Biochemical and Biophysical Research Communications 414 (2011) 282–286

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Mini Review

Concanavalin A: A potential anti-neoplastic agent targeting apoptosis, autophagy and anti-angiogenesis for cancer therapeutics

Wen-wen Li [1], Jia-ying Yu [1], Huai-long Xu, Jin-ku Bao *

School of Life Sciences & State Key Laboratory of Oral Diseases, Sichuan University, Chengdu 610064, China

ARTICLE INFO

Article history:
Received 2 September 2011
Available online 17 September 2011

Keywords:
Concanavalin A (ConA)
Anti-neoplastic
Apoptosis
Autophagy
Anti-angiogenesis

ABSTRACT

Concanavalin A (ConA), a Ca^{2+}/Mn^{2+}-dependent and mannose/glucose-binding legume lectin, has drawn a rising attention for its remarkable anti-proliferative and anti-tumor activities to a variety of cancer cells. ConA induces programmed cell death via mitochondria-mediated, P73-Foxo1a-Bim apoptosis and BNIP3-mediated mitochondrial autophagy. Through IKK-NF-κB-COX-2, SHP-2-MEK-1-ERK, and SHP-2-Ras-ERK anti-angiogenic pathways, ConA would inhibit cancer cell survival. In addition, ConA stimulates cell immunity and generates an immune memory, resisting to the same genotypic tumor. These biological findings shed light on new perspectives of ConA as a potential anti-neoplastic agent targeting apoptosis, autophagy and anti-angiogenesis in pre-clinical or clinical trials for cancer therapeutics.

1. Introduction

Plant lectins are a class of highly diverse non-immune origin, and carbohydrate-binding proteins, which contain at least one non-catalytic domain for selective recognition and reversible agglutination of cells. The non-catalytic domain is also responsible for precipitating polysaccharids and glycoconjugates through the free glycans or sugars on glycoproteins and glycolipids without altering the structure of carbohydrate [1]. According to their tertiary structures and evolutionary statuses, plant lectins can be further classified into 12 different families, including Amaranthin, *Agaricus bisporus* agglutinin, Cyanovirin, Chitinase-related agglutinin, *Euonymus europaeus* agglutinin, *Galanthus nivalis* agglutinin, Hevein, Jacalins, Lysin motif, Legume lectin, Nictaba and Ricin_B families [2]. Among the afore-mentioned 12 plant lectin families, legume lectin family is well-known for its far-ranging biological functions, such as anti-tumor, anti-fungal, and anti-viral activities [1].

Concanavalin A (ConA) is a Ca^{2+}/Mn^{2+}-dependent and mannose/glucose-binding legume lectin, which first isolated from the jack bean in 1916 [3–6]. The mature monomer of ConA is composed of 237 amino acid-residues that form 2 anti-parallel β sheets. A curved 'front' β sheet of 7-strands aligns with a flat 'back' β sheet of 6-strands. These two are connected by another 5-strands 'roof' β sheet from the front to the back. Two ConA monomers lay in an adjacent, anti-parallel and back-to-back manner to form a dimer. Two dimers form a tetramer in the same way (Fig. 1A) [7]. The structural organization of ConA is pH dependent, when the pH is above 5.5, it exists as a tetramer, otherwise a dimer [8].

Concanavalin A, the long-studied representative legume lectin, thus far has generated a rising attention for its anti-proliferative and anti-tumor activities towards various types of cancer cells. ConA has been reported to kill tumor cells targeting apoptosis, autophagy, anti-angiogenesis as well as immunomodulatory. These findings shed light on new perspectives of Concanavalin A as a potential anti-neoplastic agent for cancer therapeutics.

2. ConA induces cancer cell death targeting apoptosis

2.1. Targeting the mitochondria-dependent apoptotic pathway

Apoptosis is a mechanism by which cells undergo death to control cell proliferation or in response to irreparable DNA damage. Apoptosis is featured by unique morphological and biochemical changes, such as nucleus condensation and margination, membrane blebbing, and inter-nucleosomal DNA cleavage [9]. As the type I programmed cell death (PCD), apoptosis occurs through

Abbreviations: BHA, butylated hydroxyanisole; BNIP3, adenovirus E1B 19 kDa-interacting protein 3; ConA, Concanavalin A; COX-2, cyclooxygenase-2; Cyto *c*, cytochrome *c*; DAPK, dual-specificity protein kinase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; MEK-1, mitogen-activated protein kinase-1; MMP, matrix metalloproteinasea; MT1-MMP, membrane-type-1 matrix metalloproteinases; PI3K, phosphoinositide 3-kinase; PCD, programmed cell death; ROS, reactive oxygen species; SHP-2, SH2 domain-containing protein tyrosine phosphatase 2; SHPS-1, Src homology 2 domain-containing protein tyrosine phosphatase substrate-1; TNF, tumor necrosis factor.

* Corresponding author. Fax: +86 28 85411914.
E-mail address: jinkubao@yahoo.com (J.-k. Bao).

[1] They contributed equally to this work.

0006-291X/$ - see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbrc.2011.09.072

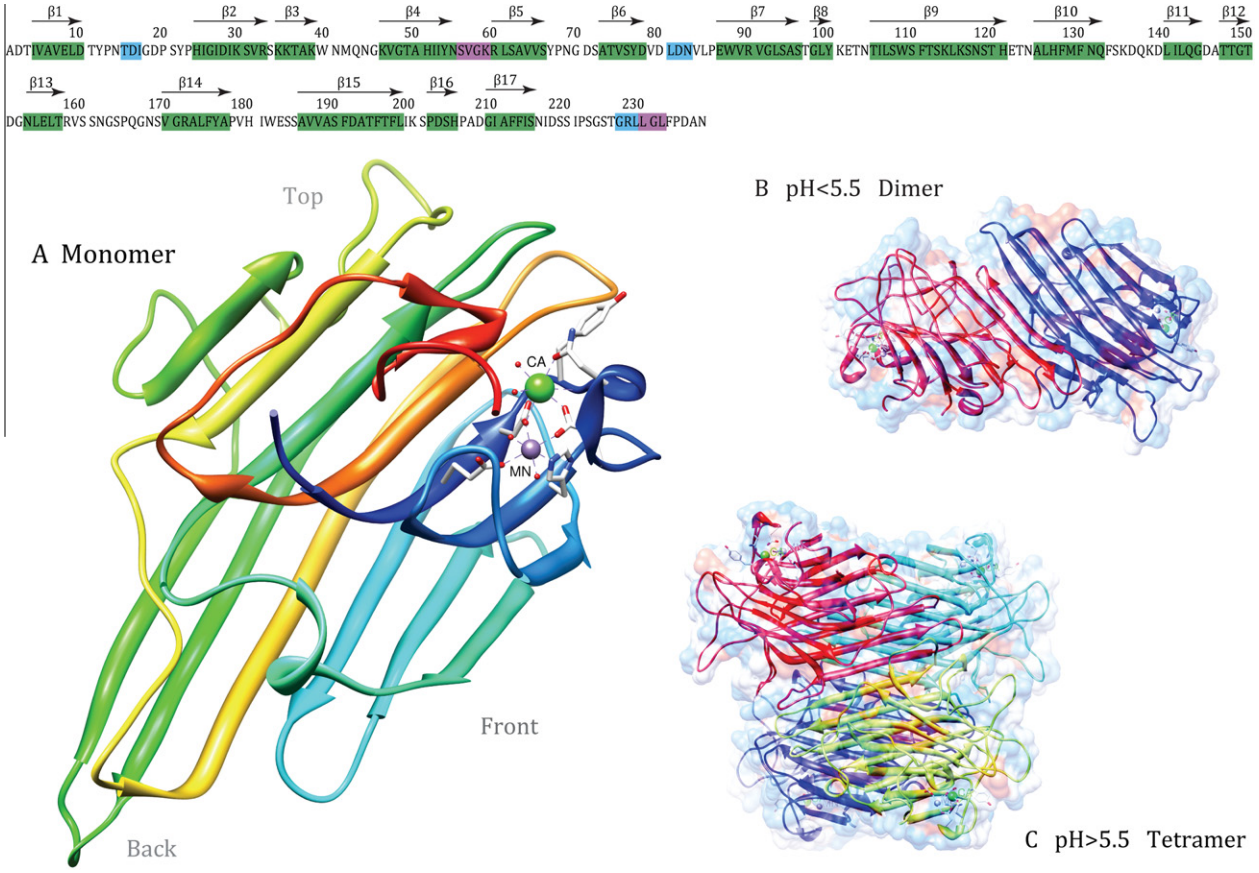

Fig. 1. Molecular structures of Concanavalin A (ConA). (A) The primary and secondary structures of ConA; (B) The crystal three-dimensional structure of ConA; (C) The quaternary structure of ConA.

two major pathways, the extrinsic pathway triggered by the Fas death receptors, and the mitochondria-dependent pathway that brings about the release of Cytocrome *c* (Cyto *c*) and activation of the death signals under stimulus [10].

A great number of studies have demonstrated that ConA induces apoptotic cell death. In 1996, Agrawal and colleagues showed that a certain concentration of ConA initiated apoptosis through cross-linking of ConA receptors on corital neurons [11]. Subsequently experiments confirmed that ConA-induced apoptotic cell death via a mitochondrial pathway in diverse types of cells, including PU-1.8 cells, human melonoma A375 cells, and human hepatocellular liver carcinoma HepG2 cells [12–14].

In the mitochondrial-dependent pathway, ConA treatment results in a decrease of mitochondrial membrane potential, and thus collapsing mitochondrial transmembrane potential. Cyto *c* is subsequently released, making up apoptosome with Apaf-1 and procaspase-9. After conjugating apoptosome, procaspase-3 turns into active caspase-3 that eventually sparks off apoptosis [15].

2.2. Targeting p73-Foxo1a-Bim apoptotic pathway in p53-null cells

p53 plays a pivotal role in regulating the cell cycle checkpoints, apoptosis, genomic integrity and DNA repair. In most human cancer cells, p53 is found to be functionally inactive, mutant or defective [16]. ConA selectively induces apoptosis in p53-null cells and shows no effects on normal cells. In cells containing functional p53, p73 is not affected by p53. In the absence of p53, p73 is often overexpressed and determines the cellular sensitivity. ConA stimulation activates p73, and thus inducing p73-dependent apoptosis, rendering the Bax/Bcl-2 ratio, blocking the survival Akt pathways, and activating Foxo1a-Bim signaling [17].

Independent of E2F1, ROS acts as a regulator of ConA-induced p73 expression. The expression of p73 activates p21, and elevates the ratio of pro-apoptotic protein Bax to anti-apoptotic Bcl-2. Under ConA stimulation, p73 blocks the activation of Akt and mediates apoptosis. The disruption of p73 activation rescues ConA [17]. PI3K-Akt pathways and the downstream targets of Akt are both crucial for cell survival. In normal cells, phosphorylation of Foxoa1, the direct substrate and a downstream target of Akt, brings about translocation of p53 from the nucleus to the cytoplasm, and inhibits apoptosis. While in p53-null cells, ConA activates p73-Foxo1a-Bim signaling to execute apoptosis. However, the normal cells with functional p53 are protected by undergoing a G2/M delay, followed by G1 arrest. The modulating phosphorylation status of Foxo1a is independent to the level of p53. Due to the inhibitory effect of p53 on the Foxo1a-Bim signaling, cells containing functional p53 are resistant to ConA-induced apoptosis.

3. ConA induces cancer cell death targeting autophagy

3.1. Targeting BNIP3-mediated mitochondrial autophagic pathways

Autophagic cell death is an evolutionarily conserved mechanism for degradation and renovation, with great significances in housekeeping, cellular differentiation, growth control, cell defense, tissue remodeling, and acclimatization. In autophagy, the double- or multiple-membrane-delimited autophagosome sequestrates cytoplasm in a large and nonspecific manner, and then fuses with lysosome. Upon nutrient deprivation or starvation, pro-survival mechanisms transfer injured cells or damaged components to self-degradative pathways. Compared with apoptosis, autophagic cell death is also known as type II PCD [18].