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Recognizing that the microbiome is part of the human immune system will advance treatment of both cancer and infections

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We propose that it is time to rethink the components of human immunity and recognize that some microbes that reside within the skin¹ are necessary to maintain immune homeostasis. These microbial cells should therefore be considered not as foreign organisms that can cause infections, but an essential part of ourselves. This is a radical change in the definition of “self” and reflects advances in technology that are driving a new paradigm shift in medicine.² The influx of information that has come from the field of “microbiome” research suggests now that the human body is a superorganism, dependent both on the cells that originated from the zygote, and on microbial cells that are inherited and exchanged with our environment.³ Recognition that microbial cells are essential for certain functions of the human superorganism has consequences for dermatology that is a radical advance from the classic germ theory of disease as formulated by Semmelweis in 1847. It is time to reconsider: what are the relevant cellular components of human skin?

An example of the consequences of perceiving some specific microbes as an integral part of self can be seen if one considers the parallels between cancer and infection. Cancer has been perceived as an intrinsic problem of body homeostasis. In contrast, infection has been considered a problem from the external environment. As our understanding of effective treatment techniques for both cancer and infectious disease have expanded, the pathways that lead to infection and cancer have converged. For example, cancer arises as uncontrolled cell growth and tissue destruction, a characteristic shared by infections. In the classic model of infection bacterial organisms create disease through invasion, evasion, and aggression.⁴ It is apparent that for this bacterial expansion to take place the ecology (host immune defense system) must be permissive. Less apparent imbalances of the microbial community are referred to as “dysbiosis,”⁵ and have been identified as contributing to the development or progression of a number of human conditions.⁶ Dysbiosis may not be observed until an

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alteration in environment allows for uncontrolled growth of the pathological organism. The key is that these organisms generally exist as a small fraction of the larger microbiome and that disruption of homeostasis allows for pathological bacterial expansion we think of as “infection.” An excellent example of the immunologic consequences of dysbiosis is seen in patients with atopic dermatitis. It has become apparent that the abnormal abundance of *Staphylococci* on the skin exacerbates allergic inflammation.⁷ In a similar fashion premalignant transformation occurs commonly in human beings but is not always “cancer.” Spontaneous regression is regularly seen in infants with localized neuroblastoma⁸ and the majority of premalignant changes are likely not diagnosed and are self-limited. Is premalignant cell behavior a mirror of microbial dysbiosis? Should infection, like cancer, be perceived as a lack of regulation of the important cells in our superorganism that happen to be microbes? The answer to these questions are “yes” if we consider the following examples.

Virchow⁹ originally made the connection between inflammation and malignancy, noting the presence of leukocytes in neoplastic tissue. It has been noted that chronic inflammation can predispose to carcinogenesis, made evident in the association of chronic intestinal or gastric inflammation with the development of colorectal cancers.¹⁰ Inflammation both affects cells by making them prone to cancerous transformation through genetic mutation and chromosomal instability, and by driving the final progression to malignancy. Normal healthy cells experience uncontrolled growth in a permissive environment through loss of homeostasis, resulting in neoplastic growth by intrinsic cellular dysregulation and immunologic impairment, a process akin to the acquisition of virulence factors observed in bacterial infection. Immunosuppressive therapies applied to patients receiving organ transplants are well known to increase the risk of both cancer and infection. Therefore, rather than being distinct entities, “cancer” and “infection” are better defined as uncontrolled growth of cells within the human superorganism. Some microbes (but not all) are as integral to the body as lymphocytes or neutrophils. A future key challenge for microbiome research is to identify these important strains and species of microbes.

Why bother redefining self as a superorganism? Evidence for the importance of this perspective can be seen from observations that successful approaches for treating neoplasms and treating infections have converged. Chemotherapy regimens incorporate multiple medications as the standard of care to manage drug resistance, whereas in infectious disease a bacterial strain’s susceptibility pattern directs antibiotic selection but is often best treated by combining multiple antibiotics. Historically this difference in drug management has arisen largely as a result of the time involved: bacteria can be rapidly cultured in vitro and rapidly treated before the development of intrinsic resistance. A prominent exception is *Mycobacterium tuberculosis*, which is more difficult to treat and requires a longer course of treatment more consistent with the time scale of oncologic treatments. Tuberculosis requires multidrug therapy, similar to chemotherapy regimens, and surveillance for the development of resistance. Conversely, genomic tests that detect genetic variations in tumors can identify particular drug vulnerabilities and therefore guide chemotherapy selection. Selecting medications based on susceptibility testing is remarkably similar, in principle, to antibiotic resistance testing. Lastly, the expansion in immunologics for the treatment of both cancers and infectious diseases is changing the way many diseases are treated. An excellent example

of this is the use of coinhibitory receptor programmed death 1 (PD-1)-blocking monoclonal antibodies being used as effective treatments for simian immunodeficiency virus (SIV) in macaques,^{11,12} and their use on solid tumors such as melanoma (nivolumab and pembrolizumab) and non-small-cell lung cancer in human beings.^{13,14} A further step in understanding this effect may come from a recent observation that the effectiveness of PD-1 blockade appears to depend on the *Bacteroides* species in the gut.¹⁵ These results suggest that the microbial elements of “self” that reside in the intestine are required for maintaining an immunologic milieu that can effectively kill tumors once cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade is achieved.

As management of infectious and oncologic diseases converge, and as we discover that our microbiome not only affects us but is in fact “us,” the line between infection and neoplasm blurs. A reclassification of disease could improve understanding and management. Disease can be called infection or cancer, but is better understood if one considers the origin of the dysregulated cell type (Table I). Extrinsic disease (infection) would incorporate diseases from microbes that are clearly not native normal human flora such as cholera, brucellosis, and bubonic plague. These can be either of prokaryotic or eukaryotic origin. The category of some intrinsic disease (eg, cancer) could also encompass infections from overgrowth of normal microbial flora such as staphylococcal infection or *Clostridium difficile* colitis, or uncontrolled cell growth seen in classic malignancies. This new system of classification would encourage enhanced collaboration across traditionally distinct disciplines such as microbiology, immunology, and oncology to allow for management techniques from these various disciplines to be unified. Advances in genomics and microbiology are creating seemingly greater divisions and compartmentalization of science but there is an opportunity now for simpler classification and greater unity in management.

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Table I

Examples of infection or malignancy are better seen as extrinsic or intrinsic disease

	Intrinsic	Extrinsic
Prokaryotic	Staphylococcal cellulitis <i>Clostridium difficile</i> colitis	Cholera Brucellosis Bubonic plague
Eukaryotic	Cancer	Ascaris Balamuthia