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# PROBIOTIC LECTINS AND GLYCOCONJUGATES RECOGNIZED BY LECTINS: SIMILARITY TO CYTOKINES, CYTOKINE INDUCERS AND IMMUNOMODULATORS

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## ABSTRACT

Probiotic lectins and their recognized glycoconjugates were studied as factors that enhance innate immunity. Lectins manifested themselves as cytokines, cytokine inducers and immunomodulators. Lectins were characterized by the potential of functioning with synthetic glycoconjugates. A partial similarity of the action of probiotic lectins with such classical cytokines as phytohemagglutinin from bean seeds and Pyrogenal was noted. Lactobacillar lectins and, to a lesser extent, bifidobacterial lectins induced the moderate production of the tumor necrosis α-factor by human blood cell cultures. The results confirm the broad prospects imitators of multi-strain probiotics (*Acilact*, others) – symbiotic/probiotic lectins that recognize and bind glycoconjugates. Among the tested synthetic glycoconjugates, the α-L-fucan analogue had the maximal effect on macrophage migration. The latter result indicates the prospects of using α-L-Fuc-containing glycoconjugates together with PL in the management of antitumor and antifungal activities of macrophages and macrophage-like monocytes.

**KEYWORDS:** probiotic lectins; cytokines; cytokine inducers; glycoconjugates; macrophages; monocytes; tumor necrosis factors; antimicrobials; communications.

## ABBREVIATIONS

*GC : glycoconjugates*

*IEF : isoelectrofocusing*

*II : innate immunity*

*LPS : lipopolysaccharide(s)*

*MMI : macrophage migration index*

*PAA : polyacrylamide*

*PAG : polyacrylamide gel*

*PHA : phytohemagglutinin from red beans*

*PL : probiotic lectins*

*TNF : tumor necrosis factor*

## 1. INTRODUCTION

The protection of the human body provides for the co-functioning of innate immunity (II) with the products of probiotic bacteria, which include probiotic lectins (PL) - proteins that recognize and bind carbohydrates and glycoconjugates (GC). We identified PL of the probiotic strains of bacteria (lactobacilli and bifidobacteria), as well as of the multi–strain probiotic *Acylact*, including strains $NK_1$, $100_{ash}$ and $K_3III_{24}$. The PL of both the strains and the consortium showed strain specificity and uniqueness in the case of *Acylact*, a probiotic with enhanced antimicrobial potential (compared to the ingredient strains). PL were characterized by molecular weights of more than 30 kD and contained systems of strongly acidic and slightly acidic (pI 4-6.5), near-neutral (pI 6.5-7.5) and alkaline/cationic (pI 6.5-9) forms. PL imitated the protective (antimicrobial and other) properties of probiotic cells and their multi-strain consortium.

The purpose of the study is to summarize our own results[1-20] on the effect of PL and the GC recognized by them on the body's II, including evaluating the potential of PL as cytokines, cytokine inducers and immunomodulators.

## 2. MATERIALS AND METHODS

Probiotic bacteria (lactobacilli and bifidobacteria) of intestinal origin were taken from the State Collection of Microorganisms of Normal Microflora of the Institute named after G.N. Gabrichevsky. Bacterial culture components (27-200 kD, pI 4-8.5) were fractionated by conventional methods, separated by isoelectrofocusing in polyacrylamide gel (IEF-PAG), proteins were extracted, and PL was identified on membrane blot prints obtained by electrotransfer from the gel. Proteins were stained using SYPRO protein blot (or PAG) stains (Bio-Rad Lab.). PL on blots were visualized by two-step treatment with GC-biotin—

Streptavidin-peroxidase. Fluorescence or chemiluminescence was recorded in an optimized real-time mode in the *BioChemi system* (UVP, Calif., USA). GC were used with repeatedly exposed mono- and di-carbohydrate residues in the form of lateral (side) branches along the linear polyacrylamide (PAA) core (a series of GC of the type $[Carbohydrate]_n$-PAA-biotin, www.lectinity.com). The effects of PL or GC on peritoneal macrophages of cultured white mice were evaluated by calculating the macrophage migration index (MMI). Phagocytosis of bacteria by cultured leukocytes (monocytes) of human peripheral blood was carried out according to a standard procedure. The effects of PL, phytohemagglutinin from red beans (PHA, the work dose as 10 mkg/ml, 48-72 h, Sigma, USA) and Pyrogenal (immunomodulatory lipopolysaccharide (LPS, The minimal dose as1 mkg/ml, 24 h) of *Salmonella typhi* (N.F.Gamalea Research Center, Moscow), activating II through a system of Toll-like receptors), were compared. Bacterial phagocytosis on the production of tumor necrosis factor (TNF-α) by stimulated leukocytes (monocytes) was investigated. TNF-α was evaluated under optimal conditions by enzyme immunoassay. Testing was performed on human whole blood cell cultures (160 µl of RPMI medium + 20 µl of cells freshly obtained from a blood donor + 20 µl of one of the three effector types, at 37$^{o}$C).

## 3. RESULTS AND THEIR DISCUSSION

**3.1.** Probiotic bacteria were characterized by L-Fuc-PAA-binding PL in protein arrays, for example, in cases of *B. bifidum* 791 (the main values of PL are about pI 3.9), *B. longum* B379M (PL mainly within pI 4.0-4.4), *L. helveticus* $NK_1$ (PL with pI 4.0-4.4 and, to a lesser extent, with pI 3.6-3.7). PL combinations were characterized by strain-specific patterns. As a rule, bifidobacterial PL were identified as more intense and extended combinations of components (dominant bands plus secondary ones) compared to lactobacillar PL.

**3.2.** MMI stimulation increased in a row: L-Fuc-PAA [α-L-fucan-like simulator] (MMI=14.5) >> D-Man-PAA [α-D-mannan-like simulator] (MMI=3.5) > D-GalNAc-PAA (MMI=1.0). This indicates the involvement of widely represented on the surface of macrophages cooperating in the action of receptor lectins with varying specificity to GC (especially to multi-antennary fucosylated Asn-glycans of complex type (with residues of L-Fuc-α-in the antennas of glycans, but not Ser/Thr-mucin-type glycans) in the process of induction/activation of the protective properties of macrophages. The results indicate the potential effectiveness of macrophages against fungi, including the genus *Candida*. The

results confirm our data on the anti-*Candida* activity of bifidobacterial and lactobacillar PL (results obtained by other independent methods).

**3.3.** In subhemagglutinating concentrations, the effect of alkaline/ cationic bifidobacterial PL (MMI=13.0), total lactobacillar PL (MMI=7.5) and acidic lactobacillar PL (MMI=7.0) on macrophages was similar to the effect of GC imitators of L-fucan and D-mannan on macrophages. Synergism was observed affecting the MMI of macrophages by PL of *Acylact* (a mixture of lactobacillar PL containing acidic, near-neutral and alkaline ones) (MMI=13.0).

**3.4.** PL of lactobacilli induced TNF-α production (126-254 pg/ml) by blood cell culture monocytes, while *B. bifidum* phagocytosis modulated (activated or blocked) TNF-α production in the range of 106-150 pg/ml in comparison with the background of spontaneous (without the influence of an inducer) TNF-α levels (126-129 pg/ml). The effects of PL and phagocytosis differed from LPS or PHA stimulation of TNF-α (182-458 and 197-271 pg/ml, respectively).

**3.5.** PL of *Acylact* (6 mg/ml; 1:10) stimulated the production of TNF-α in a manner partially similar to LPS. The effects of PL of *Acylact* were dose-dependent and exceeded the levels of spontaneous TNF-α stimulation in culture by up to 13 times (PL of *Acylact* 1:10), 3 times (PL of *Acylact* 1:100), by 40% (PL of *Acylact* 1:1000). When compared with PHA stimulation, the effects of LA were 9 times lower, but the level of TNF-α production in the presence of PL of *Acylact* (1:10) remained an order of magnitude higher than that in the control. Under the same conditions, PL of *Acylact* caused more pronounced TNF-α production compared to LPS (10 mkg/ml, 24 h), and at a dilution of 1:100, the effects of PL of *Acylact* (24 h) were up to 18 times weaker than those of LPS (1 mkg/ml, 24 h).

**3.6.** Probiotic bacteria synthesize acidic proteins capable of regulating the immune response, reacting with human IgA and IgM (PL with pI 4-4.5), as well as interacting with bacterial protein-A binding IgG and IgM (immunoglobulin forms mainly within pI 4.5-5).

PL were predominantly bound to GC-containing targets containing multiple GalNAc residues in mucin-type Ser/Thr-glycans. This indicated the possible involvement of PL in the additional deposition of IgA on probiotic bacteria and intestinal mucosa, which prevented the excretion of IgA from the body. In support of this, data indicate that after a course of *Acylact*

administration, an increase in IgA levels was observed in frequently ill children with reduced IgA levels.

**3.7.** PHA-like biological properties and some activities were more pronounced in acidic PL than in alkaline PL. In terms of cytoagglutination ability, lactobacillar PL were closer to PHA (multimeric glycoprotein containing subunits with different biological activities) compared to bifidobacterial PL.

As can be seen from the above results, it seems that a different contribution to the induction of TNF-α by blood cell cultures should be expected in relation to acidic (with an increased content of aggregation forms as nanoparticles and with the expected similarity to the influence of phagocytosis factor of cytokine induction by II cells), near-neutral and alkaline PL (with the expected similarity to PHA-stimulation of TNF-α).

In general, the dispersed (including dissociated and/or hydrolyzed, including hydrolases) forms of PL had more pronounced cytokine-inducing properties compared to (nano)particle forms of PL. PL of *Acylact* include partially hydrolyzed lectin molecules, including antimicrobial peptides with lectin properties, to a greater extent than the PL of the probiotic strains of lactobacilli that make up *Acylact*. Therefore, PL of *Acylact* manifested themselves to a greater extent as cytokine inducers compared to other PL.

Since TNF-α itself is an inducer of cytokines produced by II cells, we can talk about the influence of PL on the functional status of the II cytokine network in the human body.

The results indicate the synergism of acidic, near-neutral and alkaline lactobacillar PL as cytokine inducers. We should also expect synergy of PL and GC types as the way to construct cytokine inducers.

## 4. CONCLUSIONS

The results indicate the ability of PL to act like cytokines, cytokine inducers and immunomodulators. The data obtained indicate the expansion of the potential for the use of PL, including synergistic combinations of PL and multi-strain probiotics, in relation to the regulation of cascades of cytokines of II and correction of reduced levels of immunoglobulins in the body.

L-Fucan/derivatives of L-fucan and L-fucan/L-Fuc-binding PL of probiotic bacteria in the human body can be involved in the cross-exchange of interactome network reactions between microbiocenoses, II protective systems and adaptive immunity. Results indicate the prospects of using alpha-L-Fuc-containing GC together with PL (as carriers of GC) in the management of antitumor and antifungal activities of macrophages and macrophage-like monocytes against tumors and fungi (both expose α-L-Fuc-containing GC). PL systems can function as L-fucan/(L-fucan derivatives)-carriers of retaining/transferring/delivering and releasing therapeutic agents, prebiotics and other effector agents of GC nature such as regulators of biological activity of probiotics, inducers of cytokine production by leukocytes, participants influencing phagocytosis by monocytes or macrophages, indicators of tumor cells and synergistic antitumor promoting action agents with medications.

Functionally effective components of symbiotic/probiotic systems containing PL may be temporarily associated with prebiotic glycans and other GC immunomodulators. There is reason to believe that in microbiocenoses of mucosal biotopes of open cavities of the human body, bifidobacteria support or can support the survival of lactobacilli also through the use of L-fucan/L-fucan derivatives (including synthetic ones) that bind to PL.

**Disclosure of conflict of interest**

The authors declare no conflict of interest.

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