Scientific Research Publishing

Journal of Biosciences and Medicines, 2022, 10, 148-159
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Blood Microbiota and Cancer: Cell Wall-Deficient L-Forms of Bacteria and Fungi as Cancer-Promoting Environment

Nadya Markova

Department of Infectious Microbiology, Institute of Microbiology, Bulgarian Academy of Sciences, Sofia, Bulgaria
Email: nadya.markova@gmail.com

How to cite this paper: Markova, N. (2022) Blood Microbiota and Cancer: Cell Wall-Deficient L-Forms of Bacteria and Fungi as Cancer-Promoting Environment. *Journal of Biosciences and Medicines*, **10**, 148-159.
https://doi.org/10.4236/jbm.2022.109011

Received: August 16, 2022
Accepted: September 16, 2022
Published: September 19, 2022

Abstract

In recent years, valuable experience and insights have been gained into L-forms (cell-wall-deficient variants) of bacteria and fungi and their disease-trigger potential in cases with chronic infections, autism spectrum disorders, autoimmune and neurodegenerative diseases. Based on the concept of "internal" blood microbiota, consisting of L-forms and its relevance to health and disease, the current study aims to outline the profile of dysbiotic disorders in three cancer patients (with endometrial cancer, breast cancer and acute myeloid leukemia), all in a phase before chemotherapy. Venous blood samples from the patients and from one control healthy person, were microbiologically studied. The used novel methodology of blood microbiota assessment was based on the following phases: isolation of L-forms, development and propagation, cultivation and conversion of L-forms into classical bacteria and fungi, as well as their identification with MALDI-TOF method. From the patients were isolated L-forms of opportunistic bacteria (*Enterococcus faecalis*, *Esherichia coli*, *Enterobacter cloacae* and *Pseudomonas oryzihabitans*) and fungi such as *Rhodotorula mucilaginosa*, *Aspergillus fumigatus* and *Mucorales*. In conclusion, the common feature found for the three cancer patients was the isolation from the blood of highly associated communities consisting of morphologically indistinguishable L-bodies, which through reversion in broth, were identified as distinct bacterial and fungal species. Unlike classic bacteria or fungi causing sepsis and bacteremia/fungemia, the presence of L-forms in blood is hidden, it does not demonstrate clinical signs nor it can be detected by conventional methods. It should be noted, however, that the dysbiotic blood microbiota shows unique and individual characteristics for the concrete cancer patient, correlates to the common state of the organism and tumor localization in the body, as well as it outlines the cancer promoting role of L-forms in processes of malignization, cancer genesis and progression.

Keywords

L-Forms, Blood Microbiota, Cancer Patients

1. Introduction

The hypothesis of blood L-form microbiota has been created on the basis of accumulated knowledge about the unique nature of L-forms (cell wall-deficient variants of bacteria and fungi) [1] [2]. In general, blood L-form microbiota can be defined as community of cell wall-deficient variants (L-forms) of bacteria and fungi, present and persisting in human blood. "Dysbiotic" microbiota manifests itself with excess L-forms of opportunistic microbes (bacteria and fungi) persisting in blood and invading from the external microbiota *i.e.* from all body sites in contact with the external environment [2]. Recent studies confirm the role of persisting L-forms in some chronic infections and non-communicable diseases, and contribute to the novel insights concerning the significance of blood microbiota for microbial pathogenesis [3] [4] [5] [6] [7]. Our studies on people with multiple sclerosis (MS), Parkinson's disease, psoriasis, thyroid cancer, diabetes and autistic children revealed appearance of "dysbiotic" blood microbiota and outlined the disease-trigger potential of opportunistic bacterial and fungal L-forms [2] [6]. It is believed blood microbiota assessment could be of diagnostic and prognostic importance for the pathological processes occurring within the body [2]. In the context of L-form research, the question arises whether the overgrowth of cell wall-deficient variants (L-forms) of bacteria and fungi anywhere in the body may be associated with induction of chronic inflammation and malignancies, as well as whether dysbiotic blood L-form microbiota can contribute to cancer genesis and progression.

In this respect, reports of pathologists have demonstrated the presence of pleomorphic L-bodies (cell wall deficient forms, granules, coccoid forms, spores, and fungus-like forms) in cancerous tissues [8] [9] [10]. It is generally assumed that chronic inflammation may lead to a cancer-promoting environment through the production of carcinogenic bacterial metabolites, DNA-damages, and mutations [1] [11]. In fact, the research in this field has been focused on the host-microbiota interactions in carcinogenesis, on influence of inflammatory disorders and host immune responses in evolving tumor microenvironments by eliciting proinflammatory or immunosuppressive processes [12] [13] [14]. Most researchers focus their studies on the intra-tumor microbiome and its correlation to cancer progression across different cancers [15] [16] [17] [18].

In contrast to the usual approach of studying intra-tumor microbiota, the present study focuses the attention to cell wall-deficient variants (L-forms) of bacteria and fungi, persisting in blood and to their relationship with cancer. In this regard, the study aims to evaluate whether and how the blood L-form microbiota can reflect the source of invading microbes, respectively the site of tu-

mor localization and the grade of general dysbiosis in cancer patients, as well as whether all this can be of prognostic significance for cancer progression.

2. Materials and Methods

Blood samples from three cancer patients, respectively with endometrial cancer (female, 57y.o), with breast cancer (female, 67y.o.) and with acute myeloid leukemia (female, 34y.o.), all in the phase before chemotherapy, as well as from one control healthy person (female, 36y.o.), were microbiologically studied. Venous blood samples were taken aseptically using K2E-EDTA Vacutainer tubes (BD Vacutainer, Plymouth, UK). Informed consent for the use of the blood samples for research purposes was obtained from all participants. All blood samples were handled and anonymized, according to the national ethical and legal guidelines, while the study protocol was approved by the Ethics Committee of Scientific Studies Involving Human Experimentation at the Medical University of Sofia. The used novel methodology of blood microbiota assessment was described in detail in our previous study [3]. In brief, it was based on the following several subsequent phases: isolation of L-forms, development and propagation, cultivation and conversion of L-forms into classical bacteria and their identification by MALDI-TOF method. Two protocols designated as "classical" and "filtration" were used for the isolation of microbial L-type cultures from blood samples [3] [6]. In short, the blood sample was cultivated after a procedure of lysis with sterile distilled water at strictly fixed v/v ratio and after 30 minutes of exposure to room temperature. As per the "classical" protocol (CL), the aliquots from lysed blood samples were inoculated in tubes with Tryptic Soy Broth (TSB, Becton Dickinson) and incubated at 37˚C for 72 hours. As for the "filtration" protocol (F), after inoculation TSB was filtered through a bacterial filter with 0.2 μm pore size and was also incubated at 37˚C for 72 hours. Strictly fixed aliquots from primary broths (CL and F) were subcultured again in three variants of broth media (TSB, TSB with Gentamycin of 100 μg/ml and Sabouraud Dextrose broth-SDB with Chloramphenicol of 50 μg/ml) and parallel plated on three variant of semisolid media-TSA, TSA with Gentamycin of 100 μg/ml and Sabouraud Dextrose Agar-SDA with Chloramphenicol of 50 μg/ml. The semisolid media were solidified with 0.8% (w/v) Agar (Fluca). TSB and TSA were incubated at 37˚C, while SDB and SDA at 25˚C. Passages in broth and semisolid media were performed using the technique described in previous study [3]. All cultures were periodically observed for appearance of growth and morphological transformations within 2 months. Direct light microscopic observations of native preparations from cultures were combined with Gram and Giemsa stained smears.

Identification of isolated pure classical bacterial and fungal cultures was done by MALDI-TOF (matrix assisted laser desorption ionization-time of flight mass spectrometry method) [19].

3. Results and Discussion

In contrast to the control healthy person (female, 36y.o) from whom no micro-

bial agents were isolated, from blood of the three investigated cancer patients were isolated L-form cultures, that after recovering through reversion during cultivation in broth, were identified as the following bacterial and fungal species: 1) in patient with endometrial cancer—*Enterococcus faecalis*, *Esherichia coli*, *Rhodotorula mucilaginosa* and *Aspergillus fumigatus*; 2) in patient with breast cancer—*Pseudomonas oryzihabitans*, *Enterobacter cloacae* and *Mucorales*; 3) in patient with acute myeloid leukemia—*Enterococcus faecalis* and *Aspergillus fumigatus.* It should be noted that L-forms (cell wall-deficient variants) started to replicate in broth by using the novel methodology, described above.

A process of L-form reversion into classical/walled bacteria and fungi, was observed in all patients and it is demonstrated in Figures 1-7. Remarkably, in

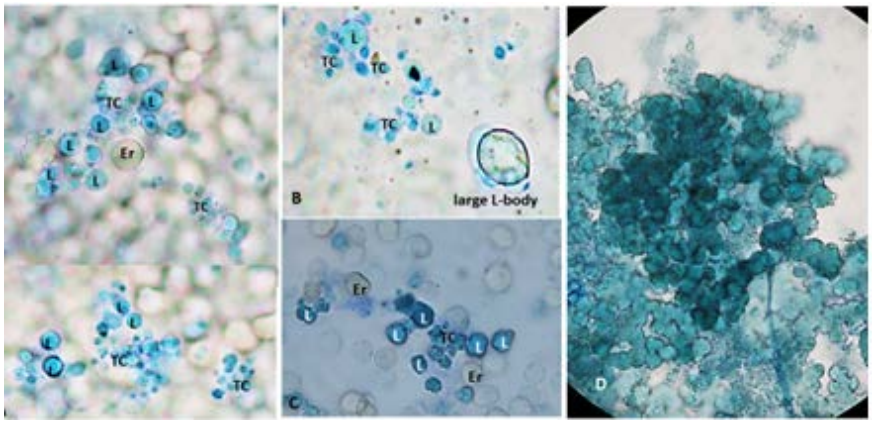

Figure 1. Formation of L-forms and development of L-form population in broth during cultivation of blood from patient with endometrial cancer. (A, B) spherical L-bodies of different size (L), around them aggregates of thrombocytes (TC); (C) spherical L-bodies, around them erythrocytes (Er); (D) culture of propagated spherical L-bodies. Native preparation from broth, contrasted with methylene blue. Magnification 1000×.

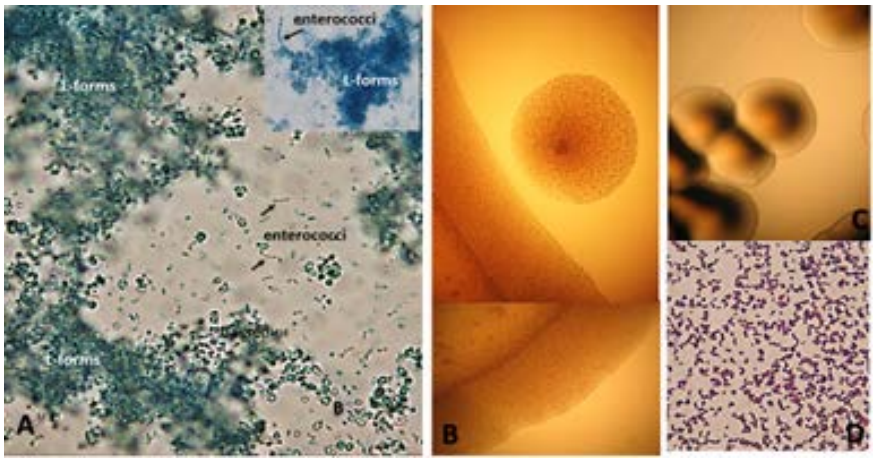

Figure 2. Conversion of L-forms into classical bacteria ((A) arrows) in broth and isolation of *Enterococcus faecalis* from blood of patient with endometrial cancer. (B) typical L-form growth and "fried egg" shaped colony on semisolid agar; (C) typical colonies of *Enterococcus faecalis*; Gram stained smear from colonies. Native preparation, contrasted with methylene blue (A). Magnification: A, D: 1000×; B: 200×.

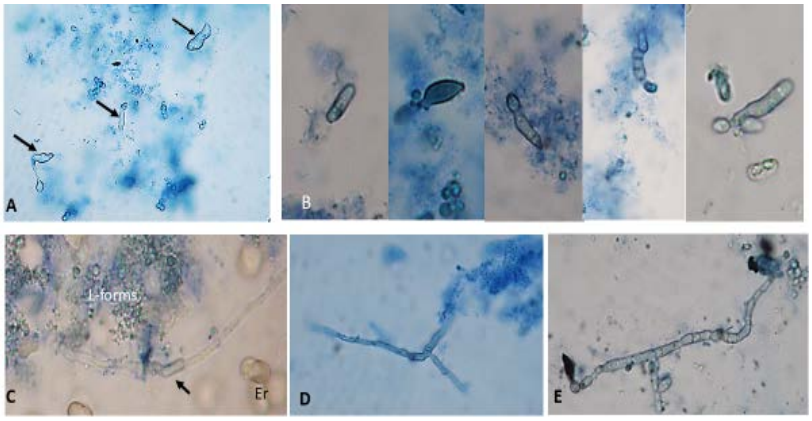

Figure 3. Observation of fungal elements from the life cycle of filamentous fungi in SDB from blood of patients with endometrial cancer. Irregular protoplastic L-bodies ((A) arrows); (B) Fungal cells (conidia); (C) Germinating and tube-producing conidia (arrow); (D, E) formation of septate hyphae. After subsequent sub-cultivation on solid media (SDA), typical growth of *Aspergillus fumigatus* was found. Magnification: 1000×.

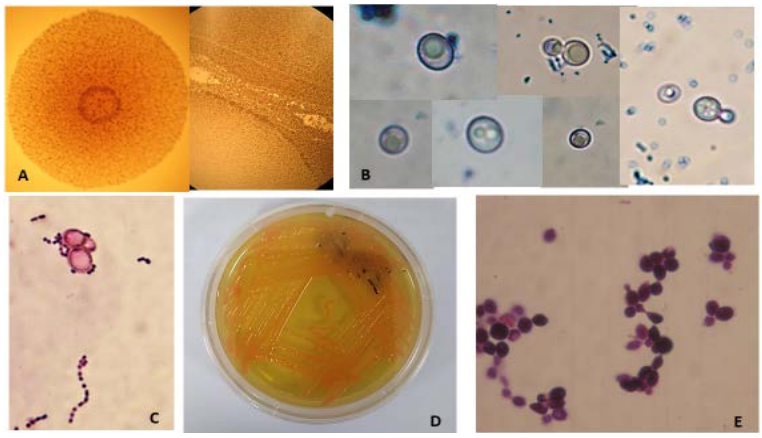

Figure 4. Mixed L-form growth of bacteria and yeasts, and isolation of *Rhodotorula mucilaginosa* from blood of patient with endometrial cancer. (A) typical for L-forms "fried egg" shaped colony; (B) yeast cells, some of them budding. Native preparation, contrasted with methylene blue; (C) yeast cells and enterococci. Gram stained smear; (D, E) pure culture and Gram stained smear of *Rhodotorula mucilaginosa*. Magnification: B, C, E: 1000×; A: 200×.

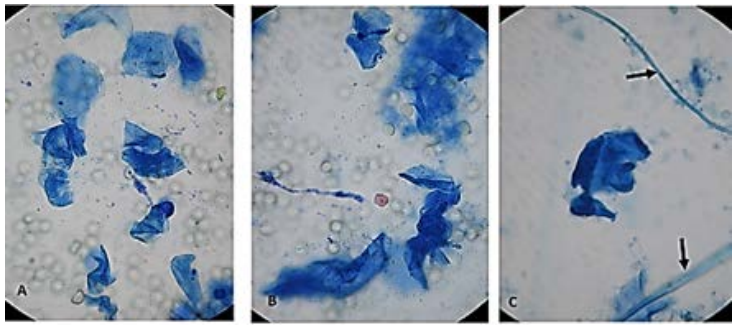

Figure 5. "Metastatic" fragments of epithelial cells observed in the early stage of cultivation of blood from patient with endometrial cancer. Native preparations from broth, contrasted with methylene blue. Magnification: 1000×.

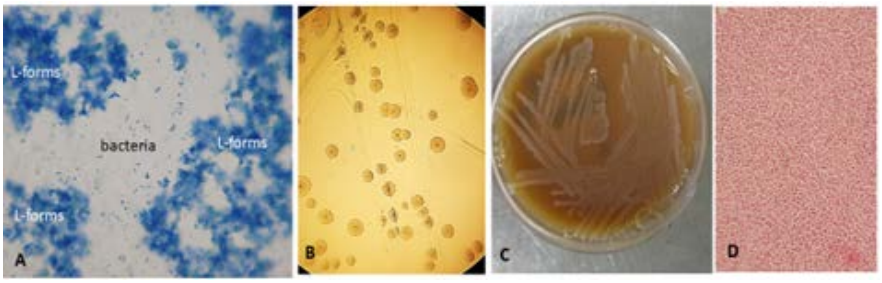

Figure 6. Conversion of L-forms into classical bacteria in broth (A) and isolation of *Enterobacter cloacae* from blood of patient with acute myeloid leukemia. (B) Typical for L-forms tiny "fried egg" shaped colonies on semisolid agar; (C) Typical colonies of *Enterobacter cloacae*; (D) Gram stained smear from colonies. Native preparation, contrasted with methylene blue (A). Magnification: A, D: 1000×; B: 200×.

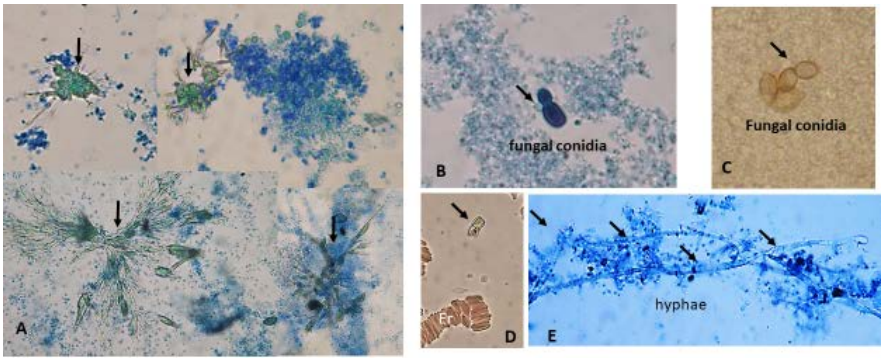

Figure 7. Observation of fungal elements from the life cycle of filamentous fungi in SDB from blood of patients with acute myeloid leukemia. (A) Fungal drusen (arrows); (B, C) Fungal cells (conidia); (D) Observation of fungal fragment (arrow) in a native preparation directly from blood, erythrocytes (Er); (E) Formation of septate hyphae. After subsequent sub-cultivation on solid media (SDA), typical growth of *Aspergillus fumigatus* was found. Magnification: 1000×.

the patient with endometrial cancer, the initial L-form appearance was noted within/among platelet aggregates (**Figure 1**). As seen in **Figures 2-4**, the combination of isolated from this patient two bacterial species (*Enterococcus faecalis* and *Esherichia coli*), together with fungal species (*Rhodotorula mucilaginosa* and *Aspergillus fumigatus)* suggests that their origin is probably from the microbiota in uro-genital tract. *Enterococcus faecalis* (enterococci) is a bacterial species that very easily transforms into a wall-less variant (L-forms) and it can enter the bloodstream from the focus of the pathology (inflammation/infection; cancer localization). Enterococci are normal inhabitants of the gastrointestinal tract. They can also be found in the genital/vaginal and anterior urethral flora. *E. coli* is often combined with *Enterococcus faecalis* as the causative agents of uro-genital infections and it is not surprising to find it in the blood as L-forms. Regarding the presence of viable fungal elements in the blood, it can be assumed that they may secrete mycotoxins with tissue-toxic and immunosuppressive effects. Future research on the detection of mycotoxins in the blood of cancer patients would be of clinical significance. Having in mind the endometrial location

of cancer in this patient and the found bacterial-fungal L-form microbiota in blood, it can be suggested that the origin of the identified microbial agents is from the uro-genital tract. Prolonged persistence of these microbial agents in uro-genital tract is probably the basis for chronic inflammation and subsequent malignization. Of special interest was the capture of "metastatic" epithelial cells in the same patient and this was possible thanks to the systemic light microscopic observations of native preparations from broth, where the blood was cultivated (**Figure 5**). It should be also noted that filamentous formations (arrows) of fungal origin were seen, located around the groups of epithelioid cells (**Figure 5(C)**). Here, it is appropriate to look for an interesting connection/association between cancer promoting role of *Aspergillus fumigatus* and the process of metastasis. There is some evidence indicating the involvement of metalloproteinase produced by *Aspergillus fumigatus* in the pathophysiology of fungal infections [20]. On the other hand, it is known that metalloproteinase produced by cancer cells is a key enzyme for metastasis due to its ability to degrade the components of the extracellular matrix, then epithelial cells lose their tight junctions and adhesive connections, resulting in infiltration and an enhanced migration ability of these cells.

Metastatic cells enter circulation and survive within it [21] [22]. Apparently, the fungi can enhance/contribute to the metastasis process through a pathway of metalloproteinase production. This hypothesis remains to be proven with future research.

From the second patient with breast cancer was once again isolated a combination of three agents—L-forms of two bacterial species (*Pseudomonas oryzihabitans* and *Enterobacter cloacae*) and one fungal isolate belonging to the *Mucorales. Pseudomonas oryzihabitans* has been considered a potential pathogen, especially in patients with mastitis, wound infections and surgical site infections [23]. The second bacterial isolate from this patient was *Enterobacter cloacae.* This species is involved in the normal intestinal microbiota in many people. However, under certain conditions (immunosuppression), it can manifest itself as an opportunistic pathogen [24]. Mucorales have been found to secrete a "mucoid secretion" which is actually extracellular polysaccharide substances. These substances are known to contribute to the pathogenesis of soft tissue edema and impaired drainage of secretions [25]. As it can be analyzed, here too, the isolated blood microbiota shows an association with cancer localization in the glandula mammae, namely local persisting infection/inflammation caused by *Pseudomonas oryzihabitans* and *Mucorales*, a subsequent malignization, together with immunosuppression, the sign of which is the translocation of *Enterobacter cloacae* from gut microbiota into blood.

It's interesting to note, that the blood microbiota of this patient was investigated again, after the chemotherapy, during the period of subsequent medicament targeted therapy. Throughout this time, the patient was concurrently on alternative antimicrobial therapy with essential oils, administered orally according to a treatment protocol.

Selection of the proper essential oils was based on antibio-aromograms (susceptibility/resistance tests against essential oils for oral use) of the three isolated cultures (*Pseudomonas oryzihabitans*, *Enterobacter cloacae* and *Mucorales*). No microbial agents (L-forms of opportunistic bacteria and fungi) were isolated in the second/control study. It should be noted that the disappearance of dysbiotic blood microbiota correlated with the process of effective cancer elimination and improvement of the patient. It is believed that when the host's protective barriers and the balance of homeostasis in the body are disturbed, the dysbiotic microbiota can negatively affect the tumor microenvironment and promote cancerogenesis [12]. In this connection, the antimicrobial-based approach in treatment of cancer comes to the fore from a holistic perspective.

From the third patient with acute myeloid leukemia were isolated L-forms of *Enterobacter cloacae* and *Aspergillus fumigatus.* Conversion of L-forms into classical bacteria and observation of elements from the life cycle of filamentous fungus are seen in **Figure 5** and **Figure 6**. *Enterobacter cloacae* is among the frequently isolated pathogens from the blood of patients with acute myeloid leukemia [26]. Its isolation from blood is explained by its translocation from the intestine into the circulation as a result of impaired barrier protection of the intestinal mucosa (suppressed mucosal immunity) in this patient.

It is important to note that all three cancer patients were examined before starting chemotherapy, as the study's aim is to focus on the initial cancer-promoting role of L-forms, without the effects of chemotherapy. In all three cases, a dysbiotic blood microbiota was outlined, demonstrated by an abundance of L-forms of opportunistic bacteria and fungi invading the circulation from the focus of the pathology (tumor localization place) or from the intestinal tract. Co-isolation of fungi with bacteria from clinical specimens has been found by other authors in risk patients with cancer, autoimmune diseases, cystic fibrosis, or organ transplants [27] [28] [29] [30] [31]. However, far more curious and less studied is the pathogenic role of L-forms of bacteria and fungi persisting in blood. Enby and Chouhan have observed microbial forms with a high degree of pleomorphism in tumors and blood of cancer patients. Of special interest is also that the authors have found a correlation between the clinical stage of cancer and morphological characteristics of these pleomorphic microbes. They believe that these forms may create tumors through local propagation in and at the expense of the tissue as substrate, thereby they may affect the metabolism and destroy the micro-structure of the tissue [10].

A variety of L-formations, such as spherical bodies and filamentous structures have been often observed by us during the cultivation of blood. However, it appears that these formations remain usually unrecognized by other researchers due to misunderstandings of the L-morphological cycle. It can be hypothesized that L-forms, due to their unusual physiology, are able to atypically modulate the host response to chronic infections and cancer. It has been found that excess of cytoplasmic membranes, produced by L-forms, is important for their prolifera-

tion [32]. Since phospholipids are a major component of all cell membranes and given that they are related to the cell transformation and tumor progression [33], we can assume that the overproduction of membranes by L-forms may also contribute to these processes. Thus, overproduction of cytoplasmic membranes by L-forms may aberrantly affect their interactions with host cells, particularly in key cellular processes such as signaling pathways, proliferation and differentiation, which may be linked to malignazion process.

Our recent L-form studies let us suggest that L-forms (cell wall-deficient variants of bacteria and fungi) are possible inducers of chronic infections, autoimmune diseases or cancer [1] [2] [6] [7]. The atypical behavior of L-forms in the human body extends far beyond the usual/known microbe-host interactions, and only a thorough study of these processes can shed light on their contribution as cancer-promoting factors.

4. Conclusion

The common feature found for the three cancer patients was the isolation from the blood of highly associated communities consisting of morphologically indistinguishable L-bodies, which through reversion in broth, were identified as distinct bacterial and fungal species. Unlike classic bacteria or fungi causing sepsis and bacteremia/fungemia, the presence of L-forms in blood is hidden; it does not demonstrate clinical signs nor can it be detected by conventional methods. It should be noted, however, that the dysbiotic blood microbiota shows unique and individual characteristics for the concrete cancer patient, without finding the same "cancer-specific" microbial species in all three patients. It correlates to the common state of the organism and tumor localization in the body, as well as it outlines the cancer promoting role of L-forms in processes of malignization, cancer genesis and progression.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Markova, N. (2017) L-Form Bacteria Cohabitants in Human Blood: Significance for Health and Diseases. *Discovery Medicine*, **128**, 305-313.

[2] Markova, N. (2020) Eubiotic vs. Dysbiotic Human Blood Microbiota: The Phenomenon of Cell Wall Deficiency and Disease-Trigger Potential of Bacterial and Fungal L-Forms. *Discovery Medicine*, **156**, 17-26.

[3] Markova, N., Slavchev, G. and Michailova, L. (2015) Presence of Mycobacterial L-Forms in Human Blood: Challenge of BCG Vaccination. *Human Vaccines & Immunotherapeutics*, **11**, 1192-1200. https://doi.org/10.1080/21645515.2015.1016682

[4] Markova, N., Slavchev, G., Djerov, L., Nikolov, A. and Dimova, T. (2016) Mycobacterial L-Forms Are Found in Cord Blood: A Potential Vertical Transmission of BCG from Vaccinated Mothers. *Human Vaccines & Immunotherapeutics*, **12**, 2565-2571. https://doi.org/10.1080/21645515.2016.1193658

[5] Dimova, T., Terzieva, A., Djerov, L., Dimitrova, V., Nikolov, A., Grozdanov, P. and Markova, N. (2017) Mother-to-Newborn Transmission of Mycobacterial L-Forms and Vδ2 T-Cell Response in Placentobiome of BCG-Vaccinated Pregnant Women. *Scientific Reports*, **7**, Article No. 17366. https://doi.org/10.1038/s41598-017-17644-z

[6] Markova, N. (2019) Dysbiotic Microbiota in Autistic Children and Their Mothers: Persistence of Fungal and Bacterial Wall-Deficient L-Form Variants in Blood. *Scientific Reports*, **9**, Article No. 13401. https://doi.org/10.1038/s41598-019-49768-9

[7] Markova, N. (2021) Novel Approach to Microbiological Study of Chronic Inflammations at Upper Respiratory Tract: Research of Blood L-Form. Microbiota. *Open Journal of Medical Microbiology*, **11**, 144-156. https://doi.org/10.4236/ojmm.2021.113012

[8] Cantwell, A.R. and Kelso, D.W. (1981) Microbial Findings in Cancers of the Breast and in Their Metastases to the Skin. *The Journal of Dermatologic Surgery and Oncology*, **7**, 483-491. https://doi.org/10.1111/j.1524-4725.1981.tb00682.x

[9] Hess, D. (2000) Can Bacteria Cause Cancer? Alternative Medicine Confronts Big Science. NYU Press, New York.

[10] Enby, E.O.H. and Chouhan, R.S. (2002) Microorganisms in Blood and Tumor Tissue from Patients with Malignancies of Breast or Genital Tract. 1994-2002. Nordisk Medicinkonsult AB, Göteborg.

[11] O'Byrne, K.J. and Dalgleish, A.G. (2001) Chronic Immune Activation and Inflammation as the Cause of Malignancy. *British Journal of Cancer*, **85**, 473-483. https://doi.org/10.1054/bjoc.2001.1943

[12] Garrett, W.S. (2015) Cancer and the Microbiota. *Science*, **348**, 80-86. https://doi.org/10.1126/science.aaa4972

[13] Bagheri, Z., Moeinzadeh, L. and Razmkhah, M. (2022) Roles of Microbiota in Cancer: From Tumor Development to Treatment. *Journal of Oncology*, **2022**, Article ID 3845104. https://doi.org/10.1155/2022/3845104

[14] Grivennikov, S.I., Greten, F.R. and Karin, M. (2010) Immunity, Inflammation, and Cancer. *Cell*, **140**, 883-899. https://doi.org/10.1016/j.cell.2010.01.025

[15] Li, W.T., Iyangar, A.S., Reddy, R., Chakladar, J., Bhargava, V., Sakamoto, K., Ongkeko, W.M. and Rajasekaran, M. (2021) The Bladder Microbiome Is Associated with Epithelial-Mesenchymal Transition in Muscle Invasive Urothelial Bladder Carcinoma. *Cancers*, **13**, 3649. https://doi.org/10.3390/cancers13153649

[16] Hussein, A.A., Elsayed, A.S., Durrani, M. Jing, Z., Iqbal, U., Gomez, E.C., Singh, P.K., Liu, S., Smith, G., Tang, L., *et al.* (2021) Investigating the Association between the Urinary Microbiome and Bladder Cancer: An Exploratory Study. *Urologic Oncology*, **39**, 370.e9-370.e19. https://doi.org/10.1016/j.urolonc.2020.12.011

[17] Gnanasekar, A., Castaneda, G., Iyangar, A., Magesh, S., Perez, D., Chakladar, J., Li, W.T., Bouvet, M., Chang, E.Y. and Ongkeko, W.M. (2021) The Intratumor Microbiome Predicts Prognosis across Gender and Subtypes in Papillary Thyroid Carcinoma. *Computational and Structural Biotechnology Journal*, **19**, 1986-1997. https://doi.org/10.1016/j.csbj.2021.03.032

[18] Chakladar, J., Kuo, S.Z., Castaneda, G., Li, W.T., Gnanasekar, A., Yu, M.A., Chang, E.Y., Wang, X.Q. and Ongkeko, W.M. (2020) The Pancreatic Microbiome Is Associated with Carcinogenesis and Worse Prognosis in Males and Smokers. *Cancers*, **12**, 2672. https://doi.org/10.3390/cancers12092672

[19] Singhal, N., Kumar, M., Kanaujia, P.K. and Virdi, J.S. (2015) MALDI-TOF Mass Spectrometry: An Emerging Technology for Microbial Identification and Diagnosis.

Frontiers Microbiology, **6**, Article No. 791.
https://doi.org/10.3389/fmicb.2015.00791

[20] Saadat, F., Zomorodian, K., Pezeshki, M., Rezaie, S. and Khorramizadeh, M.R. (2004) Inhibitory Effect of *Aspergillus fumigatus* Extract on Matrix Metalloproteinases Expression. *Mycopathologia*, **158**, 33-37.
https://doi.org/10.1023/B:MYCO.0000038429.46699.ac

[21] Thiery, J.P. (2002) Epithelial-Mesenchymal Transitions in Tumour Progression. *Nature Reviews Cancer*, **2**, 442-454. https://doi.org/10.1038/nrc822

[22] Martin, M.D. and Matrisian, L.M. (2007) The Other Side of MMPs: Protective Roles in Tumor Progression. *Cancer and Metastasis Reviews*, **26**, 717-724.
https://doi.org/10.1007/s10555-007-9089-4

[23] Tena, D. and Fernández, C. (2015) *Pseudomonas oryzihabitans*: An Unusual Cause of Skin and Soft Tissue Infection. *Infectious Diseases* (*London*), **47**, 820-824.

[24] Susan, A., Wang, J.I., Tokars, P.J., Bianchine, L.A., Carson, M.J., Arduino, A.L., Smith, N.C., Hansen, E.A., Fitzgerald, J.S. and Epstein, W.R.J. (2000) *Enterobacter cloacae* Bloodstream Infections Traced to Contaminated Human Albumin. *Clinical Infectious Diseases*, **30**, 35-40. https://doi.org/10.1086/313585

[25] de Ruiter, G.A., Smid, P., van der Lugt, A.W., van Boom, J.H., Notermans, S.H.W. and Rombouts, F.M. (1991) Immunogenic Extracellular Polysaccharides of Mucorales. In: Latgé, J.P. and Boucias, D., Eds., *Fungal Cell Wall and Immune Response*, NATO ASI Series, Vol. 53, Springer, Berlin, 169-180.
https://doi.org/10.1007/978-3-642-76074-7_13

[26] Simona, Z., Ondřej, H., Jana, P., Patrik, M., Jana, V., Magdaléna, R., Dagmar, H. and Helena, K. (2018) Occurrence and Antibiotic Resistance of Enterobacteriaceae in Acute Leukemia Patients. *Klinicka Onkologie*, **31**, 282-288.
https://doi.org/10.14735/amko2018282

[27] Botterel, F., Angebault, C., Cabaret, O., Stressmann, F.A., Costa, J.M., Wallet, F., Wallaert, B., Bruce, K. and Delhaes, L. (2018) Fungal and Bacterial Diversity of Airway Microbiota in Adults with Cystic Fibrosis: Concordance between Conventional Methods and Ultra-Deep Sequencing, and Their Practical Use in the Clinical Laboratory. *Mycopathologia*, **183**, 171-183.
https://doi.org/10.1007/s11046-017-0185-x

[28] Charlson, E.S., Diamond, J.M., Bittinger, K., Fitzgerald, A.S., Yadav, A., Haas, A.R., Bushman, F.D. and Collman, R.G. (2012) Lung-Enriched Organisms and Aberrant Bacterial and Fungal Respiratory Microbiota after Lung Transplant. *American Journal of Respiratory and Critical Care Medicine*, **186**, 536-545.
https://doi.org/10.1164/rccm.201204-0693OC

[29] Hoarau, G., Mukherjee, P.K., Gower-Rousseau, C., Hager, C., Chandra, J., Retuerto, M.A., Neut, C., Vermeire, S., Clemente, J., Colombel, J.F. and Fujioka, H. (2016) Bacteriome and Mycobiome Interactions under Score Microbial Dysbiosis in Familial Crohn's Disease. *MBio*, **7**, e01250-16. https://doi.org/10.1128/mBio.01250-16

[30] Jurdi, N.E., Filali-Mouhim, A., Salem, I., Retuerto, M., Dambrosio, N.M., Baer, L., Lazarus, H.M., Caimi, P., Cooper, B., Tomlinson, B., Metheny, L., Malek, E., Otegbeye, F., Sekaly, R.P., Ghannoum, M. and de Lima, M. (2019) Gastrointestinal Microbiome and Mycobiome Changes during Autologous Transplantation for Multiple Myeloma: Results of a Prospective Pilot Study. *Biology of Blood and Marrow Transplantation*, **8**, 1511-1519. https://doi.org/10.1016/j.bbmt.2019.04.007

[31] Vesty, A., Gear, K., Biswas, K., Radcliff, F.J., Taylor, M.W. and Douglas, R.G. (2018) Microbial and Inflammatory-Based Salivary Biomarkers of Head and Neck Squam-

ous Cell Carcinoma. *Clinical and Experimental Dental Research*, **4**, 255-262. https://doi.org/10.1002/cre2.139

[32] Errington, J., Mickiewicz, K., Kawai and Wu, L.J. (2016) L-Form Bacteria, Chronic Diseases and the Origins of Life. *Philosophical Transactions of the Royal Society B*, **371**, Article ID: 20150494. https://doi.org/10.1098/rstb.2015.0494

[33] Cheng, M., Bhujwalla, Z.M. and Glunde, K. (2016) Targeting Phospholipid Metabolism in Cancer. *Frontiers in Oncology*, **6**, Article No. 266. https://doi.org/10.3389/fonc.2016.00266