

PROBIOTICS REDUCE THE CD34+ HEMOPOIETIC PRECURSOR CELL INCREASED TRAFFIC IN ALLERGIC SUBJECTS

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Summary

An increased traffic of circulating CD34+ Hemopoietic Precursors Cells (HPC) is an important feature of systemic allergic inflammation. Bacteria and bacterial products are capable of stimulating the transcription of the maturational cytokines IL12 and IFNs through the activation of Toll-Like-Receptor and the subsequent nuclear translocation of the NF- κ B factor. In this study the probiotics differentiation/maturational effect potential on CD34+ HPC has been investigated. Fourteen consecutive subjects, 9M and 5F, aged 6-48, with clinical symptoms of asthma and /or conjunctivitis, rhinitis, urticaria, atopic dermatitis, food allergy and irritable bowel syndrome were enrolled. Allergen-specific serum IgE were found in twelve patients. Flow-cytometric measurement of peripheral blood CD34^{dim/bright} HPC values were assessed before and after 30 days of therapy, consisting in the oral administration of one sachet a day of ENDOLAC (UCB Pharma, Turin, Italy). Each sachet contained a mixture of *Lactobacillus acidophilus*, *L. delbrueckii* and *Streptococcus thermophilus* for a total of 1×10^9 live bacteria. Circulating CD34+ cell values significantly ($p < 0.001$) reduced after the treatment. ENDOLAC, thus, may improve the efficacy of the standard treatments of allergic diseases.

Key-words: Allergy - Asthma - Atopic dermatitis - Conjunctivitis - CD34 - Hemopoietic precursors - Irritable bowel syndrome - *Lactobacillus* - Probiotics - Therapy.

INTRODUCTION

The important contribution of systemic and local hemopoietic events to allergic inflammation is now supported by a consistent body of evidence. CD34+ human progenitor cells (HPC), in fact, have been identified in infiltrates at the mucosal and cutaneous peripheral sites (1, 2) as well as increased levels of circulating HPC have been reported in peripheral blood of patients suffering from allergic asthma, rhinitis and atopic dermatitis (3-7).

A reduced microbial exposure due to excessive hygienic conditions in first world countries has been proposed as a reason for the pandemic of allergic diseases, accordingly with the Hygiene Hypothesis of Allergy (8-11).

As a consequence, over the last decade, epidemiological and clinical studies have suggested a role potential for non-pathogenic microbes in the primary prevention of atopy (12-17). Furthermore probiotic bacteria have been recently defined as biological response modifiers (BRM) capable of inducing the indirect production of the maturative cytokines IL12 and IFN (18) that are known to skew the T-helper balance toward a TH1 polarization.

The purpose of this investigation was to evaluate the effect potential of a commercial probiotic on the increased peripheral traffic of immature cells in allergic patients.

MATERIAL AND METHODS

STUDY POPULATION

Fourteen subjects, 9 males and 5 females, aged from 6 to 48 years, with clinical symptoms of asthma (A), rhinitis (R), conjunctivitis (C), urticaria (U), atopic dermatitis (AD), food adverse reaction (FAR) with or without irritable bowel syndrome (IBS) were enrolled.

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The serum concentration of specific IgE to relevant food and/or inhalant allergens was screened by the standard CAP method (Pharmacia, Uppsala, Sweden). Severity of symptoms was scored on a four degrees scale ranging 0 (no symptoms) to 4 (severe, persistent symptoms) (Symptom Score 0-4). Patients under steroid treatment were excluded from the study.

All patients were treated with one sachet a day of the commercial probiotic bacteria *ENDOLAC* (UCB Pharma, Pianezza, Turin, Italy) for one month or with one sachet a day for 10 days in a month for three months. Each sachet contained a mixture of *Lactobacillus acidophilus* P-18806, 1×10^7 CFU; *Lactobacillus delbrueckii* P-18805, 5×10^6 CFU and *Streptococcus thermophilus* P-18807, 4×10^9 CFU. The symptom score and the CD34⁺ HPC peripheral values were determined in each patient before (T0) and after the treatment (T1) using a simple method recently developed and elsewhere described (7).

Briefly, To obtain information about the pool of immature circulating cells, independently from the lineage commitment (Lin^{+/+}) and the differentiation degree (CD34^{bright/dim}) we employed a modification of the Milan Protocol of Peripheral Blood CD34⁺ Cell Estimation.

Peripheral venous blood samples were collected in EDTA tubes. Three aliquots of 50 ml of whole blood were incubated, at 4°C for 25 min. in the dark, one with 15 ml of phycoerythrin (PE)-conjugated murine monoclonal antibody (MAB) specific to CD34 molecule, one with PE-conjugated MABs specific to unrelated molecules to human leukocyte antigens, and one as unlabeled control. Third class PE anti-CD34 MAB were the Anti-HPCA2, Clone 8G12 (Becton Dickinson) or PN IM 1871 (Immunotech) suitable for routine use. After red cell lysis, tubes were washed twice with 2 ml of cold phosphate buffered salt solution (PBS) (BD, Italy) at 1,200 revolution per minute (rpm) (300 g) for 7 min at 4°C and then resuspended in 500 µl of PBS.

Cell were analysed using a FACSCalibur with the software Cell Quest (BD) or Epics XL (IL) equipped with System II software. Three data parameters were acquired and stored in list mode files: linear forward scatter (FSC) (vertical axis), linear side-angle scatter (SSC) (horizontal axis) and log PE fluorescence, by gating whole viable cells. To enumerate CD34^{bright} and CD34^{dim} cells, the setting of the fluorescence analysis region 2 (R2) has been fixed with the lower limit at 10². For each measurement 10,000 events were acquired.

Results have been expressed as percentage of cells positive.

CD34⁺ cell values in healthy human controls, established in a previous experiment (7) ranged from 0.01% to 0.09%. The median was 0.03% and the interquartile range 0.02-0.06%.

STATISTICS

Data were analysed by mean of the paired t-test. A p-value < 0.05 was considered statistically significant. Overlapping significance value was obtained when data were processed with the non parametric Wilcoxon's matched paired test.

RESULTS

One month treatment with *ENDOLAC* induced a significant reduction of the peripheral traffic of the immature CD34⁺ cells in the investigated population (p= 0.001) (t = 4.44, d mean = 0.198, s d = 0.167), as well as a clinical improvement (SS reduction).

Therapy was safe and well tolerated by patients. The only side-effects recorded were two cases of diarrhoea, both occurring on the third day of administration and resolved without drugs. For these subjects treatment course was slacken down (one sachet every two days).

CD34 HPC values lowered, after the therapy, in all the subjects investigated but best outcomes resulted when T0 values were very high, that singularly were in the cases of patients n° 8, 10 and 14, all presenting irritable bowel symptoms or food adverse reactions. Favourable results were obtained also in patients n° 4 and 8, with the intrinsic form of allergy (specific IgE negative). Demographic data and results have been summarised in table 1.

DISCUSSION

The incidence and severity of atopic disorder is steadily increasing at an alarming rate meanwhile monetary constraints affect the western countries healthcare with a consequent policy aimed at lowering costs. Mentioned conditions together with a rethinking of the paradoxical effects of long-term corticosteroid-based treatments that, even highly effective in clinical management of allergy symptoms, induce pathogenetic modifications opposing the final established beneficial effects because they overturn the TH2/TH1 balance toward TH2 predominance and enhance IgE production (19-21), has induced a great deal for the research of low-cost approach to the primary prevention of atopy.

Patient	Sex	Age	Diagnosis	Spec.-IgE	S.S.T0	CD34 T0	CD34 T1	S.S.T1
1 ED	m	6	A+R+U	+	2	0.20	0.08	0
2 VT	m	28	R	+	1	0.14	0.12	1
3 LA	f	43	R+A	+	2	0.40	0.24	1
4 SC	f	48	R+U+AD	Neg.	2	0.29	0.09	1
5 OA	m	5	AD+R+A	+	2	0.34	0.15	1
6 BA	m	20	R+C	+	3	0.46	0.20	2
7 DGC	f	5	A+R	+	1	0.07	0.03	0
8 DSS	f	36	R+C+IBS	Neg.	3	0.60	0.16	1
9 FM	m	2	AD+U	+	1	0.18	0.14	1
10PF	m	16	AD+R+IBS	+	3	0.59	0.33	2
11BL	f	16	R+C+U	+	3	0.58	0.23	2
12DAM	m	12	R	+	1	0.13	0.04	0
13BP	m	8	R+C	+	1	0.13	0.10	1
14SM	m	16	FAR	+	4	1.14	0.56	1

Table 1: Study population demographic and clinical data. Values (%) of circulating immature CD34^{dim}/bright cells measured before probiotic therapy (T0) significantly reduced ($p < 0.001$) after the treatment (T1). Severity of Symptoms (0-4) before (T0) and after treatment (T1). Diagnosis: Asthma, Conjunctivitis, Rhinitis, Urticaria, Atopic Dermatitis, Irritable Bowel Syndrome.

If actually a vaccine for atopic disorders is far from being around the corner (22), a growing body of evidence supports the effectiveness of bacteria-based preventive approach (12-17), as well as the use of purified derivatives as Th1 adjuvant for allergen-specific immunotherapy (23, 24).

Since it is known that hemopoietic precursor cells contribute, together with allergen-specific Th2 clones and specific IgE to the systemic and local aspect of the allergic inflammation (7, 25, 26), outcomes of the present study indicate that ENDOLAC one-month-treatment significantly reduces the abnormal values of circulating immature cells and thus is capable of favourably affecting the allergic inflammation.

Increased CD34⁺ HPC values in patients n° 4 and 8, who presented clinical symptoms of respiratory and skin allergy but lacked serum allergen-specific IgE (intrinsic form of allergy), suggest as previously observed (7), that immature cells could be involved in the pathogenesis of intrinsic as well as extrinsic forms of allergic diseases.

Of equal interest are cases n° 8, 10 and 14. Patients complaining for conjunctivitis, rhinitis and atopic dermatitis symptoms associated with irritable bowel syndrome (IBS) (cases 8, 10) displayed at T0 the most elevated values of peripheral CD34⁺ immature cells.

The IBS is still a clinical challenge because of the limited understanding of the pathophysiology. The focus has moved to the identification of "visceral hypersensi-

tivity" (27) that is a concept close resembling the one well established for respiratory allergy (bronchial and nasal hyper-reactivity), that has been recently related as mucosal minimal persistent inflammation (MPI) to the systemic aspect of the allergic inflammation (7).

As in the past atopic dermatitis has been proposed as the "Asthma of the skin", an emerging body of evidence sustains the recent proposition for an "Asthma of the gut" (28); cellular, cytokine and chemokine Th2 profiles (29-33) have been, in fact, described in inflammatory bowel diseases. The recorded dramatic reductions of the circulating CD34⁺ cells as well as symptoms improvement after

probiotics treatment are promising for further systematic investigations (34).

Patient n° 14 suffered from food allergy. Serum was positive for milk and casein specific IgE (CAP Class IV) and he had experienced repeated emergency rescues to treat anaphylaxis and/or severe abdominal angina developed promptly after the ingestion of foods containing minimal amounts of the allergens. At the diagnosis (T0) peripheral traffic of immature cells was huge (1.14) when at T1, after three months of treatment (10 days a month) it halved (0.56). Singularly, at the end of the second month of therapy, the boy reported the accidental ingestion of a whole milk-roll (sold as oil-roll) without any consequent severe systemic symptoms; he reported in fact the transient appearance of mild abdominal pain resolved after the ingestion of one tablet of cetirizine 10 mg.

This case is suggestive for the pathogenetic implications. If beneficial effects of maturational interventions could be expected in organ allergic diseases (rhinitis, asthma and atopic dermatitis) in which the contribution of immature cells to the tissue inflammatory infiltrates is known (1-7), food allergy together with bee-venom allergy are regarded as paradigmatic IgE-mediated reactions. Furthermore no therapy other than avoidance exists.

Very recent experimental approaches, nevertheless, suggest preliminary favourable results to prevent peanut-anaphylaxis, in the animal model, administering engineered recombinant allergen with inactivated-*Listeria monocytogenes* as an adjuvant (35).

Furthermore, it has been reported that IL12 treatment is capable of inducing physicochemical modifications, mainly regarding the glycosylations, that reduce the pathogenicity of IgA (36).

Mentioned experiments, conducted with bacterial adjuvant and with IL12 raise the question whether maturative, Th1 inducing intervention might induce structural changes that reduce the IgE pathogenicity.

Concluding, it is known that bacteria interact with Toll-Like-receptors distributed on cells belonging to the innate immunity compartment. Mentioned TLRs, included in the large IL1R family, activate the NF- κ B factor nuclear translocation and the subsequent transcription of a network of genes, including those codifying for the maturational cytokines IL12 and INF (37-41).

Results of the present study demonstrate that treatment with the bacteria probiotic ENDOLAC is capable of significantly reducing the increased peripheral traffic of CD34+ immature precursor cells. Reduction was measured not only in subjects with extrinsic allergic symptoms but also in intrinsic patients who lacked serum allergen-specific IgE.

Clinical results concerning irritable bowel syndrome and food allergy are interesting but require further extensive investigations.

REFERENCES

- Kim, Y.-K., Uno M., Hamilos D.-L., Beck L., Bochner B., Schleimer R., Denburg J.-A. - Immunolocalization of CD34 in nasal polyposis. *Am J Respir Cell Mol Biol* 1999;20:388-97.
- Mastrandrea F., Cadario G., Nicotra M.-R., Natali P.-G. - Hemopoietic progenitor cells in atopic dermatitis skin lesions. *Invest Allergol Clin Immunol* 1999;9:386-91.
- Denburg J.-A., Telizyn S., Belda A., Dolovich J., Bienenstock J. - Increased numbers of circulating basophil progenitors in atopic patients. *J Allergy Clin Immunol* 1985;76:446-72.
- Denburg J.-A., Dolovich J., Harnish D. - Basophil mast cell and eosinophil growth and differentiation factors in human allergic disease. *Clin Exp Allergy* 1989;19:249-54.
- Denburg J.-A., Woolley M., Leber B., Linden M., O'Byrne P. - Basophil and eosinophil differentiation in allergic reaction. *J Allergy Clin Immunol* 1994;94:1135-41.
- Mwamtemi H.-H., Koike K., Kinoshita T., Ito S., Ishida S., Nakazawa Y. et al. - An increase in circulating mast cell colony-forming cells in asthma. *J Immunol* 2001;166:4672-7.
- Mastrandrea F., Coradduzza G., De Vita L. et al. - CD34+ cells in peripheral blood of healthy human beings and allergic subjects: clue to acute and minimal persistent inflammation. *Allergol et Immunopathol* 2002;30:209-17.
- Wills-Karp M., Santeliz J., Karp C.-L. - The germless theory of allergic diseases: revisiting the hygiene hypothesis. *Nat Rev Immunol* 2001;1:69-75.
- Yazdanbakhsh M., Kremsner P.-G., van Ree R. - Allergy, parasites, and hygiene hypothesis. *Science* 2002;296:490-4.
- Braun-Fahrlander C. - Does the 'Hygiene Hypothesis' provide an explanation for the relatively low prevalence of asthma in Bangladesh? *Int J Epidemiol* 2002;31:488-9.
- Weiss S.-T. - Eat dirt: the hygiene hypothesis and allergic diseases. *N Engl J Med* 2002;347:930-1.
- Isolaure E., Arvola T., Sutas Y., Moilanen E., Salminen S. - Probiotics in the management of atopic eczema. *Clin Exp Allergy* 2000;30:1604-10.
- Pessi T., Sutas Y., Hurme M., Isolaure E. - Interleukin-10 generation in atopic children following oral *Lactobacillus rhamnosus* GG. *Clin Exp Allergy* 2000;30:1804-8.
- Murch S.-H. - Toll of allergy reduced by probiotics. *Lancet* 2001;357:1057-9.
- Kalliomaki M., Salminen S., Arvilommi H. et al. - Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001;357:1076-9.
- Rosenfeldt V., Benfeldt E., Nielsen S.-D. et al. - Effect of probiotic *Lactobacillus* strain in children with atopic dermatitis. *J Allergy Clin Immunol* 2003;111:389-95.
- Kirjavainen P.-V., Salminen S.-J., Isolaure E. - Probiotic bacteria in the management of atopic disease: underscoring the importance of viability. *J Pediatr Gastroenterol Nutr* 2003;36:223-7.
- Mastrandrea F. - Probiotics and Immunity. Lecture. Proceed. 2° Probiotics, Prebiotics and New Food. 156-167, 7-9 September 2003, Rome, Italy.
- Akdis C.-A., Blesken T., Akdis M. et al. - Glucocorticoids inhibit human antigen-specific and enhance total IgE and IgG4 production due to differential effects on T and B cells *in vitro*. *Eur J Immunol* 1997;27:2351-7.
- Jabara H.-H., Brodeur S.-R., Geha R.-S. - Glucocorticoids upregulate CD40 ligand expression and induce CD40L-dependent immunoglobulin isotype switching. *J Clin Invest* 2001;107:371-8.
- Barnes P.-J. - Corticosteroids, IgE, and atopy. *J Clin Invest* 2001;107:265-6.
- Wohleben G., Erb K.-J. - Atopic disorders: a vaccine around the corner? *Trends Immunol* 2001;22:618-26.
- Wheeler A.-W., Marshall J.-S., Ulrich J.-T. - A Th1-inducing adjuvant, MPL, enhances antibody profiles in experimental animals suggesting it has the potential to improve the efficacy of allergy vaccines. *Int Arch Allergy Immunol* 2001;126:135-9.
- Gronlund H., Vrtala S., Wiedermann U. et al. - Carbohydrate-based particles: a new adjuvant for allergen-specific immunotherapy. *Immunology* 2002;107:523-9.
- Cyr M.-M., Denburg J.-A. - Systemic aspect of allergic disease: the role of the bone marrow. *Curr Opin Immunol* 2001;13:727-32.
- Denburg J.-A., Inman M.-D., Leber B., Sehmi R., O'Byrne P.-M. - The role of the bone marrow in allergy and asthma. *Allergy* 1996;51:141-8.
- Quigley E.-M. - Current concepts of the irritable bowel syndrome. *Scand J Gastroenterol Suppl* 2003;237:1-8.
- Riccioni G., Della Vecchia R., Guagnano M.-T., D'Orazio N. - Asthma of the gut: dream or reality? *Eur J Clin Invest* 2003;33:733-4.
- Van Damme N., De Keyser F., Demetter P. et al. - The proportion of Th1 cells, which prevail in gut mucosa, is decreased in inflammatory bowel diseases. *Clin Exp Immunol* 2001;125:383-90.
- Jugde F., Alizadeh M., Boissier C. et al. - Quantitation of chemokines (MDC, TARC) expression in mucosa from Crohn's disease and ulcerative colitis. *Eur Cytokine Netw* 2001;12:468-77.
- Berribe D., Languepin J., Ferkdadi L. et al. - Cytokines, chemokine receptors, and homing molecule distribution in the rectum and stomach of pediatric patients with ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2003;37:300-8.
- Nishida Y., Murase K., Isomoto H. et al. - Different distribution of mast cells and macrophages in colon mucosa of patients with collagenous colitis and inflammatory bowel disease. *Hepatogastroenterology* 2002;49:678-82.
- Carvalho A.-T., Elia C.-C., de Souza H.-S. et al. - Immunohistochemical study of intestinal eosinophils in inflammatory bowel disease. *J Clin Gastroenterol* 2003;36:120-5.
- Faber S.-M. - Are probiotics useful in irritable bowel syndrome? *J Clin Gastroenterol* 2003;37:93-4.
- Li X.-M., Srivastava K., Huleatt J.-W. et al. - Engineered recombinant peanut protein and heat-killed *Listeria monocytogenes* coadministration protects against peanut-induced anaphylaxis in a murine model. *J Immunol* 2003;170:3289-95.

36. Kobayashi I., Nogaki F., Kusano H. *et al.* - Interleukin-12 alters the physicochemical characteristics of serum and glomerular IgA and modifies glycosylation in a ddY mouse strain having high IgA levels. *Nephrol Dial Transplant* 2002;17:2108-16.
37. Anderson K.-V. - Toll signals pathways in the innate immune response. *Curr Opin Immunol* 2000;12:13-9.
38. Ghosh S., May M.-J., Kopp E.-B. - NF- κ B and Rel proteins: evolutionarily conserved mediators of immune responses. *Ann Rev Immunol* 1998;16:225-60.
39. May M.-J., Ghosh S. - Signal transduction through NF- κ B. *Immunol Today* 1998;19:80-8.

40. Brightbill H.-D., Libraty D.-H., Krutzik S.-R. *et al.* - Host defense mechanisms triggered by microbial lipoproteins through toll-like receptors. *Science* 1999;285:732-36.
41. Thoma-Uszynski S., Kiertcher S.-M., Ochoa M.-T. *et al.* - Activation of toll-like receptor 2 on human dendritic cells triggers induction of IL-12 but not IL-10. *J Immunol* 2000;165:3804-10.

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HOLIDAY FRAZZLE! THE AAAAI OFFERS ADVICE ON MANAGING HOLIDAY STRESS AND ASTHMA

MILWAUKEE- It's the holiday season and you haven't gotten the perfect gifts for everyone on your list yet and your house has to be cleaned before guests come over. Not only can the hustle and bustle of the holidays make you feel frazzled, they can affect your asthma as well.

Although asthma is not a disease that is caused by one's state of mind, all signs point to a strong relationship between asthma attacks and emotional upsets. For the 17 million Americans with asthma, this means keeping your stress in check. While some stressors are shown to be healthy for your overall well being, others can be a significant trigger for asthma.

"Uncontrolled emotions stimulate nerves that can cause muscles in the airways to tighten as well as altering immune balance that could promote airway inflammation," said Gailen D. Marshall, Jr., MD PhD FAAAAI.

"Understanding what causes asthma and how stress can negatively affect it, particularly around the busy holiday season, is important to properly maintain asthma control."

Symptoms of asthma can include:

- Coughing.
- Chest tightness.
- Shortness of breath.
- Wheezing.

Without proper management, the severity of asthma can intensify. Additionally, a person with asthma will usually be more relaxed if they understand and have more control over their own asthma. Not knowing how to handle it can cause fear, anxiety, depression or just plain frustration - any of which could make the person's asthma much worse.

Since asthma is a chronic disease, it requires continuous management and treatment, not just when it gets bad. Therefore, you should not wait until the holidays to think about treatment. Planning and managing your asthma year-round can make the stress of the holidays a bit easier.

Methods of managing stress include a realistic schedule such as shopping, work, getting proper rest and nutrition and saving time for relaxation and fun. The holiday season is a time that is known to be difficult for some and brings feelings of anxiety and depression. If symptoms become severe, professional intervention may be necessary.

Well-managed asthma can include using proper medications. People with asthma have inflamed airways which can become even more inflamed after exposure to various triggers. The main purpose of asthma medications is to reduce this inflammation. Make sure you follow your physician's instructions on the appropriate use and dosage of your prescribed medications.

The better informed you are about your asthma triggers and management, the less asthma symptoms will interfere with your activities. It is important to avoid your triggers, work with your physician on a management plan, take appropriate medications as prescribed and, especially during the holidays, relax! Together, you and your allergist/immunologist can work to ensure that asthma does not interfere with your optimal quality of life, or your holiday season!

To find an allergist/immunologist in your area or to learn more about allergies and asthma, call the AAAAI Physician Referral and Information Line at 1-800-822-2762 or visit the AAAAI Web site at www.aaaai.org.

The AAAAI is the largest professional medical specialty organization in the United States representing allergists, asthma specialists, clinical immunologists, allied health professionals and others with a special interest in the research and treatment of allergic disease. Allergy/immunology specialists are pediatric or internal medicine physicians who have elected an additional two years of training to become specialized in the treatment of asthma, allergy and immunologic disease. Established in 1943, the Academy has nearly 6,000 members in the United States, Canada and 60 other countries. The Academy serves as an advocate to the public by providing educational information through its Web site at www.aaaai.org.