Review

A Novel Molecular Model of Plant Lectin-Induced Programmed Cell Death in Cancer

Zheng Shi,^{a,#} Wen-wen Li,^{b,#} Yong Tang,^{*,c} and Li-jia Cheng^{*,a}

^aSchool of Medicine, Chengdu University; Chengdu 610106, China; ^bUCL Institute of Ophthalmology; 11–43 Bath Street, London EC1V 9EL, U.K.; and ^cSchool of Acupuncture and Tuina, Chengdu University of Traditional Chinese Medicine; Chengdu 610075, China.

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Plant lectin, a class of highly diverse non-immune origin and carbohydrate-binding proteins, has been reported to specially induce cancer cell through programmed cell death (PCD) pathways (apoptosis and/or autophagy), shedding lights on screening promising anti-cancer candidate agent for further therapeutic trials. However, the complicated molecular mechanisms by which plant lectins induced the programmed death of tumor cells, have not yet been fully clarified. Here, we summarized a novel model, based on vast amount of research, by which plant lectins eliminate various types of cancer cells *via* three major pathways, including a) direct ribosome inactivating, b) endocytosis-dependent mitochondrial dysfunction and c) sugar-containing receptors binding. A better understanding of the role of plant lectins played and further elucidation of the strategies targeting PCD would provide a new clue for the applications and modifications of plant lectin as a potential anti-cancer agent from bench to clinic.

Key words plant lectin; programmed cell death; molecular model; autophagy; apoptosis; drug development

1. INTRODUCTION

Plant lectins, also known as phytohemagglutinin, are complexes of oligosaccharides and proteins, which contains at least one non-catalytic domain for selective recognizing and agglutinating cells reversibly, or for precipitating polysaccharose and glycoconjugates through the free glycans on glycoproteins and glycolipids without altering the structure of carbohydrate.¹⁾ Based on the molecular structures and evolutionary statuses, plant lectins are further categorized into twelve families, namely Amaranthin, *Agaricus bisporus* agglutinin, Cyanovirin, Chitinase-related agglutinin, *Euonymus europaeus* agglutinin, *Galanthus nivalis* agglutinin (GNA), Jacalins, Lysin motif, Hevein, Legume lectin, Nictaba, and Ricin-B families, respectively.²⁾ These 12 plant lectin families are well-known to possess extensive biological functions, such as anti-fungal, anti-viral and anti-neoplastic activities.^{3,4)}

Over the last two decades, owing to the binding specificities, researchers have utilized plant lectins to recognize the subtle distinctions between malignant cells and non-malignant cells to discriminate tumor from benign and the degree of glycosylation associated with metastasis.⁵⁾ Specially, lectin–glycan interactions have critical functions in a variety of physiological and pathological processes, including immune inflammatory responses and tumor progression. Lectin–glycan recognition systems have been reported to facilitate the initiation, execution and resolution of cell death, functioning domains of representative lectins and their carbohydrate specificity were presented in Table 1.⁶⁾

A few plant lectins, such as mistletoe lectin (ML) have been adopted for alternative cancer therapy in clinical trials (Gastric cancer, phase 4; non-small-cell lung cancer, phase 2).¹³⁾ In addition, ML has been reported to reduce the side-effects as

adjuvant agents during radiotherapy and chemotherapy.¹⁴⁾ With in-depth investigations, plant lectins, as sophisticated microarray reagents for specially recognizing tumor in diagnosis, treatment and prognosis of cancer, so far have generated more attention due to their remarkable anti-tumor activities toward a variety of cancer cells.^{15,16)}

To date, plant lectins have been widely reported to inhibit pro-survival pathways (e.g., angiogenesis, Wnt signaling, and protein synthesis), and especially induce apoptosis as well as autophagy, by which cancer undergo programmed cell death (PCD).^{17–19)} However, the specific mechanisms of which remain nubilous. After summarizing vast amount of experimental and theoretical research, we proposed a model of how the plant lectins induce PCD.

2. A NOVEL MODEL OF PLANT LECTIN-INDUCED PCD

We observed that plant lectins could initiate cell death *via* three major pathways, including 1) direct ribosome inactivating, 2) endocytosis-dependent mitochondrial dysfunction 3) and/or sugar-containing receptors binding (Fig. 1).

2.1. Direct Ribosome Inactivation? MLs were classified as type II ribosome-activating proteins, which have drawn more and more attention owing to their unique anti-cancer abilities and therapeutically applications. Members in ML subfamily are normally consists of two chains: an A-chain containing three conserved individual domains, and a B-chain which transports A chain into the cytoplasm after binding to certain sugar-chains or sugar-containing receptors on the cellular outer membrane.²⁰⁾ Subsequently, its A-chain inhibits protein synthesis by inactivating 28S ribosomes on endoplasmic reticulum (ER)²¹⁾ (Fig. 1A).

2.2. Endocytosis-Dependent Mitochondrial Dysfunction? In addition, plant lectins such as Concanavalin A

[#]These authors contributed equally to this work.

*To whom correspondence should be addressed. e-mail: tangyong@cduetcm.edu.cn; chengljia@cdu.edu.cn

Table 1. Overview of Several Typical Plant Lectins Carbohydrate-Binding Motifs

Lectin domain	Carbohydrate specificity	Examples	Reference
<i>Galanthus nivalis</i> agglutinin domain	Man, oligomannosides, high-man <i>N</i> -glycans, complex, <i>N</i> -glycans	GNA, ASA II, ASAL, ACA, LOA	7
<i>Agaricus bisporus</i> agglutinin domain	T-Antigen	ABA, MarpoABA	6
<i>Nicotiana tabacum</i> agglutinin domain	GlcNAc-oligomers, high-man <i>N</i> -glycans	NICTABA, PP2	7
Legume lectin domain	Man/Glc, Gal/GalNAc, (GlcNAc) _n , Fuc, Siaa2→3Gal/GalNAc, Complex <i>N</i> -glycans	PHA, ConA, Gleheda, PSA, GSII	8
Hevein domain	Chitin, high-man, Man, <i>N</i> -glycans	Hevein, UDA, WGA, HFR3	9
Ricin-B domain	Gal/GalNAc, Siaa2→6Gal/GalNAc	Ricin, SNA-I	8
Jacalins	Gal, T-antigen, Man, <i>N</i> -glycans	Jacalin, Heltuba, HFR1	10
Amaranthins	T-Antigen	Amaranthin, HFR2	11
Class V chitinase homologs	Blood group B, high-man <i>N</i> -glycans	RobpsCRP	6
<i>Euonymus europaeus</i> agglutinin domain	Blood group B, high-man <i>N</i> -glycans	EEA	10, 12

Fig. 1. A Summarized Molecular Model for Plant Lectin-Induced PCD

(A) MLs and Ricin-B family lectin bear apoptosis-inducing activities towards cancer cells by targeting different stages of apoptotic pathways via directly inactivate ribosome. (B) Some lectins, taking ConA for example, depended on endocytosis and selectively localize on mitochondrion in cancer cell, and autophagic cell death was initiated. (C) Some lectins such as ConA and PCL bind certain sugar-containing receptors on the surface of cancer cells, subsequently apoptosis was triggered.

(ConA), could be internalized to and subsequently bind to the mitochondria via clathrin-mediated endocytosis after binding to mannose moiety of the glycoproteins on the cellular membrane (Fig. 1B).

The internalized plant lectins were reported to result in a significant decrease of mitochondrial membrane potential (MMP), and thus releasing the cytochrome *c* (Cyto *c*) which eventually sparks off apoptosis. The reduction of mitochondrial transmembrane potential was also reported to initiate autophagy via the inductions of Bcl2/adenovirus E1B 19kDa-

interacting protein 3 (BNIP3) or Beclin-1.^{22,23)}

2.3. Binding Sugar-Containing Receptors on the Cell Surface? Interestingly, the third way is less-known. Several plant lectins, such as ConA and *Polygonatum cyrtoneura* lectin (PCL) are reported to bind to the sugar-containing receptors on the cell surface to directly inhibit anti-death/survival pathways (Fig. 1C), suggesting sugar-binding specificity might be one of the main reasons motivating the anti-tumor activity.^{24,25)}

In this model, three pathways are closely interlinked. The

ML from Ricin-B family that own A- and B-chains, bind to the membrane receptors before inactivated the ribosome.²⁶⁾ ConA, the most representative legume lectin, could bind to matrix metalloproteinase family receptors on cell membrane to inhibit angiogenesis, establish immunological memory *via* antigens, as well as induce PCD through endocytosis.²⁷⁾ Interestingly, the endocytosis-dependent PCD related to lectin-receptors binding on mitochondria outer membrane. As for the PCL of GNA family, PCL-Fas binding would initiate caspase-dependent apoptosis, similarly the PCL-epidermal growth factor receptor (EGFR) binding inhibits both apoptotic and autophagic cell death.²⁸⁾

3. PREDICTIONS AND OBSERVATIONS OF THE NEW MODEL

3.1. Activating Pro-apoptotic and Blocking Anti-apoptotic Pathway In contrast to necrosis, apoptosis is a highly regulated and controlled process of cell death which controls cell proliferation or functions as a defense systems in response to failure of DNA damage repairmen. As one of the 12 major anti-cancer mechanisms, plant lectins activate pro-apoptotic and blocks anti-apoptotic pathways in cancer cell models.²⁹⁾

The ML-1 and other Ricin-B family members' stimulation initiated apoptosis *via* extrinsic pathway by activating caspase-8 in Jurkat leukemic T cells, and mitochondria-mediated pathway independently of p53 in hepatocarcinoma cells. Khil *et al.* reported Korean mistletoe lectin broke down MMP in mitochondrial pathway, releasing Cyto *c* as well as increasing of the level of reactive oxygen species (ROS), and thus activating caspase-3 to form apoptosome in COLO cells.³⁰⁾ Feng *et al.* reported that ML-1 activated transforming growth factor (TGF)- α , dephosphorylated Bcl-2 independently of p21 and p53 to promote apoptosis. Chinese mistletoe lectin-I was reported to down-regulate the expression of miR-135a, b and up-regulate the levels of target gene APC; thereby, decreasing the downstream Wnt signaling activity in CLY and HT-29 cells.³¹⁾ Moreover, ML-1-A-Chain activated jun N-terminal kinase (JNK) dissociated BAX and BAD from 14-3-3 by translocating the pro-apoptotic proteins, including Bax and Bad to mitochondria.³²⁾ In addition to ML-1, ML-2 induced apoptosis *via* mitogen-activated protein kinases (MAPK) signaling, activation of SAPK/JNK and p38 pathways as well as inhibition of extracellular-signal regulated kinases 1/2 (ERK1/2) pathway. Korean mistletoe lectin was reported to kill COLO cells in a time-dependent and dose-dependent manner by activating caspases and inhibiting expression of anti-apoptotic molecules (*e.g.*, nuclear factor-kappaB (NF- κ B), X-linked inhibitor-of-apoptosis protein (XIAP), and Akt/protein kinase B).³³⁾

For proteins with legume lectin domains, tumor cells underwent mitochondria-dependent apoptosis.³⁴⁾ MMP collapses upon legume lectin treatments, procaspase-3 turned into active caspase-3 which conjugated with apoptosome resulting in conditions of irreparable DNA damage. However, in p53-null cells, ConA induced apoptosis through activation of p73. The tumor suppressor p73 played a significant role in rendering the ration of Bax/Bcl-2, blocking the survival Akt pathway, as well as activating Foxo1-Bim signaling that execute apoptosis. Furthermore, *via* activation of IKK-NF- κ B-cyclooxygenase (COX)-2, SHP-2-MEK-1-ERK, SHP-2-Ras-ERK signaling, ConA was reported inhibit survival in tumor cell model.^{35,36)}

Under the treatment of PCL, apoptosis was induced with the activation of caspase-3,-8,-9.³⁷⁾ The PCL treatment also abrogated the glutathione antioxidant system, and promoted ROS accumulation that subsequently activated p38 and p53signaling.³⁸⁾ In addition, PCL further promoted apoptosis by blocking Ras-Raf and phosphoinositide 3-kinase (PI3K)-Akt pathways in L929 cells.

3.2. Promoting Autophagic Cell Death Pathways, with/without Apoptosis Autophagy is an evolutionarily conserved mechanism for degradation and renovation of superfluous macro-complexes and in eukaryotic cells. Plant lectin would also promote cancer autophagic cell death with/without apoptosis.³⁹⁾

Liu and colleagues reported that ConA inducedautophagy only in hepatoma cells through BNIP3-mediated mitochondrial pathway. BNIP3 is a cell death-inducing factor whose main function is to determine the on/off state of the mitochondrial permeability transition pore.⁴⁰⁾ Therefore, BNIP3 decreases membrane potential on molecular lever, and thus initiating autophagy after ConA internalizing to mitochondria surface.⁴¹⁾

In contrast, Liu *et al.* reported that as a member of GNA, PCL induced autophagic death *via* activation of mitochondrial ROS-p38-p53 pathway in A375 cells, as well as *via* blocking Ras-Raf and PI3K-Akt pathways in L929 cells.^{42,43)} The signaling pathways discussed above, revealed an complicated relationship between apoptotic and autophagic death upon PCL treatments.

4. *VIA* THIS MODEL, IS PLANT LECTIN A PROMISING ANTI-CANCER DRUG TARGETING PCD?

Plant lectin has been reported to remarkably inhibit growth of a variety of cancer cell models. Since 1989, plant lectins have been used as a class of reliably biochemical, cytological, and histochemical probes to distinguish non-malignant from malignant cells that are otherwise non-detectable with available monoclonal antibodies.⁴⁴⁾ Since 1993, plant lectins have drawn great attention by their remarkable PCD inducing activities, propelling the research of plant lectin to a new level.⁴⁵⁾ Vast amount of studies have been carried out with the aim to clarify the specific molecular mechanisms or clinical benefits of plant lectins.^{17,46)} In addition, as a T cell mitogen *in vivo*, plant lectins killed cells by stimulating immune system.⁴⁷⁾ An immune memory would be generated after plant lectin-induced eradication, therefore resisting to the same genotypic tumor.

However, is plant lectin a promising anti-cancer drug targeting PCD? Collectively, we believe the experimental results have been rather positive and promising. Several typical lectins, such as MLs, ricin and *Phaseolus vulgaris* lectin, have been utilized as potential anti-tumor drugs or adjuvant therapeutic agents in clinical treatment for over two decades,⁴⁸⁾ the majority of plant lectins are still cytotoxic. When plant lectins selectively kill cancer cells, there would be concomitant toxic effects on normal cell and animal model. It is worth mentioning that legume lectins have been reported to trigger TNF- α -mediated hepatitis in mice.⁴⁹⁾ The side-effects present a difficult challenge for further applications of plant lectin in medicine, although a great quantity of experiments have been dedicated to the molecular modification.⁵⁰⁾

5. CONCLUSION

Based on extensive research have been carried out, three major pathways are summarized with the aim to unveil the mystery of plant lectin-induced PCD in this study, therefore providing basic guidance for pre-clinical and clinical trials. We believe a better understanding of the role plant lectin played and further elucidation of the strategies targeting PCD would provide a new clue for the further investigation of plant lectin as a potential anticancer drug candidate from bench to clinic.

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Conflict of Interest The authors declare no conflict of interest.

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