PROSPECTIVE

Tissue-Specific Immunoregulation: A Call for Better Understanding of the “Immunostat” in the Context of Cancer

William Pao1, Chia-Huey Ooi1, Fabian Birzele1, Astrid Ruefli-Brasse1, Michael A. Cannarile2, Bernhard Reis3, Sebastian H. Scharf3, David A. Schubert1, Klas Hatje1, Nadege Pelletier1, Olivia Spleiss1, and John C. Reed4

Summary: Checkpoint inhibitor therapy has been a breakthrough in cancer research, but only some patients with cancer derive substantial benefit. Although mechanisms underlying sensitivity and resistance to checkpoint inhibitors are being elucidated, the importance of organ-specific regulation of immunity is currently underappreciated. Here, we call for a greater understanding of tissue-specific immunoregulation, namely, “tissue-specific immunostats,” to make advances in treatments for cancer. A better understanding of how individual organs at baseline regulate the immune system could enable an improved precision medicine approach to cancer immunotherapy. Cancer Discov; 8(4): 395–402. ©2018 AACR.

INTRODUCTION

One of the most remarkable accomplishments in the history of cancer research has been the recent demonstration that patients with metastatic cancer can live for years after treatment with immunotherapy. A significant number of patients with metastatic melanoma or lung cancer treated with the main type of immunotherapy—anti–PD-(L)1 checkpoint inhibitor (CPI) antibodies—have achieved at least 5-year overall survival (1, 2). Such long-term survival was rarely seen in these diseases with previous forms of anticancer treatment, including chemotherapy and targeted therapies. Patients with other cancers, including bladder cancer, renal cell carcinoma, head and neck cancer, Merkel cell carcinoma, and gastric cancer, also derive benefit from CPIs (3). Despite this progress, however, only ∼10% to 15% of patients experience at least a partial response to monotherapy, and even fewer achieve durable clinical benefit (4). Thus, a major objective in the field of oncology is to develop new therapies that broaden or deepen the benefit of cancer immunotherapy (CIT).

Another important goal is to define with greater precision who will and who will not benefit from CIT.

Currently, a complete mechanistic understanding of CIT-induced antitumor responses remains to be elucidated. From the immune system perspective, those patients most likely to benefit have preexisting adaptive T-cell immunity (5) and an immune set point (reviewed in ref. 5) most likely contributes to the magnitude of antitumor control. From the tumor cell perspective, those patients most likely to benefit appear to have a higher burden of somatic mutations. A “higher mutational load” is thought to generate a more robust antitumor immune response due to a higher probability of the generation of neoepitopes that facilitate T-cell recognition (8, 9). Consistent with this concept, anti–PD-1 antibodies have recently been approved for the treatment of cancers with microsatellite instability (MSI), a condition of genetic hypermutability that results from impaired DNA mismatch repair (10).

Despite an improved notion of how the immune system can be harnessed to treat cancers, currently the field suffers from an underemphasis on the importance of tissue-specific immunity and how each organ’s immune system may affect cancer development and treatment. Just as cancers arise in different organs and harbor unique genetic features, various organs, such as the skin, blood, and gut, have different immune systems that behave in distinct ways. We hypothesize that such tumor cell–extrinsic differences could alter the sensitivity of certain tumor types to CIT. Here, we emphasize the need for a greater understanding of tissue-specific immune regulation, or what we call “tissue-specific immunostats,” to advance treatments for cancer. Understanding how individual organs at baseline in a healthy environment and in a cancer setting regulate the immune system could enable an improved precision medicine approach to CIT.

DIFFERENT ORGANS GIVE RISE TO CANCERS WITH DISTINCT GENOMIC PROFILES AND SENSITIVITIES TO ANTICANCER THERAPIES

A central dogma of cancers is that they arise in cells of origin from various tissues due to the stepwise accumulation...
of mutations in oncogenes and tumor suppressor genes. Comprehensive DNA profiling of tumors has revealed that even though some overlap exists, the genetics of cancers vary greatly by tumor type and also among individual patients, indicating that cancer is a personal disease of each patient's tumor genome (11). Using tumors that arise from the skin, blood, and gut as reference points, melanomas that arise from melanocytes in the skin display genomic profiles and somatic mutations distinct from leukemias in the blood and colorectal cancers in the gut, respectively [data from The Cancer Genome Atlas (TCGA)]. These differences result in widely divergent therapies for each tumor type, even if key targetable “driver mutations” are shared. More specifically, ~50% of melanomas harbor recurrent BRAF mutations, which are amenable to treatment with BRAF and MEK inhibitors (12), but BRAF mutations are rare in leukemias (with the exception of hairy cell leukemias; ref. 13) and found in only 10% of colorectal cancers (14). Due to intrinsic cell signaling properties in melanomas versus colorectal cancers, the former are highly sensitive to single-agent BRAF inhibitors whereas the latter are not (15). Along the same lines, leukemias harbor recurrent IDH2 and FLT3 mutations, which are rare in melanomas and colorectal cancers. IDH2 and FLT3 inhibitors (enasidinib and midostaurin, respectively) are approved in leukemias but not in the other two cancer types. Finally, colorectal cancers frequently harbor KRAS mutations which are rare in melanomas and leukemias (16). Anti-EGFR antibodies are approved for use in KRAS–wild-type colorectal cancers but not in any melanomas or leukemias. These examples highlight that frequencies of mutational events in tumor cells arising from different organs can dictate the sensitivity or resistance of agents in cancers. What about immune systems? Do they also inherently vary according to site of origin?

THE IMMUNE SYSTEM DIFFERS ACCORDING TO ANATOMIC SITE

The immune system can be thought of as a series of defenses that protect the body against entities recognized as non-self. Pathogens, such as viruses, bacteria, fungi, and parasites, and other immunogens, such as foreign objects, foreign cells, or even cancer cells, induce responses from the immune system. The first defense is anatomic—physical, chemical, and biological barriers that prevent invaders from entering the body. The next level of defense is the innate immune system, which provides an immediate, nonspecific response to invaders. Cells of the innate immune system include natural killer (NK) cells, mast cells, eosinophils, basophils, macrophages, and neutrophils. These cells directly kill, ingest pathogens, or release chemicals that disrupt the ability of pathogens to function or multiply. Finally, specific types of pathogens induce the third level of defense, the adaptive immune system, which provides a long-term, specific response. The adaptive immune system is observed predominately in jawed vertebrates. Cells of the adaptive immune system include T lymphocytes [CD8+ killer T cells, CD4+ helper T cells, regulatory T cells (Treg), including “natural” Tregs that develop in the thymus and “induced” Tregs that arise in the periphery from CD4+ FOXP3+ conventional T cells, etc.], which broadly kill other cells or help induce or regulate a memory response, and B lymphocytes (B cells), which produce antibodies. In the adaptive response, immune cells learn to recognize the antigen specifically; this recognition capability is preserved in the body in the form of “memory” B and T cells, leading to lifelong protection against a pathogen. The next time the body encounters a similar antigen, the adaptive immune system mounts a faster, stronger response because a long-lived pool of T- and/or B-cell clones with specificity for the pathogen continues to circulate and rapidly expands via proliferation upon reengagement with these antigens. Activated immune cells are counterbalanced by Tregs and other immunosuppressive cells, such as myeloid-derived suppressor cells or certain types of macrophages. Another cell type, dendritic cells, links the innate immune system with the adaptive; dendritic cells can directly sense microbial ligands (e.g., Toll-like receptor ligands) but also present antigen to T cells to shape the adaptive immune response.

At a high level, the immune system may be viewed as a single structure that is distributed throughout the body to provide host defense against pathogens wherever these may enter or spread. However, because the types of foreign invaders may vary by anatomic location, the immune system has evolved to customize host defense accordingly. This concept can be illustrated by comparing some key features of the cutaneous, systemic, and mucosal immune systems in the skin, blood, and gut, respectively.

The cutaneous immune system is designed to prevent infection through the skin. In addition to providing a physical barrier to the outside world, the skin is also an active immune organ, comprised of a highly complex network of innate and adaptive immune cells. One feature of the cutaneous immune system is that responses against invading pathogens are usually highly confined. That is, defense at a specific site on the skin is localized and does not result in skin from the entire body becoming involved in the response. Otherwise, a localized skin infection would lead to whole-body desquamation.

The systemic immune system developed to attack infections in blood circulation. Any level of bacterial infection is life-threatening; left unchecked, bacteremia can kill patients within 24 hours. Unlike the cutaneous immune system, the systemic immune response is not localized, per se. A consequence is that the immune response against pathogens in blood can lead to sepsis, hypoperfusion, hypotension, and ultimately severe damage to multiple organs throughout the body in order to clear the infection.

The mucosal immune system prevents infections at thin and permeable sites near the surfaces where most pathogens invade. Mucosal surfaces are located throughout the body at areas of gas exchange (the lungs), food absorption (the gut), sensory activities (eyes, nose, mouth, and throat), and reproduction (uterus and vagina). Like the cutaneous immune system, immune responses induced within one compartment of the mucosal immune system are largely confined to that particular compartment.

The gut mucosal immune system in particular highlights the concept of tissue-specific immunoregulation. The gut acts as a portal of entry to a vast array of foreign antigens in the form of food and food-related organisms. As such, the immune system has evolved mechanisms to avoid a vigorous immune response to food antigens (17) as well as commensal microorganisms (18), while at the same time ensuring detection and killing of pathogenic organisms gaining entry through the gut. If the mucosal immune system were not finely tuned, it would be frequently and nonspecifically activated every time the host...
ingests a meal. Indeed, patients lacking such immunoregulation often suffer from inflammatory bowel disorders (19).

**ORGAN-SPECIFIC IMMUNITY: STUDIES IN MICE**

To illustrate further the concept of organ-specific immune systems, ideally one could cite studies involving comprehensive analyses of multiple organs from humans, but such studies are logistically difficult to conduct and therefore limited (20). By contrast, comprehensive studies on organ-specific differences in immune systems have been conducted in model organisms such as mice. Although mouse models cannot replicate the human immune system, we will briefly refer to mouse data for illustrative purposes. The summarized examples are not meant to constitute an exhaustive review of the field.

**Immune Cell Composition**

Because the immune system has evolved to customize host defense accordingly, the composition of the immune system in different organs is distinct. For example, in one study (21), B cells accounted for slightly more than half of hematopoietic cells in the spleen (representing the systemic immune system) but only about one third in Peyer’s patches (small masses of lymphatic tissue found throughout the ileum region of the small intestine). T cells accounted for one third of the cells in spleen versus two thirds in Peyer’s patches. The percentage of cells positive for CD4 was one fifth in spleen versus half in Peyer’s patches (21). In skin, mice harbor large populations of resident γδ T cells, whereas γδ T cells comprise only a small percentage of splenic T cells (22). Intraepithelial lymphocytes (IEL) isolated from the gastrointestinal tract of normal mice contain a relatively high percentage of CD8αα heterodimers characteristic of other peripheral T cells (23).

The composition of Tregs also varies vastly by organ type. For example, of the CD4+ T cells present in the gastrointestinal tract of adult mice, 10% to 20% are Tregs (24), compared with 20% to 60% in skin. The majority of Tregs found in the GI tract are peripheral Tregs induced by commensal microbes, compared with Tregs in mouse skin, which appear to be thymus-derived and accumulate in the skin during a specific window of neonatal development (25).

Studies in mice have further revealed an important role for tissue-resident memory CD4+ and CD8αα+ T cells in protective immunity to site-specific pathogens in the skin (26). Similarly, mucosal sites such as intestine also contain tissue-retained memory populations that do not recirculate (27).

A distinct lineage of CD4+ T cells, called Th17 cells, regulates tissue inflammation by producing IL17 (28, 29). Th17 cells play an important role in the induction of protective immunity against bacterial and fungal infection at specific mucosal sites such as the gut, lung, and oral cavity (30).

**Phenotypic Functions**

In addition to differences in cellular composition, the phenotypic functions of immune cells differ in various organs. For example, the proliferative responses of normal mouse IELs to T-cell mitogens are much weaker than those of splenic T cells (31), yet these cells still possess normal cytotoxic responses (32). This property, along with inducible populations of immunosuppressive Tregs (17), potentially contributes to tolerance of mucosal immune cells to various dietary antigens and beneficial microorganisms.

**Soluble Factors**

Various organs also harbor different soluble microenvironmental factors that may be more or less conducive to immune stimulation. For example, the cytokine TGFβ is known to play an important role in mediating balanced responses specifically within the gut mucosa between harmful and harmless bacteria to prevent inflammatory disorders and maintain homeostatic regeneration of tissues (reviewed in ref. 33).

Another factor that is divergent in skin, spleen, and gut is IL10. This anti-inflammatory cytokine is produced predominantly by leukocytes, including T cells, B cells, monocytes, macrophages, and dendritic cells, as well as by some epithelial cells. In leukocytes, IL10 acts on both innate and adaptive immune cells and has a broad range of immunomodulatory activities that suppress proliferation, cytokine secretion, and costimulatory molecule expression of proinflammatory immune cells. IL10 is critical for intestinal mucosal homeostasis, as IL10- and IL10 receptor (IL10R)–deficient mice develop spontaneous intestinal inflammation but rarely display dermatopathology or systemic autoimmunity (34), thus illustrating a gut-specific role for this lymphokine. Consistent with these findings, patients with deleterious mutations in IL10, IL10RA, or IL10RB present predominantly with severe inflammatory bowel disease within the first months of life (35).

**Antibody Isotypes**

Finally, another difference among organs is the production of tissue-specific antibody isotypes. For example, an important mechanism specific to gut mucosa to promote immunity in the absence of inflammation is the production of immunoglobulin A (IgA). IgA binds polymeric Ig receptors on the basolateral surface of intestinal epithelial cells and is then translocated across the epithelial cells to the gut lumen. IgA mediates protection at the mucosal barrier by two mechanisms: High-affinity antibodies neutralize toxins and pathogens and low-affinity antibodies inhibit the adhesion of commensal bacteria to epithelial cells. Collectively, these mechanisms aid in keeping bacteria in the gut lumen without inducing inflammation that would damage the mucosal barrier (33).

**ORGAN-SPECIFIC IMMUNITY: STUDIES IN HUMANS**

For human immunology, most of our understanding of immunity comes from the study of immune cells derived from peripheral blood, which is easily accessible. Less is known regarding immune-cell activation and differentiation in lymphoid and mucosal tissue sites. Moreover, in humans, studies on immune cells in tissue sites are limited to using individual tissues surgically excised because of disease (20). However, emerging data also show that different tissues harbor varying compositions of immune cells.

Through the collaboration of the New York Organ Donor Network, the organ procurement organization for the greater
New York metropolitan area, investigators have obtained access to multiple lymphoid and mucosal tissues from individual organ donors with a healthy immune system. From each donor, blood and eight different healthy tissues including multiple lymphoid tissues (spleen, inguinal, mesenteric, and bronchial/lung-draining lymph nodes) and mucosal tissues including the lung, small-intestine regions (jejunum and ileum), and colon were obtained. A multidimensional analysis of T cells throughout the human body from 24 different donors ages 15 to 60 years revealed distinct compartmentalization of naive, effector, and memory CD4+ and CD8+ T-cell subsets intrinsic to the tissue site that is remarkably consistent in diverse individuals. Memory CD4+ (defined as CD45RO+ or CD45RO−) T cells represent the majority subset in mucosal tissues, apparently accumulating in lymphoid tissue throughout life. CD8+ T-cell subsets, by contrast, are maintained as naive cells (defined as CD45RA+CCR7+) in lymphoid compartments over decades, with memory CD8+ T cells mainly found in mucosal sites and terminal effector T cells confined to circulation. Importantly, memory T cells in all tissues specifically upregulate CD69 expression, a marker of T-cell receptor (TCR)–mediated activation, which distinguishes tissue-resident (as defined by CD69+) from circulating (as defined by CD69−) populations. Functionally, the majority of tissue-resident T cells were quiescent or IL2-producing memory CD4+ T cells, followed by IFNγ-producing memory CD8+ T cells, with IL17 production confined to memory CD4+ T cells in mucosal compartments (20).

In our own studies, we used published single-cell immune cell signatures of macrophages, T cells (and NK cells, as the referenced analysis categorizes T and NK cells together), and B cells (36) to estimate the relative abundance of these cell types in organs derived from healthy individuals, including but not limited to skin, blood, and gut, using the Genotype-Tissue Expression (GTEx) project database (refs. 37–40; Fig. 1A). The data demonstrate that the relative abundance of these cell types in different organs is highly variable. For example, the macrophage gene expression signature is more enriched in lung and spleen than in colon and skin. For B cells, spleen and blood have the highest levels, with a gradual reduction of B-cell prevalence and an increase in cell-to-cell variability from ileum (high number of B cells) to transverse colon to a very low abundance in the small-mucosal colon. A similar pattern is observed for T/NK cells. Lung, ileum, skin, and most transverse colon samples have high Th17 signature scores, which are relatively lower in spleen. Th1 signature scores are high in lung, spleen, and blood, but much lower in skin. The Th2 signature is most enriched in lung. Regulatory T-cell signatures for “normal” and “induced” Tregs (i.e., cells that arise in the periphery from CD4+ FOXP3+ conventional T cells) show a very interesting pattern: “Normal” Tregs are relatively higher in lung and spleen and lower in liver, whereas “induced” Tregs are relatively higher in colon but lower in spleen.

Collectively, these analyses clearly show that each organ has its own diverse immune cell composition distinct from that of other organs.

THE ORGAN-SPECIFIC IMMUNE SYSTEM DIFFERS IN DIFFERENT HUMAN CANCER TYPES

Using the same approach as above, we estimated the relative abundance of macrophages, T cells (and NK cells), and B cells in different cancers and matched normal tissues using TCGA. These data show that the relative abundance of immune cells is also highly variable in cancers (Fig. 1B), including in melanomas, leukemias, and colorectal cancers. Notably, compared with matched tissues from healthy individuals, many cancer types display much greater variability in expression (see, for example, lung tumors versus matched normal tissue in Fig. 1B). Whether the immune cell composition is consistently distinct in some way across various tumor types remains to be determined, and the implications of these differences for CIT are currently unclear. Nevertheless, the data together with the genomic data as described above illustrate that different cancer types may differ not only by genetics but also by their organ-specific immunologic microenvironments. Consistent with these data, a recent paper integrated the molecular profiles of over 10,000 tumor samples across 23 cancer types and found that the intertumor heterogeneity of immune infiltration may be caused by both cancer genetic variations as well as the disease-specific expression pattern of the chemokine/receptor network (41).

CONCEPT OF THE IMMUNOSTAT AND HOW IT MAY AFFECT HOW CIT WORKS

Given the customization of host defense according to organ site, it is highly plausible that different organs regulate immune responses in different ways (Fig. 2A). Although some may have a relatively “low” threshold for activation (e.g., blood), others may have a much higher tolerance for activation (e.g., gut). Just as a thermostat automatically controls heating or cooling equipment to maintain temperature at a constant level or within a specified range, an “immunostat” would automatically control the level of immune cell activation within an organ to maintain an equilibrium of self versus non-self recognition to protect the host from foreign antigens while not overreacting to self-antigens. Applied to tumor development, the immunostat concept would propose that tumors arise within a particular immunologic context related to their anatomic origin. This co-development presumably shapes the manner by which the immune system initially interacts with the cancer cells and the strategies that cancer cells develop to evade the organ-specific immune system. Taken a step further, if various immunostats exist in different anatomic sites, then one hypothesis to explain why CPIs display differential monotherapy activity against cancers is that differences in the amount of inherent immunoregulation in organs limit the ability of checkpoint blockade monotherapy to unleash the adaptive immune response in those organs. Of course, exceptions may exist; for example, as stated above, MSI-positive tumors appear to respond to CPIs regardless of tissue of origin, which may be due to an overwhelming number of neoantigens that override tissue-specific immunoregulation (10). However, MSI cases also appear to represent an outlier situation rather than the norm. We discuss below factors that may influence the immunostat and thus affect sensitivity to CIT.

FACTORS THAT MAY INFLUENCE TISSUE-SPECIFIC IMMUNITY

A comprehensive catalog of factors that contribute to immunostats within each organ is not currently available. Our intent
here is not to review in detail these factors, which include differences in immune cell composition, cell differentiation status, thresholds for T-cell activation, soluble mediators, and trafficking and homing abilities (Fig. 2B). Here, we will highlight just a few examples. More extensive reviews have been published on these various targets (42–44). We further acknowledge that organ-specific factors may also differ among individuals, depending upon their age, antigen exposure, etc., but a baseline understanding of tissue-specific immunity still needs to be elucidated.

**Immune Cell Composition**

As discussed above, different tissues harbor varying amounts of innate versus adaptive immune cells in addition to regulatory or suppressor cells. Depending upon the composition, some tissues may have lower or higher thresholds for immune cell activation.

**Cell Differentiation Status**

As discussed above, the immune cells residing within different tissues have varying degrees of differentiation. A prime example of this is the heterogenous nature of exhausted T cells. During chronic infections due to persistent antigen exposure and/or inflammation, the process of memory T-cell differentiation becomes markedly altered, involving progressive and hierarchical loss of effector functions, sustained upregulation and coexpression of multiple inhibitory receptors, altered expression and use of key transcription factors, metabolic derangements, and a failure to transition to quiescence and acquire...
antigen-independent memory T-cell homeostatic responsiveness (42). Each organ may harbor a distinct set of exhausted T cells, depending upon the level and nature of antigens encountered.

**Thresholds for T-cell Activation**

T-cell activation is a highly regulated process, involving both positive and negative pathways. Stimulatory receptors that promote T-cell activation include but are not limited to CD28, CD40 (also known as TNFRSF5), OX40 (also known as TNFRSF4), GITR (also known as TNFRSF18), 4-1BB (also known as CD137 and TNFRSF9), and ICOS (reviewed in refs. 43, 44). Inhibitory receptors are crucial negative regulatory pathways that control autoreactivity and immunopathology. They include PD-1, LAG3, 2B4 (also known as CD244), CD160, TIM3 (also known as HAVCR2), CTLA4, BTLA, VISTA, etc. They are usually transiently expressed in functional effector T cells during activation, but various levels of higher and sustained expression are found in exhausted T cells (42). Heterogeneous expression of both stimulatory and inhibitor receptors in T-cell populations within organs and their variable capacity to activate/inhibit T cells may contribute to organ-specific immunostats.

**Soluble Mediators**

Soluble mediators further regulate T-cell responses. Examples include immunosuppressive cytokines such as IL10 and TGFβ and inflammatory cytokines such as type I IFNs and IL6 (42).

Additionally, antigen encounter by T lymphocytes induces important metabolic changes that form a feedback loop to the immune response. Specifically, immunosuppressive enzymes modify nutrient availability, leading to the production of toxic metabolites. One class of enzymes, produced predominantly by myeloid cells, catalyzes the amino acid tryptophan—namely, indoleamine 2,3-dioxygenase (encoded by IDO1 or IDO2) and tryptophan 2,3-dioxygenase (encoded by TDO). Another class of enzymes catalyzes the amino acid arginine—namely, arginase 1 and 2 (encoded by ARG1 and ARG2). These enzymes produce proapoptotic metabolites, such as the kynurenines (from tryptophan), which suppress the function of T lymphocytes. Another class of enzymes are the ectoenzymes expressed on the cell surface of T cells, CD39 and CD73. These dephosphorylate extracellular ATP, which is immunostimulatory, to adenosine, which is immunosuppressive (45). Heterogeneous expression of soluble mediators within organs may also contribute to organ-specific immunostats.

**Trafficking and Homing Abilities**

Immune responses against infection are controlled spatiotemporally by a coordinated arrangement of “rolling and adhesive steps” enabling circulating leukocytes, and importantly
T cells, to leave the blood (extravasate from blood vessels) and infiltrate diseased tissue under hemodynamic flow conditions. The acquisition of highly specialized T-cell “homing” receptors, including adhesive receptors, chemokines, and other promigratory molecules, is critical to this process. Briefly, the steps in this cascade involve: (i) tethering and rolling adhesive interactions of the blood-borne cell onto the endothelial surface; (ii) integration of chemokine-mediated signaling within the milieu (via chemokine receptors expressed on the circulating cell), leading to integrin activation; (iii) integrin-mediated firm adherence of the cell onto the endothelial surface; and (iv) endothelial transmigration (46). Such trafficking and homing is organ-specific; indeed, the multistep homing mechanisms for T effector cell recruitment to skin and gut are already known to be distinct (46).

In the future, assuming access to normal human tissues through clinical trials, we anticipate that many new tools will elucidate with greater accuracy the factors that regulate organ-specific immunity. For example, single-cell sequencing (38) combined with quantitative and spatial proteomic analysis (47, 48) is already being used to elaborate the specific immune ecosystem of different tissues in normal and disease conditions. Once we have a complete understanding of each organ-specific immunostat, we will be able to anticipate with much greater precision how to treat cancers that arise in different organs with specific CIT cocktails.

**WHAT ABOUT PRIMARY TUMORS VERSUS METASTASES? LIVER AS AN EXAMPLE**

A natural question that arises within the immunostat framework is whether tumor cell metastases display features of immunoregulation different from their sites of origin or their new sites of growth. This area of research is currently not well understood. Although the very existence of metastases within an organ already demonstrates escape from the immune system, it is likely that metastatic lesions located in different organs will be subject to context-dependent immunoregulation. Emerging clinical data with metastatic melanoma are supportive of this concept. In a phase I trial with the anti–PD-1 antibody pembrolizumab involving 112 patients, a 64% objective response rate (ORR) was observed in patients with metastatic disease to lungs versus a 16% ORR in patients with metastatic disease to the liver (49). Consistent with these findings, a multicenter retrospective study in patients treated with the anti–PD-1 antibodies pembrolizumab or nivolumab (n = 337) showed a 56% ORR in patients with no liver metastases versus a 28% ORR in patients with liver metastases (50). Thus, at least in the liver, tissue-specific factors may modulate the sensitivity of tumor deposits to CIT. Mechanistic reasons for this discrepancy are unclear but presumably are not due to a pharmacokinetic effect (i.e., lack of drug reaching the liver). Further, because it is reasonable to assume that melanoma metastases in the liver and other organs harbor the same mutational load, the differential sensitivity could be due to differences in tissue-specific immunoregulation.

**CONCLUSION**

In summary, just as cancers arise from different organs with different genetic features, each organ has its own immune system with different immunologic features. Organ-specific immune systems likely contribute to the way cancers develop and subsequently to their sensitivity or resistance to various CITs. Taken one step further, organ-specific immune systems may also contribute to immune-associated toxicities upon exposure to immunotherapies. Currently, our understanding of how “immunostats” regulate tumor responses to the immune system is suboptimal. As we develop more molecules targeting different components of the immune system, we will need to adopt a smarter approach toward early drug development, hopefully identifying a priori which patients may or may not benefit from a particular monotherapy or combination therapy. A greater understanding of how immune systems are regulated within various organs and how cancers interact within their respective immune contexts could ultimately help to optimize and personalize CIT for patients.

**Disclosure of Potential Conflicts of Interest**

All authors have stock ownership in Roche.

**Acknowledgments**

This work was supported by F. Hoffmann-LaRoche AG. The authors acknowledge the American Association for Cancer Research and its financial and material support in the development of the AACR Project GENIE registry, as well as members of the consortium for their commitment to data sharing. Interpretations are the responsibility of study authors. The GTEx Project was supported by the Common Fund of the Office of the Director of the NIH, and by NCI, NHGRI, NHLBI, NIDA, NIMH, and NINDS. The data used for the analyses in Fig. 1 were obtained in part from the GTEx Portal on May 27, 2016. The results shown in Fig. 4 were in part based upon data generated by the TCGA Research Network (http://cancergenome.nih.gov/). Editorial support in the form of copyediting, referencing, and formatting was provided by Christine M. Michael, Ph.D. The authors had sole control of the content of this article.

Received November 22, 2017; revised January 26, 2018; accepted February 1, 2018; published first March 15, 2018.

**REFERENCES**


Published OnlineFirst March 15, 2018; DOI: 10.1158/2159-8290.CD-17-1320

Downloaded from cancerdiscovery.aacrjournals.org on September 13, 2021. © 2018 American Association for Cancer Research.
Understanding of the "Immunostat" in the Context of Cancer Tissue-Specific Immunoregulation: A Call for Better


*Cancer Discov* 2018;8:395-402. Published OnlineFirst March 15, 2018.

Updated version

Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-17-1320

Cited articles

This article cites 49 articles, 14 of which you can access for free at:
http://cancerdiscovery.aacrjournals.org/content/8/4/395.full#ref-list-1

Citing articles

This article has been cited by 8 HighWire-hosted articles. Access the articles at:
http://cancerdiscovery.aacrjournals.org/content/8/4/395.full#related-urls

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, use this link http://cancerdiscovery.aacrjournals.org/content/8/4/395.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.