Microbial lectin cofunction with lytic activities as a model for a general basic lectin role

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1. SUMMARY

Lectins are ubiquitous proteins, which exhibit a specific and reversible sugar-binding activity. They react with glycosylated macromolecules and cells and may coaggregate them and lead to their lysis or alterations. Various lectin biological effects are well known, but their basic biological function is considered as yet unknown. In the present review, an experimental evidence and theoretical considerations are forwarded for supporting our suggestion that the general basic lectin or lectinoid (lectin-like protein) function in microorganisms, plants and animals is a cofunction enabling the activities of key lytic enzymes (lysins: glycosidases, proteases, esterases, phosphatases, hemolysin, etc.). The lectin service is: homing onto glycosylated receptors, anchoring to them and induction of cooperative conformational effects which enable their counterpart lysin activity on exogenous or endogenous target molecules and cells. The ‘lectin-lysin’ pair may reside in the same molecule, or in linked subunits. It may also be formed by cofunction of two separate entities originating from one or two (homogenous or heterogenous) cell sources. The lectin and lysin may be free or cell-bound components located intra or extracellularly. The final result of their cofunction is practically irreversible; either cell and macromolecule lysis for nutrition, homeostasis and protection or cell alteration, reorganization and new productivity.

Our suggestion emphasizes the prominent analogy of lectins to lytic enzyme positioning sites (LEPS), immunoglobulins and polypeptide hormones. The lectin analogy to LEPS and immunoglobulins is exhibited in the lectin-dependent cell and macromolecule lysis for nutritional and homeostatic purposes or for protection, respectively. The hormone-like lectin activity is exhibited in the lectin-dependent cell alterations. In addition to similar functions and effects, the analogy also includes the properties and behavior of these proteins. The suggested hypothesis is based on experimental evidence from microorganisms, plants and animals. It envisions the lectin and lectinoid function in cell attacks on glycosylated molecules or cells, cell-substratum and cell-cell interactions (fusion, invasion, etc.), cell transformation and formation of special structures. All of them according to a developmental program, or special (especially unfavourable) environmental...
conditions. The lectin resistance to proteolysis and unfavourable pH or temperature is in accord with the suggested hypothesis.

2. INTRODUCTION

The first description of lectin hemagglutinating activity, by the protein ricin of *Ricinus communis* seeds, was forwarded by Stillmark 100 years ago [1]. This hemagglutination was shown to be reversible and inhibitable by D-galactose. During the following century, many additional lectins, specifically inhibitable by various sugars, were described in plants, animals and microorganisms [2–6]. Their specific binding was compared to that of enzymes and antibodies [4], which were both excluded from lectins by definition [7].

The lectins, including those of microorganisms, have been shown to be very useful for various scientific, medical, agricultural and biotechnological systems, including [3,8]: detection of sugars in solutions, on macromolecules and cells, detection and identification of blood groups and bacteria, protein purification and cell fractionation, mitogenic stimulation of peripheral lymphocytes [9], examination of chromosomes and diagnosis of genetic or chronic diseases characterized by immunodeficiency (cancer, etc.), as well as reduction of cancer cell tumorigenicity [8,10]. They have been demonstrated to be involved in various biological systems, including: adhesion of symbiotic [11] and pathogenic [12] microbes to their host for the establishment of infection, and the adhesion of cancer cells to tissues and organs for the production of metastases [13–17]. They have also been described as being involved in protecting eukaryotic organisms against infecting microorganisms [18], by enabling their lysis [19] or phagocytosis [20,21], and in the removal of senescent macromolecules and cells [22–24] by similar mechanisms. However, the central question in lectinology — the general or basic lectin function was not answered. Based on our studies on *Pseudomonas aeruginosa*, and the relevant literature on microbial, plant and animal lectins, we offer the suggestion that the general basic lectin role is a cofunction with lytic entities (lysins) analogous to that of lytic enzyme ‘positioning sites’ (LEPS) [25], immunoglobulins and hormones. The lectin–lysin pair may exist on the same or adjacent molecules (Fig. 1), originating from the same cell or from different cellular sources. Their cooperative function may lead to either cell and macromolecule lysis (LEPS and antibody-like lectin activity) or to cell alteration, reorganization and production of new structures or products (hormone-like lectin activity).

The support for this hypothesis is based on a wide experimental evidence, indicating: (a) a close structural, genetic and physiological association between lectin and lysin production (paragraph 3), (b) a striking analogy between lectin, LEPS and immunoglobulin function, properties and behavior (paragraph 4), (c) numerous examples for lectin cofunction with coexisting lytic activities (paragraph 5), (d) a clear analogy between lectin and polypeptide hormone function and effects (paragraph 6), as well as (e) a broad experimental evidence showing that inhibition of the reversible lectin binding by sugars, prevents the irreversible effects induced by the associated lysins (paragraph 7).

3. AN EVIDENCE FOR A CLOSE STRUCTURAL, GENETIC AND PHYSIOLOGICAL ASSOCIATION BETWEEN LECTINS AND LYSIN PRODUCTION

The evidence for genetic-physiological association between lectins and lysins includes: (a) the lectinoid enzymes and toxins which are composed of both components in the same molecule, or
associated subunits, resembling the LEPS-containing hydrolytic enzymes [25]; (b) adjacent lectins and enzymes coexisting on cell surfaces; and (c) lectin–lysin cofunctioning pairs produced by one or by two cell types, resembling the antibody-complement association. In microorganisms and plants there are many examples of lectinoid lysins, including the most powerful microbial and plant toxins [26–34], which are composed of two domains or subunit types (Figs. 1:1 and 2:1): A—exhibiting a lytic or toxic activity, and B—a lectin or lectinoid (lectin-like protein, confronting with the classical lectin definition [7] due to lack of either coaggregating activity or defined sugar specificity). The toxic A domains of some bacterial exotoxins (e.g. Corynebacterium diphtheriae and Pseudomonas aeruginosa) block protein synthesis in the attacked target eukaryotic cells by ADP-ribosylation of elongation factor-2 (EF-2) in the presence of NAD [26,27]. Similarly, A domains of some plant [28–33] and shiga [34] toxins inhibit protein synthesis via ribosomal deterioration mediated by N-glycosidase [29–32]. Other powerful bacterial toxins (cholera, tetanus, botulinus, etc.) also exhibit a similar A-B structure and cofunction. Removal of B from A, does not necessarily prevent the latter in vitro lytic activity on its isolated cell-free substrate, but prevents its effect on the intact cells (Fig. 2:3) and the intracellularly located substrate [26–32].

During our studies on Pseudomonas aeruginosa lectins, we have found that there is a physiological and genetical association between lectin production and protease, hemolysin and pyocyanin levels (8,35–37]. Lectin-lacking strains were devoid of the lytic activities and lectin-deficient strains and mutants had low levels of these activities. Reciprocal confirmation of the linkage was attained by the demonstration that genetically defined protease-deficient mutants of P. aeruginosa were found to be poor lectin producers [38]. The resistance of P. aeruginosa lectins to protease (a property also shared by many plant and animal lectins) fits the cofunction hypothesis. A genetic association between lectinoid adhesins and hemolysin may also be deduced from the literature describing the cloning of the adhesin-encoding genes in Escherichia coli [39,40] and from the simultaneous existence of a sialophilic lectin and sialidase in the membrane of influenza A virus [41–43]. Cell surface-bound A and B domains, either linked in the same molecule, or bridged by the cell membrane, may function like the A-B-containing cell-free macromolecules (Fig. 1).

Examples from plants and animals include the α-galactosidases with lectin activities in Vicia faba [44], the temporal regulation of the production of the lectin Con A and α-mannosidase in the seeds of Canavalia ensiformis [45,46] and the lectin-linked sialyltransferase on Hodgkin’s cells [47]. Additional examples of lectin-lysin coexistence in microorganisms may be deduced from the literature describing lectin or hemagglutinin purification from associated lysins [2].

4. THE ANALOGY BETWEEN LECTINS, LEPS AND ANTIBODIES

In addition to their lytic active site the lytic enzymes, acetylcholinesterase and chymotrypsin, display a ‘positioning site’ [25], LEPS, which is involved in their homing and binding to the substrate ‘positioning group’ (Fig. 3:1,2). This binding enables best exposure of the substrate sensitive
Fig. 3. The analogy between the LEPS, lectin and antibody receptor-binding sites (B): (1) The anionic B of acetylcholinesterase, which binds the positively charged trimethylammonium group of acetylcholine, (2) The hydrophobic B of chymotrypsin which binds tryptophan (T), (3) The saccharophilic B lectin, or lectinoid, which binds the sugar (S) residue, and (4) the antibody which binds the antigen (Ag). All of them cofunction with associated lytic activities: esterase, protease, glycosidase (O or N-glycosidases) and complement, respectively.

group to the enzyme lytic site for its decomposition [25]. In a similar way antibody binding to antigen-bearing macromolecules or cells conditions their lysis by complement (Fig. 3:4). We suggest that lectin role (Fig. 3:3) is analogous to that of the above described LEPS and antibodies. They behave as ‘saccharophilic LEPS’ or antibodies cofunctioning with various lysins. The lectin or lectinoid specificity for glycosylated molecules ensures their homing to cells and to extracellular matrix (glycocalyx), which are specified by glycosylated receptors. They bind to sensitive cells (displaying the compatible sugars on their surface) and induce membranal changes which enable the entrance of the A domain into the cell for attaining contact with its sensitive intracellular target [26–33]. The lysins, which may reside with the lectins in the same molecule or in adjacent location, display various lytic or toxic activities, including: sialidase [41–43], O-glycosidases [44], N-glycosidases [29–32], glycosyl or sialyl transferases [47], NAD-ADP ribosyltransferase of EF-2 [26,27], proteases [48], and hemolytic activities. If the purpose of the lysis is nutritional, it may be compared to chymotrypsin activity, if it is homeostatic, to acetylcholinesterase and if protective, to the immune lysis.

In addition to the above discussed lysis-enabling receptor-binding cofunction, the lectins share with LEPS and immunoglobulins several other features, including:

1. A wide distribution in nature. Lectins and LEPS are ubiquitous and immunoglobulins are produced in vertebrates.

2. Multimeric structure and cooperative interactions, which may exhibit allosteric regulation and induce conformational-structural alterations in cell membranes and macromolecules.

3. Specificity to their receptors.

4. A reversible interaction with their receptors, which may result cell or macromolecule coaggregation, inhibitable by simple compounds which
2. SIMPLE SUGARS

LECTIN

ANTIBODY

COMPLEMENT

3. HAPTEN

Fig. 4. Acetylcholine decomposition (1) by acetylcholinesterase esteratic site (A) is prevented (X) by competitive inhibition of the enzyme anionic positioning site with trimethylammonium derivatives. Similarly, glycosylated macromolecule or cell lysis by (A) of lectinoid toxins or enzymes is inhibited by simple sugars (S) derivatives (2), and antigen (Ag)-bearing macromolecule or cell lysis by complement is inhibited by haptenes (Hap-R) (3).

are smaller than their natural receptors (Fig. 4): (a) lectin interaction with sugar-bearing macromolecules and cells is inhibited by simple sugars (Figs. 2:2 and 4:2); (b) LEPS-substrate interaction is inhibited by their positioning group derivatives (Fig. 4:1); and (c) antibody-antigen reaction is inhibited by the respective hapten (Fig. 4:3). (5) Their reversible interaction leads, in the presence of their lytic counterparts, to practically irreversible effects. (6) A competitive inhibition of their reversible interaction may prevent the ultimate irreversible effect (Figs. 2:2 and 4:1-3) before its initiation. (7) In the absence of inactivation of the associated A lytic counterpart the irreversible lytic process is prevented, but B still binds to the target molecules and cells (Fig. 2:3) and may coaggregate them (precipitate macromolecules and agglutinate cells). The binding and aggregation are sensitive to competitive inhibition by sugars. (8) Resistance to the lytic action of their counterparts and to the essentially unfavourable conditions inducing their production and function. (9) Their production is constitutively low and inducibly massive, increasing only when needed [49–51] and fading after the termination of their function. (10) Cells and macromolecules which lack specific receptors for them (the positioning groups, specific sugars and antigens, respectively), as an essential trait, or due to receptor removal by enzymes, are resistant to the reversible coaggregating and the irreversible lytic effects (Fig. 2:4).

A most interesting and profound support for the above described analogy between lectins, LEPS and antibodies, is their overlapping functions and mutual replacement. Examples for LEPS replace-
Fig. 5. Comparison of the hemolysis by (1) lysin (Lyt. Enz.) depending on lectin (Lect) binding to the cell sugar (S) and by (3) complement (C) depending on antibody binding to the antigen (Ag). Similarly, phagocytosis (and subsequent lysis) of erythrocytes may depend on their trapping by the phagocyte surface lectins (2) and immunoglobulins (4).

Fig. 6. Non-immune phagocytosis of a microbe by a polymorphonuclear cell (PMN) mediated by PMN lectin (CL) binding to the microbial sugars (©), by microbial lectin or adhesin (MAd) binding to the PMN sugars, or by foreign lectins (e.g. PA of Pseudomonas aeruginosa [20]).

Fig. 7. Microbial lectin (Lec I and Lec II) binding to sugars (S) of the animal cell (or the latter cell lectin binding to the microbial sugars), enable the lytic attack on the animal cell by the microbial glycosidases (Enz I), protease, hemolysin and other lytic and toxic factors. Exotoxins of the same microbe, possessing lectinoid domains of their own (top), may function independently of the cell-surface lectins.

ment by lectins are the lectinoid glycosidases [44] protease [48] and glycosyl or ADP-ribosyl transferases [26,27]. Antibody-like lectin activity is well known in invertebrates [4,18,19,51,52] and other organisms devoid of immunoglobulins, including the vertebrate embryo [51], as well as in vertebrate non-immune phagocytosis [20,21] (Figs. 5 and 6). The lectin specificity is lower (broader reactivity) than that of antibodies. Lectin-mediated trapping and degradation of sugar-bearing macromolecules or cells (Figs. 5–7) was also described in hepatocytes [22] and in other cell types, including free living unicellurals [5]. Similarly, most cells and many macromolecules bear sugars which react with such lectins.

5. EXAMPLES FOR CELL-FREE AND CELL-BOUND LECTIN (OR LECTINOID) COFUNCTION WITH COEXISTING LYSINS

Examples for lectin or lectinoid cofunction with toxins or lysins coexisting on the same or on linked molecules, are best represented by the above described microbial, plant and animal lectinoid toxins and enzymes [2,26–34,44,47] (paragraph 3).

In addition to the lectinoid enzymes, there are numerous examples of subcellular microbial and plant lectin or lectinoid cohesion (not via the sugar-binding site) with lysins and toxins [2]. These include descriptions of purified lectin contamination by lytic factors [2] and reports on pure lectin effects (e.g. inhibition of fungus growth by the purified chitin-binding lectin of wheat germ ag-
glutinin [53]), which were later found to be due to contamination by lytic activities (e.g. chitinase activity). A considerable direct evidence for lectin interaction with hydrolytic enzymes is found in the literature describing the interaction of immobilized lectins (lectins bound to Sepharose columns) with such enzymes. The interaction between Con A and the α-mannosidase and α-galactosidase [54] of *Canavalia ensiformis* seeds [45,46] is a well known example.

A clear cut example of cell surface lectin cofunction with adjacent lytic activity (Fig. 1:2) is that the influenza A virus sialophilic lectin and sialidase [41-43]. The lectin homing onto sialic acid-bearing cells facilitates the degradation of the cells receptors by the sialidase and enables the following membranal fusion [55,56]. Surface lectins and lectinoid adhesins of many other microorganisms also condition their lysin attacks on the host cells (Fig. 7) [6,8,57,58].

Among the fungal examples are the insect-attacking *Conidiobolus lamprauges*, which produces a chitin-binding lectin and accompanying chitin-degrading activity, hemolysin and protease [57] and the lectins of the nematophagous fungi [58].

Animal examples include the phagocyte and hepatocyte membranal lectins which enable the degradation of target molecules by the intracellular lysosomal enzymes of these cells (Fig. 8:top). The hepatocyte membranal lectin is involved in the removal of circulating desialylated glycoproteins [21] leading to their decomposition by the intracellular lysosomal enzymes. Internal hepatocyte lectins were reported to contribute to the lysosomal enzyme trafficking [59]. The cofunction may also involve lectin and lytic entities of heterologous origins (Figs. 6:PA and 8:middle and bottom). An example is the microbial lectins or lectinoids which are involved in trapping (and subsequent lysis) of the bacteria which bear them [20,21] and other bacteria [20] (Fig. 6) by phagocytes. Another example is animal cell lysis by bacterial or cancer cells due to cofunction of the target cell lectins with the lysins of the attacking cells. The condition is similar to that described in Fig. 7, but instead of the bacterial lectin binding to the host cell sugars, the host cell lectins interact with the microbial sugars, leading to the same result.

6. THE ANALOGY BETWEEN LECTINS AND POLYPEPTIDE HORMONES

Exogenous lectin interaction with cell membrane receptors (Fig. 8:middle), or endogenous lectin interaction with exogenous glycosylated macromolecules, may enable endogenous key lytic activities which trigger a cascade of cellular reactions culminating in hormone-like induced cell transformation. A well known example is the insulin-like effects of Con A and wheat germ agglutinin [60]. The involvement of key lytic enzymes in this effect may be supported by the facts that: (a) both hormones and lectins were reported to enable phosphoinositide hydrolysis and subsequent activation of protein kinase [61] and (b) trypsin activity was reported to similarly affect the system [62]. The mitogenic stimulation of peripheral lymphocytes [9] is an example for hormone-like lectin activity. These hormone-like lectin-dependent phenomena may also be specifically inhibited by adding sugar in the initial stage of the lectin reversible interaction with the cell surface before enabling the triggering lytic activities. Polypeptide hormones also share (with lectins, LEPS...
and immunoglobulins) most of the properties de-
scribed in paragraph 4.

7. EXPERIMENTAL EVIDENCE SHOWING
THAT INHIBITION OF THE LECTIN OR
LECTINOID REVERSIBLE INTERACTION
COMPETITIVELY INHIBITS THE ASSOCI-
ATED IRREVERSIBLE LYTIC PROCESSES

The practically irreversible hydrolytic decom-
position of acetylcholine by the esteratic site of
acetylcholinesterase is competitively inhibited by
compounds which bind to the LEPS of this en-
zyme (Fig. 4:1). Similarly, the irreversible lysis of
antigen-bearing macromolecules and cells by com-
plement is competitively inhibited by haptns
which bind to the antibody (Fig. 4:3). The same
rule exists also in the lectin-dependent lytic sys-
tem: sugars may competitively inhibit the lytic
activities associated with the lectins (Figs. 2:2 and
4:2). This rule is an important component in the
theoretical considerations of the herein suggested
lectin–lysin cofunction hypothesis. Therefore, we
forward a wide-spectrum experimental evidence
from microorganisms (viruses, bacteria and fungi),
plants and animals, showing that prevention of
irreversible lytic activities is obtained by an early
competitive, or non-competitive, inhibition of the
reversible lectin (or lectinoid) binding to their
receptors. The competitive inhibition may be ob-
tained by sugars (Figs. 2:2 and 4:2) or by com-
peting foreign lectins. The non competitive inhibi-
tion may be based on inactivation of the lectin (or
lectinoid), as well as on masking or removal of its
target cell receptors (Fig. 2). These are represented
by the following examples:
(1) Addition of L-rhamnose (6-deoxy-L-mannose),
or a lectin from Streptomyces which binds this
sugar, competitively inhibits the lysis of the
bacterium Lactobacillus casei by its bacteriophage
[63]. Similarly, Con A competitively inhibits lysis of
Bacillus subtilis by its bacteriophage [64,65].
(2) The fusion of influenza A virus with eukaryotic
cell membrane, culminating in lysis of the latter,
was shown to be dependent on its lectin
[41–43,55,56]. Desialylated cells are resistant to
the virus.

(3) The lytic activity of nematophagous fungi is
inhibited by sugars [58].
(4) The toxic and cytolytic effects of the lectinoid
microbial (cholera, shiga, diphtheria, Pseudo-
rnonas, tetanus and botulinus) toxins are inhibited
by sugars or glycoconjugates resembling the glyco-
sylated membrane lipid or protein receptors of the
sensitive cells [26,27]. The interesting point in this
regard is the fact that Bacillus thuringiensis glyco-
sylated toxin insecticidal activity, caused by its
interaction with lectinoid receptors in the larval
mosquito gut, is also inhibited by sugars [66].
(5) The plant toxins (ricin, abrin, modeccin, isidor,
etc.) are similarly inhibited by sugars [28–30]
(6) The lectin-dependent microbial lysis in
vertebrates and invertebrates was shown to be
blocked by sugars [19–21] or by competing lectins
[20].
(7) The degradation of circulating desialylated gly-
coproteins by hepatocytes is inhibited by removal
of their unmasked galactose residues which are
trapped by the hepatocyte surface lectins [22].
(8) Cancer cell metastases are prevented by sugars
which bind to the cancer cell [13,14,17] or to the
liver lectins [15,16], depending on which one of
them enables the cancerous cell settlement.
The lectin or lectinoid (either exogenous or
endogenous) importance for the targeting of the
lysin (bound to either lectin or glycosylated mole-
cules) to sensitive cells has found an important
application in cancer lectinothapery [51,67–70].
Lectins or lectinoids (as well as monoclonal anti-
bodies) which recognize the cancer cell receptors,
or glycoconjugates which are recognized by the
cancer cell lectins (or lectinoids) may be used for
targeting drugs (or monoclonal antibodies) to these
cells.

8. CONCLUSIONS AND FUTURE WORK

According to the herein suggested hypothesis,
lectin basic role is that of a cofactor which enables
the function of key lytic activities. The latter lead
to either cell and macromolecule lysis for nutri-
tional, homeostatic and protective purposes or
trigger cell alteration and reorganization needed
for developmental, functional or survival pur-
poses. Future work is desired for confirmation of this suggestion, which envisions lectins as lysis-enabling receptor-binding cofactors, including:
(1) Looking for the lytic counterparts of known lectins. Many of them are yet unknown. Their discovery and the study of their role may contribute enormously to the understanding of lectin functions.
(2) Looking for new lectin–lytic pairs in systems involving profound macromolecule or cell (including cell population) lysis or transformations (developmental, malignant, or environmentally induced): cell growth or division, sporulation, fertilization, germination, cell–substratum and cell–cell interactions (symbiosis, commensalism or parasitism, cell protection, fusion, and wound healing). Lectin interaction with exogenous glycosylated macromolecules or cells may also lead to conformational changes which enable the adjacent lysin activity. In many of these conditions appearance and involvement of lectins [49,50] and special metabolic activities were separately described, mostly without demonstration of a lysin–lectin linkage.
(3) Construction of neo lectin–lysin pairs (or half pairs which would cooperate with existing counterparts in the target cells) and examination of their biological effects and applications for medical, industrial, biotechnological and other scientific and applicative fields.
(4) Examination of lectin involvement in lytic phenomena and cell alterations which are induced by glycosylated macromolecules.

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