo* mainly through the Akt/FoxO/mTOR signaling pathway [48] (Fig. 1).

More than 30 genes have been reported to have an important role for the process of mTOR- independent induction of autophagy [49].