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Overview of Lectin Applications in Cancer Diagnosis

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ABSTRACT

Lectins are a large group of ubiquitous proteins found in animals, plants, fungi and bacteria that recognize specific carbohydrate targets. Lectins play an important role in cell recognition and communication, host-pathogen interactions, embryogenesis and tissue development. Recently, lectins have emerged as important biomedical tools that have been used in the development of immunomodulatory, anti-pathogenic and anticancer agents. Several lectins have been shown ability to discriminate between normal cells and tumor cells due to their different glycosylation patterns. Furthermore, the specific binding of lectins to cancer cells has been shown to trigger mechanisms that can promote the death of these abnormal cells. Herein, the importance of lectins-carbohydrates interactions in cancer therapy and diagnosis is reviewed.

Keywords: Lectins, Anticancer activity

INTRODUCTION

Cancer is a class of diseases in which a group of cells display the traits of uncontrolled growth, invasion and sometimes metastasis. These three malignant properties of cancers differentiate them from benign tumors which are self-limited, do not invade or metastasize. Most cancers from a tumor**,** but some like leukemia do not.

Cancer may affect people at all stages, but the risk tends to increase with age. Nearly all cancers are caused by abnormalities in the genetic material of the transformed cells. These abnormalities may be due to the effects of carcinogens, such as tobacco smoke, radiation, chemicals or infectious agents. Other cancer promoting genetic abnormalities may be randomly acquired through errors in DNA replication or are inherited and thus present in all cells from birth.

Genetic abnormalities found in cancer typically affect the two general classes of genes. Cancer promoting oncogenes are often activated in cancer cells, giving those cells new properties. This includes hyperactive growth and division, protection against programmed cell death, loss of normal tissue boundaries and their ability to become established in diverse tissue environments. Tumor suppressor genes are often inactivated in cancer cells, resulting in the loss of normal functions in those cells, such as accurate DNA replication, control over the cell cycle, orientation and adhesion within tissues.

Legume seeds have significance in human and animal nutrition worldwide. Recent progress in glycobiology is mainly focused from those of leguminosae family. More than 600 species have been screened for lectin and many are currently under process for purification and characterization [1]. The major sources of lectins include mature seed which contain nearly 10% of the total protein along with carbohydrates, dietary fibers, minerals and vitamins. In addition to these nutritional components, some anti-nutritional compounds are also found in biologically significant amounts in raw seeds such as enzyme inhibitor, phenolic, phytates, flavonoids and lectins [2]. The major storage protein of the seeds happens to be the bulk of lectin available in cotyledons. Among the various naturally occurring chemical compounds found in the food legumes, lectins reveal diverse biological significance, both deleterious and beneficial [3].

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Lectin concentration in legume seeds is varied with their protein content, e.g. kidney bean seeds (2.4-5.0%), *Glycine max* (0.8%) and *Pisum sativum* (0.6%) contents lectin, respectively [4]. Phytohemagglutinin and Concanavalin-A are the best studied legume lectins for their biomedical applications. According to Gatehouse et al. [5], legume lectin involved in plant-microbes interaction by binding to the cell surface of microbes, e.g. Concanavalin A and other lectins protect the plants against the *Callosobruchus maculatus* beetle. The plant-microbe interaction is an important mechanism which contributes in the biological control of plant pathogens.

Lectins-based cancer diagnosis

Owing to their high selectivity and specificity for certain glycan structures, lectins have been investigated for their potential in cancer diagnosis. One of the successful clinical translations of lectin being used in diagnosis tools is *Lens culinaris* agglutinin (LCA). LCA, a plant lectin extracted from lentil seeds bind specifically to α-1-6 fucose, can be used to diagnose hepatocellular carcinoma (HCC) [6,7]. LCA-based HCC diagnosis relies primarily on a specific affinity of the lectin for Alpha-fetoprotein-L3 (AFP-L3), a malignant tumors specific isoform of AFP glycoprotein. A commercial clinical kit for AFP-L3 serum concentration was subsequently developed for HCC diagnosis [8], which quickly became a valuable clinical alternative to more expensive and sophisticated techniques such as CT scans and MRI imaging [7]. Today, LCA-based HCC diagnosis is an FDA approved HCC clinical diagnosis tool covered by the health insurance of the Japanese Medical Service [9] and used by leading cancer treatment centers across the US [10]. LCA/AFP-L3 interaction has also been investigated to diagnose and monitor testicular tumor activity [11]. Lectins have also been investigated for their potential in ovarian cancer diagnosis. Cancer antigen 125 (CA125) and human epididymis protein 4 (HE4) are two FDA-approved glycoprotein biomarkers for ovarian cancer. *Amaranthus caudatus* agglutinin (ACA), *Artocarpus integrifolia* agglutinin (AIA), *Arachis hypogea* agglutinin (AHA), *Vicia villosa* lectin (VVL), *Griffonia simplicifolia* agglutinin I (GSA I) and *Ulex europaeus* agglutinin I (UEA I) form a group of lectins that recognize Thomsen Friedenreich antigen, Thomsen-nouvelle and sialyl-Thomsen Friedenreich glycan alterations of CA125 and HE4 [12-15]. Targeting CA125 glycan alterations with VVL, Chen et al. [14] were able to distinguish benign ovarian neoplasms from invasive epithelial ovarian cancer with a specificity of 61.1% at 90% sensitivity. Other studies have also shown that wheat germ agglutinin (WGA) and Glycine max agglutinin (GMA) could potentially be used for ovarian cancer diagnosis [16,17]. Because CA125 glycan alteration includes an increase in core-fucosylated bi-antennary monosialylated glycans; LCA and UEA which specifically recognize α-1-6 fucose and α-1-2 fucose, respectively, have been investigated for their potential in ovarian cancer diagnosis [18,19]. Furthermore, *Pinellia ternata* lectin (PTL), a lectin recently isolated from mushroom, specifically bind α-1-6 fucose residues and could potentially be used in diagnosis of ovarian cancer, breast cancer and pancreatic cancer [20].

Using PHA, Kim et al. [21] successfully identified 26 new colorectal cancer candidate biomarkers that showed 100% specificity and sensitivities greater than 50%. Similarly, using principal component analysis and hierarchical clustering to analyze glycoarrays from five (5) plant lectins, Qui et al. [22] found that except for peanut agglutinin (PNA), all the other lectins tested (Con A, SNA, AAL, MAA-II) successfully distinguished colorectal cancer samples from normal controls. Although, ConA and SNA differentiated normal control samples from cancer samples, these two lectins did not show a good efficiency of discrimination between adenoma and cancer samples. On the contrary, addition of differentiating normal control samples, AAL and MAA-II were better at segregating adenoma from cancer samples. Therefore, AAL and MAA-II could potentially be used for the diagnosis of colorectal cancer equally for the study of disease progression. Furthermore, to distinguish metastatic from non-metastatic breast cancer patients, Fry et al. [23] designed lectin microarrays consisting of 45 lectins with different binding preferences. Serum and urine samples were analyzed for binding differences. Four lectins, *Aspergillus oryzae* lectin (AOL), *Galanthus nivalis* agglutinin (GNA), RCA 120 and *Phaseolus vulgaris* erythroagglutinin (PHA) showed a significant binding difference between sera from metastatic and non-metastatic patients [23]. AOL is a core fucose (α-1-6-fucosyl)-specific fungus lectin, GNA is a plant lectin that preferentially recognizes mannose-rich glycans and RCA 120 is a galactose-binding plant lectin [24-27]. *Trichosanthes japonica* agglutinin-I (TJA-I), RCA 120 and *Bauhinia purpurea* lectin (BPL) also showed significantly higher binding in metastatic compared to non-metastatic urines samples, suggesting that patient urine sample may contain potential glycosylated biomarkers for metastatic breast cancer diagnosis. TJA-I and BPL are two plant lectins that bind specifically α-2-6 linked sialic acid and Galβ1-3GalNAc (T-antigen), respectively [28,29].

CONCLUSION

In summary, the use of lectins for cancer diagnosis, imaging and treatment has received a lot of attention among researchers. Although the clinical translation of these findings is still a major hurdle, the field of lectinology is expected to grow at a faster pace in the coming years. Nevertheless, new investigations will probably have to explore safe and effective drug delivery system strategies for lectins, in order to maximize their use and increase the likelihood for their clinical translation. However, lectin-induced inflammation, toxicity and their resistance to digestive enzyme are some of the major arguments against

these potent proteins [30-33]. The scientific community is expected to address these concerns as well.

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