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Cancer and the Metaorganism

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Conflicts of interest: LZ has held research contracts with Glaxo Smyth Kline, Incyte, Lytix, Kaleido, Innovate Pharma, Daiichi Sankyo, Pilege, Merus, Transgene, 9 m, Tusk and Roche, was on the on the Board of Directors of Transgene, is a cofounder of everImmune, and holds patents covering the treatment of cancer and the therapeutic manipulation of the microbiota. GK has been holding research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Tollys, and Vascage. GK is on the Board of Directors of the Bristol Myers Squibb Foundation France. GK is a scientific cofounder of everImmune, Osasuna Therapeutics, Samsara Therapeutics and Therafast Bio. GK is in the scientific advisory boards of Hevolution, Institut Servier, Longevity Vision Funds and Rejuvenon Life Sciences. GK is the inventor of patents covering therapeutic targeting of aging, cancer, cystic fibrosis and metabolic disorders. GK's brother, Romano Kroemer, was an employee of Sanofi and now consults for Boehringer-Ingelheim. The funders had no role in the design of the study; in the writing of the manuscript, or in the decision to publish the results.

Summary

Pathogenic shifts in the gut microbiota are part of the 'ecological' alterations that accompany tumor progression and compromise immunosurveillance. The future management of health and disease including cancer will rely on the diagnosis of such shifts and their therapeutic correction by general or personalized strategies, hence restoring metaorganismal homeostasis.

Introduction

The holobiont or metaorganism is composed by a compendium of host cells and an approximately ten-fold higher number of microbial cells that are mostly contained in the gut but are also found in other (e.g. respiratory and genito-urinary) tracts, on the body surface, and – mostly in a pathological context – extopically in tissues as well (**Fig. 1A**). The maintenance of organismal health relies on the integrity of the gut barrier and the spatial and temporary containment of perturbations affecting this organ ¹. Approximately 200 square meters of a thin layer composed by the lamina propria, epithelial cells and mucus separate – and simultaneously integrate – the two components of the metaorganism, i.e., the human host and the intestinal flora. The gut microbiota is characterized by the stunning diversity of thousands of bacterial species (which are well studied) but also fungi, viruses, parasites, archaea and candidate phyla radiation (which all are barely explored) ² (**Fig. 1A**). Organismal health is associated with a richly diverse but stable, balanced microbial ecosystem (a state known as eubiosis) preferentially containing favorable commensals that fulfill their functions in the gut (such as digestion of complex molecules and generation of micronutrients including vitamins of the B series and polyamines), and elimination of the pathogens without compromising the intestinal barrier, thus avoiding local and systemic inflammation as well as pathogenic immune responses against food allergens ².

In contrast to health-associated eubiosis, aging and age-associated diseases including cancer are associated with dysbiosis, a state of reduced in ecological diversity coupled with an increased abundance of harmful (pro-inflammatory, potentially invasive and/or oncogenic) microbes and a corresponding reduction of useful commensals. Dysbiosis appears to be a common hallmark - or "meta-hallmark" - of both aging and cancer ³. Many of the harmful bacteria that can be identified by metagenomic shotgun sequencing of fecal material as cancer-associated are found across an entire spectrum of age-associated diseases. Such diseases include a variety of cancer types as well as other conditions including autoimmune, cardiovascular, gastrointestinal, inflammatory, neurological and metabolic diseases ^{4,5}

In this commentary, we will discuss the mechanisms tying dysbiosis to disabled cancer immunosurveillance and develop our vision on the future diagnosis and treatment of dysbiosis.

From correlation to mechanisms

The cause-effect relationship between cancer and dysbiosis is likely bidirectional. Preclinical experiments indicate that subcutaneously inoculated, barely detectable cancers can precipitate alterations in the autonomous nervous system of the gut with an increase in beta-adrenergic signaling and a reduction of vagal cholinergic input combined to induce transient epithelial barrier permeability that culminates in long-lasting dysbiosis dominated by Gram-positive species of the *Enterocloster* genus ⁶. The resulting 'stress ileopathy' (which is accompanied by villous atrophy, apoptosis of ileal crypt cells, ectopic proliferation of tyrosine hydroxylase expressing enteroendocrine cells, villus vasoconstriction, as well as a dysbalance between sympathetic and cholinergic signaling) is non-specific in thus far that it is also observed in non-malignant diseases, suggesting that such histopathological and functional perturbations of the gut constitute a general feature of various pathologies ¹. Importantly, pharmacological blockade of beta-adrenergic receptors has a broad positive impact on the outcome of cancer treatments. Whether such an effect is secondary to the resolution of stress ileopathy is suggested by mouse experiments ⁶, yet awaits further clarification in human studies.

Conversely, there is ample evidence that dysbiosis subverts cancer immunosurveillance. Thus, both in laboratory mice and patients with cancer, treatment with broad-spectrum antibiotics causes dysbiosis and reduces the efficacy of immune checkpoint inhibitors (ICIs) targeting PD-1 or PD-L1 ⁷ or that of adoptive CAR-T cell transfer ⁸. Moreover, fecal microbial transplantation (FMT) from healthy subjects in a state of eubiosis improves the response of cancers evolving in antibiotic-treated mice and that of melanoma patients to PD-1 blockade ^{7,9}. Clinical responses correlate with long-term engraftment of the donor microbiota and an increased abundance of favorable bacteria ⁹. These findings point to the possibility of therapeutically intervening on the intestinal microflora for improving the immunological (and overall) fitness of the host, thereby conferring improved control of tumor progression.

Mechanistically, dysbiosis can suppress cancer immunosurveillance by multiple pathways. This ranges from (i) the depletion or malabsorption of micronutrients required for proper immune function (such as vitamins B3 and B5 as well as spermidine); (ii) the lack of microbial-associated molecular patterns (MAMPs, which, by analogy to pathogen- or danger-associated molecular patterns, PAMPs and DAMPS, act on pattern recognition receptors) required for the activation of Toll-like receptors 2 and 4 and the maintenance of an appropriate 'immune tonus'; (iii) depletion of microbes that stimulate cross-reactive anticancer immune responses targeting cancer genome-encoded antigens; (iv) depletion of microbes that translocate into tumors to infect malignant cells, thereby stimulating local immune responses; (v) stimulation of a general pro-inflammatory state with emergency hematopoiesis and neutrophilia (which is one of the worst poor prognosis markers in cancer patients); as well as (vi) long-range perturbations of the immune system caused by reduced thymopoiesis (required for the generation of new T cell repertoires) or (vii) trafficking of immunosuppressive cells from the gut to tumors and tumor-draining lymph nodes. This latter effect is mediated by a perturbation of bile acid metabolism leading to the downregulation of mucosal addressin cell adhesion molecule 1 (MAdCAM-1) on high epithelial venules in ileal Peyer patches. Since MAdCAM-1 is required to retain immunosuppressive T cells expressing the integrin $\alpha 4/\beta 7$ in the gut, loss of MAdCAM-1 expression causes such immunosuppressive cells to be released from the ileum.

$\alpha 4/\beta 7$ -positive regulatory T cells then reach the tumor microenvironment and tumor-draining lymph nodes through the blood stream ¹⁰.

Hence, there are multiple possible connections between dysbiosis and suppressed cancer immunosurveillance, likely reflecting the complex co-evolution of host-pathogen interactions. Theoretically, these connections offer multiple possibilities for therapeutic interventions ranging from (i) supplementation of deficient micronutrients and (ii) pathogen recognition receptor ligands, (iii) provision of specific microbes producing cross-reactive antigens or (iv) translocating into tumors, (v) anti-inflammatory drugs, (vi) thymopoiesis stimulators or (vii) Treg-depleting medications ¹¹. Although all these possibilities have been tested in mice, none of them has been evaluated in dysbiosis-centered clinical trials.

The intricate dual relationship between cancer and dysbiosis (cancer that causes dysbiosis and dysbiosis that disrupts the immune control of cancer) calls for therapeutic countermeasures. Presently, there are two major hurdles for implementing microbiota-centered interventions in routine cancer therapy. First, there are no rapid methods for diagnosing dysbiosis and hence to define the patient population in need of restoring eubiosis. At this point, protocols for sampling and conserving stools, extracting DNA, sequencing and bioinformatic analyses are not rigorously standardized and typically require more than two months to yield results, which is incompatible with clinical practice. Second, there are major problems in the implementation of dietary interventions (due to the reluctance of most individuals to accept long-lasting changes in their lifestyle) and FMT (due to potential safety issues and a clear problem of scalability), calling for alternative methods for the treatment of dysbiosis.

Future diagnostic procedures for the detection of dysbiosis.

Rapid and cost-effective dysbiosis diagnosis tools are being developed (**Fig. 1B**). This includes the use of 'smart toilets' for sampling stools, standardized low-cost stool conservation and DNA extraction kits, robotized metagenomic sequencing instruments, as well as universally applicable software packages for automated bioinformatics analyses. Accumulated knowledge on the functional role of individual bacterial species, as well as the topological analysis of co-occurrence networks, may be used to dissect the ecological properties of the microbiota and distinguish positive (useful/immunostimulatory/anti-inflammatory/tumor suppressive) and negative (harmful/immunosuppressive/pro-inflammatory/pro-carcinogenic) species, attributing each of them a score. The ratio between positive and negative scores then yields a combined score ('toposcore') that distinguishes eubiosis and dysbiosis ¹². Alternatively, it might be attempted to reduce the high dimensionality of the microbiota to a few species representative of eubiosis and dysbiosis and then to determine their presence and abundance in stool samples by polymerase chain reaction (PCR). Although this latter procedure might reduce timelines and costs, it would be incompatible with metagenomic data prospection for the future optimization of the bioinformatic pipeline. Indeed, it cannot be excluded that the generation of ever-more-refined reference databases will offer alternatives to the species-centered approach, for instance by focusing on functionalities such as microbiota-encoded metabolic, immunogenic or inflammation-relevant modules that then could be analyzed in a taxonomy-agnostic fashion.

Uncertainties that must be solved by exploring large cohorts of patients across countries, as well across medical and oncological specialties, regard the following questions: (i) Can dysbiosis be defined across different geographic regions and social strata with rather disparate dietary habits, using the same algorithm? (ii) Is there only one universal dysbiosis or are there taxonomically and functionally different types of dysbiosis that are associated with distinct pathologies? An affirmative answer to question No. 1 would lead to the broad implementation of dysbiosis diagnoses, calling for the identification of universal features of gut health. In contrast, the identification of specific disease-associated biomarkers in the context of question No. 2 may greatly facilitate the personalization of gut microbiota-centered treatments. (iii) Is it possible to gain additional insights into the gut microbiota by non-genetic methods including mass spectrometric analyses of microbial proteins, riboproteins, lipoproteins, membrane lipids and liposaccharides or metabolites? (iv) Do host-specific parameters that respond to dysbiosis, such as biomarkers of gut permeabilization and systemic inflammation, circulating soluble MAdCAM-1 protein (which is a proxy of ileal MAdCAM-1 expression) or ileum-derived suppressive T cells¹⁰, provide useful complementary information? Would such host-centered biomarkers constitute a diagnostic alternative to the in-depth examination of the microbiota? (v) Finally, does the diagnosis of dysbiosis in an otherwise apparently healthy individual predict the imminent diagnosis of cancer or other age-related diseases, hence justifying preemptive measures to intercept the threat? This latter question has important implications because a sizeable fraction of undiseased controls, approaching 20% of healthy (?) volunteers, do exhibit features of dysbiosis^{2,5,7}.

Future microbiota-centered therapeutic interventions

Several ongoing clinical trials explore the utility of FMT for oncological indications, mostly in the context of ICIs. If successful, these trials will spur additional interest in microbiota-centered therapies, inform on optimal administration routes, useful shifts in the intestinal ecosystem that improve ICI activity, as well as on donor/recipient compatibility with respect to gastrointestinal or systemic toxicities.

However, we predict that FMT will be gradually replaced by alternative approaches (**Fig. 1B**): (i) Complex fecal-like ecosystems might be manufactured in specialized bioreactors resembling artificial guts, hence avoiding the use of primary fecal material. (ii) More likely, polyclonal consortia of favorable bacteria could be generated by admixing individual strains that have been cultured separately, hence facilitating standardization and quality control. If administered to individuals that have pretreated with combinations of broad-spectrum antibiotics, such artificial microbiota could be used to replace/reset the gut microflora. (iii) Individual bacterial strains could be orally administered after their lyophilization (or sporulation) and encapsulation, hoping that such monoclonal probiotics can induce durable ecological changes in the gut microbiota and the immune system. As a proof-of-concept, a randomized Phase I trial demonstrated that oral administration of a specific *Clostridium butyricum* strain extends progression-free survival in patients with metastatic renal cell carcinoma treated with ICIs¹³. (iv) Theoretically, the efficacy of monoclonal probiotics could be boosted by genetic engineering, for instance to enhance the production of immunostimulatory metabolites (such as arginine or spermidine), pattern recognition ligands (such as ligands of Toll-like receptor-2) or antigens that elicit immune responses crossreacting

with tumor-associated antigens. However, in countries that currently ban the commercial use of genetically modified organisms, regulatory hurdles may impede any progress of this kind.

As an alternative to live bacteria, which admittedly bear an intrinsic biosafety risk, several approaches may be considered. (i) In specific cases, heat-inactivated (pasteurized) bacteria conserve biological activity, as this has been demonstrated for the antidiabetic effects of *Akkermansia muciniphila*¹⁴. However, it is not yet clear whether the anticancer activity of another *Akkermansia* strain, *A. massiliensis*, or that of *Clostridium butyricum* would be maintained after pasteurization. (ii) Prebiotics may stimulate the expansion of useful bacteria, as this has been suggested for purified fibers. (iii) On theoretical grounds, specific antibiotics may eliminate harmful bacteria but phages or vaccines against pathobionts should be developed for the targeted elimination of such bacteria (iv) Moreover, so-called postbiotics representing bacterial products including specific bacterial metabolites (such as short chain fatty acids, vitamins B3, B5 and B12 or spermidine) and MAMPs may be administered with the scope of reinvigorating anticancer immune responses. (v) Finally, therapeutic agents that we suggest to call 'past-postbiotics' could be administered to ameliorate the host response to dysbiosis, for instance by enhancing intestinal barrier function, by preventing the downregulation of MAdCAM-1, or by corrective interventions on the metabolic, inflammatory and immune systems. It can be theorized, but remains to be proven, that such past-postbiotics (such as biliary salts upregulating MAdCAM-1) break the vicious cycle that locks the holobiont in a dysbiotic state^{1,3}.

Hence, it is possible that life biotherapeutics will be progressively replaced by a more classical pharmacological approach in which chemically defined molecular entities are administered in the form of anti-, pre-, post- and past-postbiotics to obtain therapeutic effects. Possibly, (part of) this armamentarium will be deployed in the form of combination treatments.

Universal *versus* personalized treatments and a perspective

The view that dysbiosis occurs in a uniform fashion is likely an oversimplification. Depending on additional insights from large biomarker discovery campaigns that explore both the microbiota and the host by complementary 'omics' technologies (genomics, epigenomics, transcriptomics, proteomics, lipidomics, metabolomics, immunomics etc.), it is possible that several different types of dysbiosis will be discovered (**Fig. 1B**). As an example, it appears that both the absence and the excess of *Akkermansia* species in the gut flora has a negative prognostic impact on anti-PD-1 responses of non-small cell lung cancer patients, suggesting the existence of at least two variants of dysbiosis¹⁵. Whether such disparities reflect different starting points (such as distinct initial pre-disease ecosystems) or distinct trajectories leading to dysbiosis remains to be determined.

Irrespective of the precise etiology of these variations, they probably will impact the development of microbiota-centered interventions. In the aforementioned example, supplementation with *Akkermansia* should only be envisaged for those patients who lack this genus in the gut, not for those who carry an excess of *Akkermansia* species. However, it is still possible that the total replacement/resetting of the microbiota by FMT or polyclonal

probiotics, as well as treatment with post- or past-postbiotics would have a general positive impact on dysbiotic individuals, irrespective of the abundance of individual bacterial strains.

Hence, one of the most important questions arising in the field is whether universal treatment strategies of dysbiosis can be implemented or whether different types of dysbiosis will require individually tailored therapeutic interventions.

Regardless of the answer, it appears clear that the vision of cancer as a disease composed by the primary tumor and its metastases is a non sequitur. Even the consideration that tumors contain immune effectors and potentially disease-relevant microbes neglects the importance of the entire metaorganism for the development, progression and therapeutic response of neoplasia. The discovery of the gut microbiota as a major modulator of cancer immunosurveillance invites us to consider cancer as a systemic disease of the meta-organism. In this context, we are witnessing the dawn of a new ‘ecological’ era of oncology that will transcend the tumor-centric and immunological visions of cancer, giving way to the exploration of its metabolic, neuroendocrine and vascular connections to the holobiont. We anticipate that the conquest of this terra incognita will inaugurate the upcoming revolution(s) in the prevention and treatment of neoplasia. Future prophylactic and therapeutic interventions on cancer will rely on the restoration of metaorganismal homeostasis.

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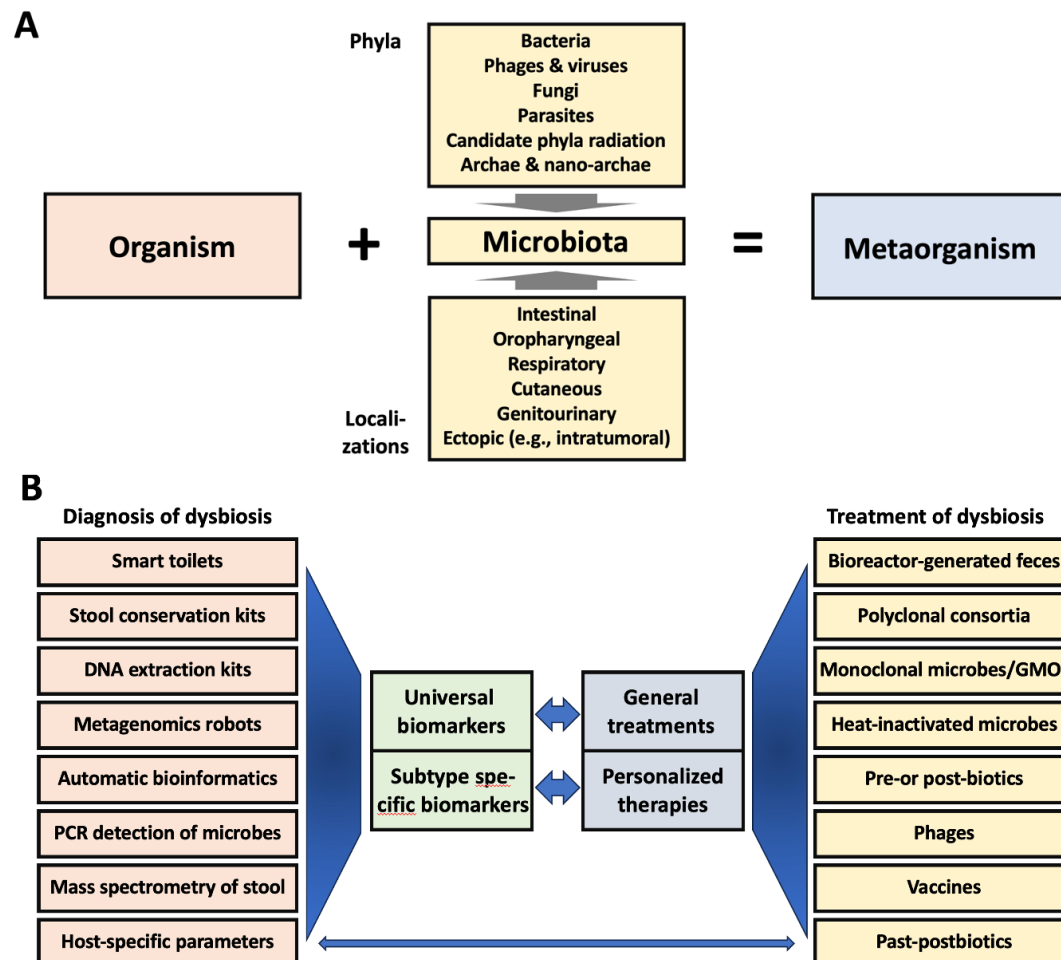


Figure 1: Metaorganism and cancer.

A. Definition of the metaorganism. The metaorganism is the compendium of the organism and its microbiota with its distinct phyla and anatomical localizations.

B. Diagnosis and treatment of cancer-relevant dysbiosis. A standardized arsenal of methods will be deployed to detect metagenomic alterations in the feces (or intestinal content sampled by intelligent capsules), detect individual species by polymerase chain reactions (PCR), use non-genomic ‘omics’ technologies that can be based on mass spectrometry or detect host parameters affected by the microbiota (such as plasma proteins modified by dysbiosis, intestinal permeabilization and inflammation). These methods will yield universal biomarkers of dysbiosis and/or dysbiosis subtype-specific biomarkers that then require general and/or personalized corrective measures, respectively. Potential treatments of dysbiosis include bioreactor-made feces-like material, standardized polyclonal consortia, monoclonal microbes (that can be genetically modified organisms, GMOs), microbes that are heat-inactivated microbes (or rendered replication-deficient by other methods), as well as prebiotics (to expand useful microbes), phages, vaccines against pathobionts or low-spectrum antibiotics (to eliminate harmful microbes), postbiotics (which are microbial products) and past-postbiotics (which mimic the beneficial effects of eubiosis on the host). The use of these later agents may be specifically influenced by the quantification of host-derived biomarkers.