Received: 8 December 2021 | Revised: 18 March 2022 | Accepted: 22 March 2022

DOI: 10.1002/bies.202100285

BioEssays

REVIEW ESSAY

Prospects & Overviews

The solid tumor microenvironment—Breaking the barrier for T cells

How the solid tumor microenvironment influences T cells

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Abstract

The tumor microenvironment (TME) plays a pivotal role in the behavior and development of solid tumors as well as shaping the immune response against them. As the tumor cells proliferate, the space they occupy and their physical interactions with the surrounding tissue increases. The growing tumor tissue becomes a complex dynamic structure, containing connective tissue, vascular structures, and extracellular matrix (ECM) that facilitates stimulation, oxygenation, and nutrition, necessary for its fast growth. Mechanical cues such as stiffness, solid stress, interstitial fluid pressure (IFP), matrix density, and microarchitecture influence cellular functions and ultimately tumor progression and metastasis. In this fight, our body is equipped with T cells as its spearhead against tumors. However, the altered biochemical and mechanical environment of the tumor niche affects T cell efficacy and leads to their exhaustion. Understanding the mechanobiological properties of the TME and their effects on T cells is key for developing novel adoptive tumor immunotherapies.

KEYWORDS
immunology, mechanobiology, tumor microenvironment

INTRODUCTION

As cancer remains one of the largest challenges of modern medicine, much effort has gone into novel treatments. At the front line of the battlefield are immunotherapies targeting immune checkpoint inhibitors, helping to reinstate potent anti-tumor efficacy of endogenous T cells.[1] However, the presence and activation of T cells in the tumor microenvironment (TME) are of utmost importance to cancer remission. Tumor tissue and cells exhibit morphological, physical, biochemical, and genetic features different from healthy tissues and cells, although they originate from the body's own cells.[2–4] These features are very important in the classification of tumors, cancer research, treatment planning, and prognosis of patients.[4–6] Tumors are commonly classified into solid (e.g., carcinoma, sarcoma, melanoma, etc.) and non-solid (hematological neoplasms or blood cancers such as leukemia, lymphoma, and myeloma), depending on whether the tumor tissue contains liquid areas or not.[7–9] Solid tumors constitute the majority of all cancers and cancer deaths, and in this respect, because of the vast diversity, are cumbersome to tackle and necessitate research across disciplines.[10]

One of the important discoveries in tumor research is that the physical properties of TME play a decisive role in tumor development, antitumor immunity, and response to antitumor therapy in solid

Abbreviations: CAF, cancer-associated fibroblast; CTL, cytotoxic T lymphocyte; ECM, extracellular matrix; IF, interstitial fluid flow; IFP, interstitial fluid pressure; PDGF, platelet-derived growth factor; IL-10, interleukin 10; IL-35, interleukin 35; TAM, tumor-associated macrophage; TCR, T cell receptor; TGF-β, transforming growth factor-beta; Treg, regulatory T cell; TME, tumor microenvironment; VEGF, vascular endothelial growth factor

TABLE 1 Physicochemical properties of TME: Contributors and consequences

Mechanism	Hyperpermeable vasculature Nonfunctional lymphatics Compression of lymphatics and vessels	Increased fibrillar matrix deposition Contraction of the cells		
		Increasing volume of tumor tissue Compression by surrounding tissue	Crosslinked fibers	
			Tensile stress	Alignment and linearization of fibrillar matrix
	Fluid pressure/flow	**Solid stress**	**Stiffness**	**Microarchitecture**
Consequence	Induction of matrix metalloproteinase activity	Stimulation of tumorigenic pathways	Increased epithelial-mesenchymal transition Growth factor secretion Angiogenesis Enhanced immune cell infiltration	Actomyosin contractility Contact guidance for migration of cancer cells Induction of matrix metalloproteinase activity Modulation of β1 integrin expression Alterations of gene expression Genomic instability
	Low glucose, O_2, and pH High lactic acid and ROS Prevention of drug/immune cell delivery Secretion of immunosuppressive and angiogenic molecules (HIF-1α, TGF-β, IL-10, VEGF, etc.) Expression of immune checkpoint receptors (PD-1, etc.) Activation of Tregs and CTL exhaustion			
	Activation of CAFs Activation of YAP/TAZ down-stream pathways Invasion and metastasis			

Abbreviations: CAF, cancer-associated fibroblast; CTL, cytotoxic T lymphocyte; HIF-1α, hypoxia-inducible factor 1 alpha; IL-10, interleukin 10; PD-1, programmed cell death protein 1; ROS, reactive oxygen species; TAZ, transcriptional coactivator with PDZ-binding motif; TGF-β, tumor growth factor-beta; Treg, regulatory T cell; VEGF, vascular endothelial growth factor; YAP, Yes-associated protein (Nia et al.,[12] Lim et al.,[18] Zhang et al.[29]).

tumors.[11] After the cornerstones for understanding cancer development at the cellular level were named,[2] the physical properties of TME were recently discussed under four main headings by Nia et al.[12]: (1) solid stress, (2) interstitial fluid pressure (IFP) and fluid flow (IF), (3) stiffness and material properties, and (4) microarchitecture (see Table 1). Although the body of literature considering the above factors is growing, the relationship between TME and T cells, which are the chief commanders in antitumor immunity,[13] is an under-researched area. The presence and activity of tumor-infiltrating T cells have been associated with a good prognosis in many cancer types.[14–17] However, TME poses a strong barrier to tumor infiltration by T cells, and this barrier is also seen as a reason for failure in adoptive T cell therapy.[11,18,19] While metabolic/biochemical profile of the TME on T cells and immunotherapy has been recently reported in the literature in detail (see the review of Lim et al.[18]), in this review, the effects of the mechanobiological features of TME on tumor-infiltrating T cells are discussed.

ECM MICROARCHITECTURE AND STIFFNESS INFLUENCE TUMOR INFILTRATION

The TME is a complex and abnormal structure, which is composed of various cells within an altered fibrillar extracellular matrix (ECM) (collagen, fibronectin, hyaluronan, etc.).[20] The main difference between normal and tumor ECM is the increase in deposition of fibrillar matrix components (such as collagen and fibronectin) and an increase in protein crosslinking as well as linearization. In combination, leading to increased stiffness,[21] varying between 100% and 1400% between healthy tissues and their respective solid tumors[21–26] (see also Table 1 of our recent review[27]). As the tumor grows, ECM stiffness increases, and collagen fibers are arranged in a parallel anisotropic orientation (tumor-associated collagen signature), which inhibits non-tumor cells but accelerates tumor cell proliferation. This is caused by the activity of tumoral stromal/mesenchymal cells, fibroblasts, and tumor-associated macrophages (TAMs).[11] Increasing cytoskeletal tension with increasing stiffness promotes focal adhesion coalescence.[21] Parallel anisotropic orientation of collagen acts as contact guidance for tumor cells, and together with linearization facilitates their migration, tissue invasion, and colonization.[28,29] Unfortunately, the resulting TME microarchitecture with parallel anisotropic alignment, linearization, and crosslinked matrix restricts the access for immune cells and drugs into the tumor, rendering treatment complicated (see Figure 1A).[11,29]

In many cases, tumor rejection starts with the infiltration of the tumor cells by immune cells including T cells after the initial cytotoxic T lymphocyte (CTL) response. T cells are more successful at infiltrating the restrictive ECM and bypassing obstacles in the ECM than other immune cells.[30,31] Collagen contrarily affects the infiltration of T cells and their migration within the TME. On the positive side, it stimulates faster T cell migration compared to chemokine-dependent migration.[32] T cells interact with the ECM via integrins, which direct and enable migration. Once integrins are blocked, migration stops.[33] However, when collagen is present in the matrix, T cell migration continues despite the β1-integrin blocking antibody. In other words, the effect of collagen on the direction and speed of T cell migration is seen as determinative.[34] On the contrary, migration and infiltration of T cells is significantly reduced, once a certain collagen density is

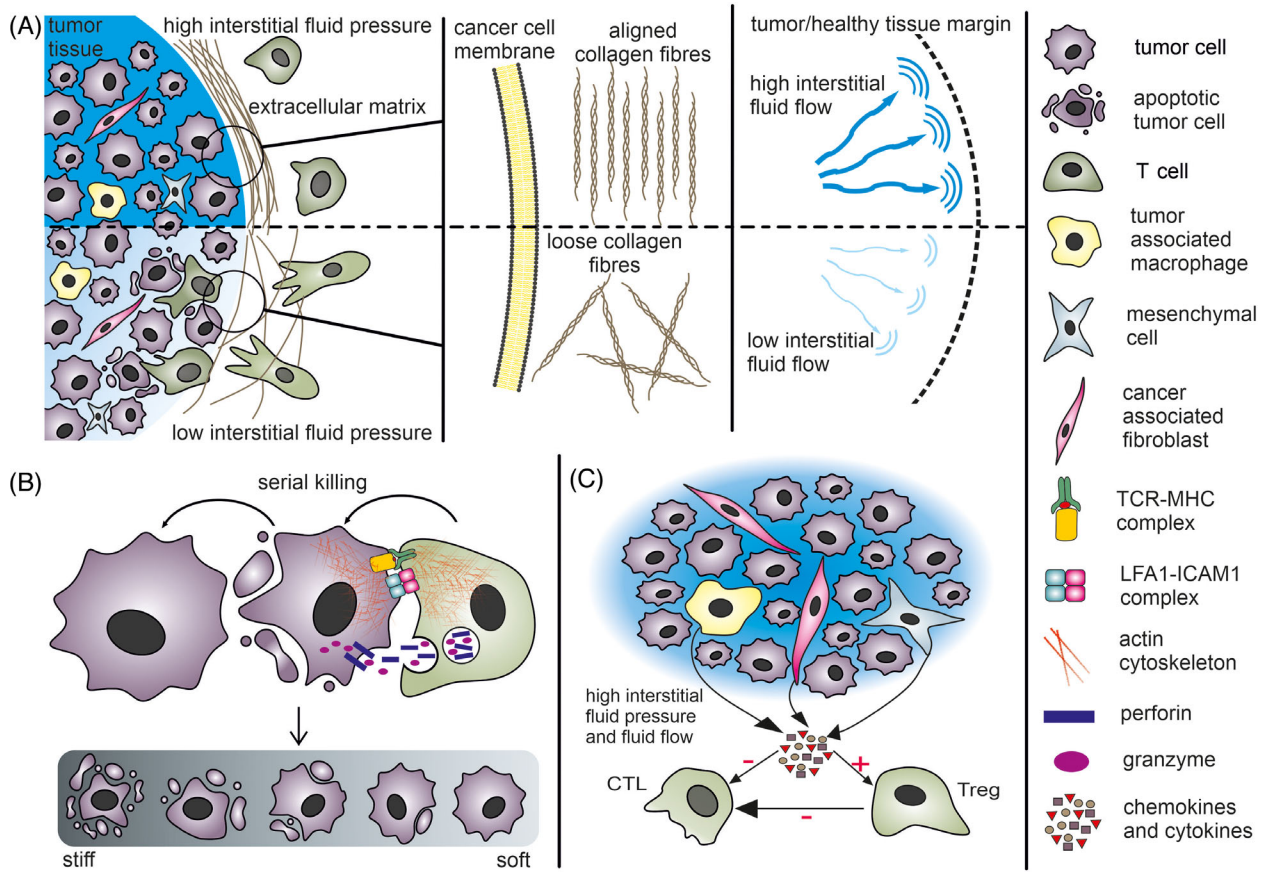

FIGURE 1 The complex relationship between tumor microenvironment and T cells. (A) Aligned collagen fibers in the tumor extracellular matrix, high interstitial fluid pressure in the TME and interstitial fluid flow from tumor center to periphery impede T cells to infiltrate the tumor tissue; (B) Serial killing capacity depends on matrix stiffness. The immunological synapse between CTL and tumor cell is established and the actin cytoskeleton is linked to the complex to exert mechanical force across the synapse. CTL released perforin and granzyme molecules to kill tumor cells and stiffer conditions enhance the serial killing capacity of CTLs. (C) High interstitial fluid pressure and fluid flow in the TME trigger the tumor-associated cells to release chemokines and cytokines which suppress CTLs and potentiate Tregs. Tregs can also inhibit CTLs directly (CTL: cytotoxic T lymphocyte, Treg: regulatory T cell, TCR: T cell receptor, MHC: major histocompatibility complex, LFA1: leukocyte-specific integrin, lymphocyte function-associated antigen-1, ICAM1: intracellular adhesion receptor-1)

reached,[34] in example, when space between the fibrils is smaller than 5 μm.[32] A recent study by Sun et al. showed that discoidin domain receptor 1 (DDR1)'s extracellular domain (DDR1-ECD) facilitates collagen fiber alignment, hence immune exclusion. Upon knock-out and capture by monoclonal antibodies specific to DDR1-ECD, T cell invasion was restored, resulting in triple-negative breast cancer remission for 10 out of 18 mice.[35] This potential new strategy to alter the ECM is promising and together with optimizing T cell infiltration through the restrictive ECM could provide a potential cure. T cells therefore must break free from the ECM confinement and move forward, drastically altering, that is, deform, their cell bodies through actin cytoskeletal dynamics (cell deformability).[36,37]

Both ameboid movements with pseudopodia and mesenchymal-like movement with lamellipodia are seen in terms of the 3D motility of T cells in tissue. T cells can switch between these two movement patterns according to ECM conditions (mesenchymal-ameboid plasticity).[38] Within the lymph nodes, T cells can reach high speeds by ameboid movement.[39] In a recent study, Tabdanov et al.[40] investigated the motility of activated T cells in tumor tissue on a "2.5D" structured surface with nanogrooves as a model system. Unlike 2D, "2.5D" surfaces contain topographic features (folds, grooves, etc.) that cause changes in membrane curvature on one side of the cell.[41] As the matrix stiffness of the "2.5D" substrate increased, in-groove interactions, amoeboid movement, and migration speed of activated T cells decreased.[40] This indicates that TME architecture and mechanical properties are the main factors that prevent T cell infiltration. Perturbation or fine-tuning these specific features could potentially provide a tool to optimize infiltration into the complex 3-dimensional tumor architecture to finally target cancer cells.

ECM MICROARCHITECTURE AND STIFFNESS INFLUENCE T CELL ACTIVATION AND CYTOTOXICITY

Once T cells have overcome the TME barrier, activation and killing capacity become important. T cell activation and cytotoxicity were shown to increase not only with high stiffness of their environment

but also with direct force application under in-vitro conditions (for details please see our recent review).[42] Therefore, it is predicted that increased mechano-signaling in TME may support antitumor immune response activation.[43] As the immunological synapse is established, the complex is linked to the actin cytoskeleton of the CTL in order to exert mechanical force across the synapse,[44–46] enabling the CTL's to kill the target cell,[44,45] via perforin accumulation.[44] The synergistic effect of the applied force and perforin potentiates the killing capacity of CTL enabling serial engagements (see Figure 1B).[44,47,48] For example, when perforin and ovalbumin-specific T cells are added to ovalbumin-loaded B16 melanoma cell culture, T cells apply more mechanical force and more perforin pores are formed on cancer cells in the stiffer matrix (50 kPa vs. 12 kPa), with higher killing capacity.[44] As solid tumor cells are stiffer because of their cytoskeletal contractility and contributions from ECM rigidity, CTLs killing capacity is high, however, for circulating tumor cells and metastasis this tremendously changes as tumor cells separated from the TME become softer with the development of immune tolerance.[49–51]

T cells interact with tissues and cells through the formation of actin-rich microvilli, also shown to establish the immunological synapse, through penetration into the antigen-presenting cell.[52–54] Besides their exploratory role in searching for antigens,[55] microvilli can regulate T cell signaling by forming areas with high membrane curvature and T cell receptor (TCR) enrichment.[56] The formation of high membrane curvature is considered to be accompanied with biological processes, such as regulating the assembly of signaling microclusters. It has been shown that antigen recognition by T cells is facilitated by formation of protrusions (200–1000 nm in diameter), which is associated with amplified and sustained signaling at the tip of the microvilli, but also couples the signaling zone via the actin network to the nuclear envelope. Recent studies from others and our own, suggests that sporadic nonspecific TCR phosphorylation can occur at the tip of microvilli, where CD45 is sterically excluded through the formation of tight contacts to the antigen-presenting cell.[57,58] Our recent publication using nanoporous substrates, led to a strongly enhanced T cell activation and proliferation, compared to flat substrates.[59] Together the signal processes mediated through microvilli represent potential targets for immune therapies as well as to facilitate an enhanced tumor infiltration and killing capacity.

HIGH IFP AND IF SUPPRESS T CELL INFILTRATION

As the cancer cells proliferate, the area occupied by the solid tumor within the healthy tissue increases. The tumor as well as its surrounding is exposed to compressive stress, mechanical stretching and tensile stress at the tumor/healthy tissue margin (i.e., solid stress).[60] Blood vessels and lymphatics in the tumor tissue are compressed, resulting in vascular instability with reduced capacity and impairment of blood supply critical for oxygen and nutrient needs.[61] To overcome the blood supply problem, tumor cells induce angiogenesis by secreting various molecules, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), etc.[62,63] As a result, new vessels are formed within the tumor, but this vascularity is prominent with its abnormal and ineffective nature, such as hyperpermeability.[63,64] Subsequently, increased fluid and macromolecule (e.g., albumin) flow into the tumor. The accumulation of albumin in TME increases osmolarity, triggering inflammation[65] and ECM production through cancer-associated fibroblasts (CAF).[28,66] Increased IF and fluid pressure within the tumor cause mechanical stress on the tumor margin.[67] As the lymphatic system is dysfunctional with hyperpermeable vessels, IF and IFP increase lead to hypoxia, further triggering angiogenesis.[68] In humans, interstitial pressure in normal tissue ranges between -2 and -0 mmHg, while IFP in tumor tissue, is generally elevated at around 10–40 mmHg, varying between different tumor types and different regions of the tumor tissue.[69–73] In case of progressive and treatment-unresponsive melanoma tissue, the IFP can increase up to 100 mmHg.[69] Increasing IF and mechanical stress in ECM together induce transforming growth factor-beta (TGF-β) release from tumor stromal cells. TGF-β further increases stromal stiffening by increasing CAF differentiation, contraction, and ECM remodeling as TGF-β stimulates collagen-I production in CAFs.[74]

To reduce IF and IFP within the TME, antiangiogenic treatment was applied in breast tumors together with the inhibitory anti-VEGF antibody (bevacizumab) or with the VEGF receptor tyrosine kinase inhibitor (cediranib), resulting in necrotic tumor and enhanced T cell infiltration.[75,76] Anti-angiogenic therapy provides vascular normalization and homogeneous intratumoral blood supply.[77] In a different study, IFP was significantly decreased with the anti-PDGF receptor kinase antibody (imatinib) with similar positive results on patient's survival.[68] In addition to anti-angiogenic treatments, some studies aimed to reduce IFP and IF indirectly by reducing density, contraction, stiffness, and epithelial-mesenchymal transition in the TME with the help of radiotherapy[78] and pharmacological agents targeting vasculature, cells, and ECM components (vascular disrupting drugs (tubulin ZD6126),[79] vasodilators (e.g., hydralazine),[80] chemotherapeutics (e.g., taxanes targeting integrins),[72] TGF-β1 inhibitors,[81] dexamethasone,[82] etc.). There were also studies using some physical methods (e.g., hyperthermia,[83] and photodynamic therapy[84]) for the same purpose. Furthermore, Chen et al.[32] showed that antigen-specific transmigration of T cells into a microfluidics-based cancer model was stalled under elevated hydrostatic pressure (see Figure 1A). In summary, extravasation only is possible from peripheral well-organized vessels which are exposed to low IFP.

CYTOKINE SECRETION IS INFLUENCED BY IFP

High IFP, mechanical stress together with stiffness increase the secretion of cytokines and chemokines from tumor cells and tumor-associated cells (stromal/mesenchymal cells, TAMs, etc.)[85,86] causing the suppression of TILs. In particular, while CD8+ T cell function decreases, regulatory T cell (Treg) activity increases (see Figure 1C).[67] The multipotent immunosuppressive cytokine TGF-β plays a primary role in the regulation of the T cell-mediated immune

response and the development of immune tolerance.[87,88] In the presence of TGF-β, T cell activation is blocked mainly by the inhibition of TCR signaling.[89] Co-stimulation of the TCR and TGF-β receptor II on CD4+ T cells in the TME stimulates the transcription factor forkhead box protein p3 (Foxp3) expression, which in turn enables the conversion of CD4+ T cells to suppressor Tregs.[89–91] Foxp3 is specifically expressed in Tregs and is responsible for the continuation of Treg functions and immunosuppressive effects at full capacity.[92] Tregs also inhibit cytokine secretion from T helper 1 and T helper 2 cells and the activation of CD4+ and CD8+ T cells.[91] TGF-β suppresses tumor-infiltrating effector T cells by Mothers against decapentaplegic homologs (Smad)-mediated down-regulating of the expression of granzyme, perforin, and interferon genes.[93] In addition to its immunosuppressive effects, TGF-β also inhibits the function of tumor-infiltrating T cells through triggering of the epithelial-mesenchymal transition and CAF proliferation.[94,95] Tregs in the TME provide the continuation of the immunosuppressive effect by secreting cytokines TGF-β, interleukin 10 (IL-10), and interleukin 35 (IL-35).[96,97] TGF-β, IL-10, and IL-35 together reduce the antigen presentation of dendritic cells and the function of T helper cells and cytotoxic T cells.[97] In some in vitro cancer studies, the addition of IL-10 and TGF-β to the medium has shown a marked increase in tumor progression and a noticeable decrease in antitumor immunity with suppressed inflammatory cytokine secretion.[98,99] In addition, IL-10 and IL-35 together are believed to be responsible for T cell exhaustion and the expression of some inhibitory receptors in the TME.[100]

The high IFP and IF within the TME prevent T cells from killing tumor cells, with exact mechanisms still unknown. Further research will be necessary to decipher those mechanism to provide effective methods with minimal side effects/complications for the patient to increase infiltration of tumor tissue by T cells and to activate tumor-infiltrating T cells despite high IFP. Potential strategies could include effectively lowering the IFP within the TME or to desensitize T cells to high IFP.

CONCLUSION AND OUTLOOK

In summary, Tolkien would have described Bilboes path from the Shire to Mordor as long and difficult, in a similar fashion T cells are confronted with a big hurdle to enter into the TME in order to fulfill their task. How on this path physical properties of TME affect T cells remains largely unknown. Considering the remission rates and treatment success of solid tumors, it is clear that TME stands as a formidable fortress against immuno- and pharmacotherapy agents. The mechanisms by which the restricted migration of T cells to the tumor center, their limited contact with cancer cells or their insufficient killing capacity needs further investigation. How can T cells be equipped or fine-tuned against these pushbacks? Or how can TME be modified to increase treatment success? How can the methods developed in vitro be used for therapies with maximum efficiency but minimum side effects? Is there general concepts, that can be applied to all solid tumors and to what level does it need to be tissue specific? Undoubtedly, answering these key questions requires a multidisciplinary approach, and it is exciting to have scientists teaming up to combine their expertise investigating the role of physical properties to optimize efficacy of novel immune therapies. Working together with clinicians from early stages onwards will be necessary to even the path to clinical success. Model systems have to be chosen wisely in order to transition from preclinical to clinical research.

ACKNOWLEDGMENTS

We would like to thank Tamara Zünd for critical feedback on the manuscript. E.K. thanks Human Frontiers Science Program (RGY0065/2017) and Volkswagen Stiftung Experiment! Grant No.95664. H.S. appreciates funding from the Philipp Schwartz Initiative.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Simsek, H., & Klotzsch, E. (2022). The solid tumor microenvironment – breaking the barrier for T cells. *BioEssays*, *44*, e2100285. https://doi.org/10.1002/bies.202100285