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Review

Rethinking the Therapeutic Strategy for Tumor Treatment

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Abstract

Over the past 30 years, a growing body of literature has described advances and theoretical merits of tumor immunotherapy. Nevertheless, its clinical efficacy in oncology remains limited. Based on this observation, we posit that beyond intrinsic tumor immune factors including immunogenicity, immune checkpoints and the tumor microenvironment (TME), surgery and systemic chemotherapy also substantially influence immunotherapy outcomes. Concurrent use of surgery, systemic chemotherapy and immunotherapy carries non-negligible therapeutic conflicts. This bears critical implications for the overall therapeutic strategy of tumors, particularly in the management of "hot tumors." Against the backdrop of widespread "therapeutic conflicts" in clinical oncology, on the basis of tumor immunology principles and theoretical reasoning, we propose that contemporary anti-tumor paradigm warrant critical re-evaluation and refinement. Notably, for hot tumors with favorable immunogenicity, immunotherapy ought to serve as the primary therapeutic modality. Four core principles should guide the management of most tumors: 1. First, define tumor immunogenicity via tissue biopsy. 2. Abide by the tenets of cancer immunotherapy to minimize therapeutic conflicts among surgery, systemic chemotherapy and immunotherapy. 3. Apply local percutaneous interventional therapy to "rapidly and completely" ablate tumor lesions while retaining tumor antigens and remodeling the TME. 4. Sustain the systemic integrity of immunotherapy to circumvent the "Liebig's barrel effect" within immunotherapeutic regimens. Adoption of these four principles may enhance overall therapeutic efficacy, lower procedural injury and treatment-related costs, and carry particular significance for hot tumor management.

Keywords: therapeutic conflicts; therapeutic strategy; hot tumors; local interventional therapy; systemic integrity of immunotherapy

1. Background

The United States enacted the National Cancer Act of 1971[1], which placed cancer control among national strategic priorities, advances in cancer therapeutics have accelerated substantially. A broad spectrum of tumor therapies has emerged, including surgery, chemotherapy, radiotherapy, ethanol ablation, microwave and radiofrequency thermal ablation, focused ultrasound ablation, cryoablation, irreversible electroporation (IRE), photodynamic therapy, gene-based therapy, and diverse immunotherapies. In the global history of disease management, few fields have witnessed basic and clinical research invested with such high-level support, massive scale, long duration and substantial expenditure as oncology[2]. Nevertheless, cancer therapeutic outcomes continue to yield incremental annual gains yet few transformative breakthroughs[3–6]. This perplexing predicament arises not only from the intrinsic complexity of oncology, but also, plausibly, from long-standing theoretical and principled flaws embedded within established tumor treatment paradigms. As clinicians, we ought not to accept limited therapeutic gains achieved at the price of substantial physical morbidity and exorbitant treatment-related costs for patients with cancer.

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To address challenges in tumor treatment, we must first clarify the fundamental causes and biological mechanisms underlying tumor initiation, progression, and curative eradication. Only then can we grasp the core of the issue, foster beneficial effects while circumventing detrimental ones, and achieve superior therapeutic outcomes.

2. Determinants of Tumor Progression and Regression

If Coley's toxin therapy, established in 1891 by William Coley, the father of tumor immunology, is taken as the starting point of tumor immunology research, cancer therapeutics has achieved tremendous advances across cellular to molecular scales over the subsequent 130 years. Particularly during the past three decades, core tenets of tumor immunology, together with discrete immunological processes and components, have been progressively consolidated in textbooks and specialized monographs on cancer immunotherapy[7], forming a coherent theoretical framework with broad consensus. Tumorigenesis, tumor growth and metastasis stem from multifactorial, heterogeneous immune escape, which is tightly linked to the complex TME[8–19]. Sufficient tumor antigen presentation, checkpoint blockade, remodeling of the TME, and preserved homeostasis and integrity of the immune system constitute the prerequisites for tumor eradication[20–33]. Accordingly, the magnitude of the immune response, the susceptibility of immune cells to suppressive signals, and the homeostasis and integrity of the immune system collectively govern whether a tumor enlarges, metastasizes, or regresses. These foundational concepts are well-established and ought to serve as the rationale and guiding principles for designing anti-tumor therapeutic strategies. This consideration applies especially to "hot tumors", which feature robust CD8+ T-cell infiltration within the tumor parenchyma, high tumor mutational burden, abundant functional antigens, predominantly positive PD-L1 expression, and an inflamed TME.

Once we establish that host immune function governs whether tumors progress or regress, it becomes intuitive to conceptualize the overall therapeutic strategy for cancer at a strategic level: given that tumor growth, metastasis, and eradication are predominantly determined by immune competence, cancer management ought to prioritize immune-associated variables and be oriented toward sustaining robust, functional host immune responses. This represents a straightforward foundational logic. While many tumors exhibit low immunogenicity and derive limited benefit from currently available immunotherapies, the theoretical underpinnings of cancer immunotherapy are increasingly validated by experimental evidence and constitute a rational therapeutic direction. Approaches are available to boost tumor immunogenicity, enabling conversion of cold tumors into hot tumors[34–48]. Even for cold tumors, mitigating immune and organ injury induced by surgery and systemic chemotherapy confers therapeutic advantages. Hot tumors with favorable immunogenic profiles warrant particularly rigorous adherence to immunological principles.

In summary, within the framework of systemic cancer immunotherapy, surgical intervention and systemic chemotherapy deserve re-evaluation regarding their respective benefits, drawbacks, indications, and technical implementation. Systematic investigations and comprehensive multifactorial comparative analyses are therefore needed to maximize the clinical benefit of immunotherapy for a larger cohort of patients, while minimizing avoidable tissue morbidity and treatment-related costs.

3. Therapeutic Conflicts in Clinical Oncology

A substantial body of evidence demonstrates that both surgery and systemic chemotherapy impair host immune function[49–61]. Given the established role of host immunity in cancer control, tumor-debulking interventions should follow the principle of preserving immune integrity wherever feasible. Furthermore, cryoablation, IRE [62–65], and several other modalities have long been shown to eradicate tumor tissue without compromising host immunity. These approaches retain tumor antigens and potentiate adaptive anti-tumor immunity. Nevertheless, hot tumors are still predominantly managed with surgery and systemic chemotherapy. These modalities disrupt host

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immune function and blunt the efficacy of immunotherapy. Such therapeutic conflicts represent a critical and underappreciated challenge in contemporary clinical oncology.

Although these therapeutic conflicts have long existed in clinical practice, technical optimization of surgery and systemic chemotherapy has remained the primary focus of clinical innovation. This paradigm brings substantial avoidable morbidity, patient distress and treatment-related costs, while imposing inherent limits on therapeutic efficacy. In particular, continued reliance on surgery and systemic chemotherapy as first-line strategies for hot tumors constitutes a core issue when re-evaluating cancer treatment paradigms. While we recognize the historic, invaluable contributions of surgery and systemic chemotherapy to cancer care, iterative refinement and technological evolution are inherent features of biomedical progress. Accordingly, further investigation is warranted to characterize, understand, and mitigate these clinical therapeutic conflicts.

3.1. Conflicts Between Surgery and Immunotherapy

Although surgery enables effective tumor resection, this section objectively evaluates its immune-related adverse effects under the framework of immunological principles. As tumor immunology matures, it is critical to characterize and mitigate therapeutic conflicts between surgical resection and host immunity. Furthermore, non-surgical ablative modalities are already widely implemented clinically, with ongoing opportunities for technical refinement and expansion.

3.1.1. Direct Immunosuppression Induced by Surgery

Tang F, Tie Y et al. reported that surgical trauma directly induces immunosuppression [49]. Multiple additional studies have documented postoperative reduction of natural killer (NK)-cell activity, expansion of myeloid-derived suppressor cells (MDSCs) and angiogenic factors, impaired immune surveillance, together with proliferation and activation of regulatory T cells (Tregs)[66–72]. These immune-suppressive events create a permissive microenvironment for dormant cancer cells to reawaken and proliferate, potentially driving tumor recurrence and metastasis and explaining rapid postsurgical disease progression observed clinically.

Because surgery intrinsically imposes immunosuppression and represents a risk factor for recurrence and metastasis, stratified comparative analyses incorporating tumor subtyping are warranted. Within the context of systemic immunotherapy, head-to-head evaluations should compare surgical resection versus local interventional approaches capable of complete tumor ablation.

3.1.2. Lymph Node Dissection Compromises Dendritic-Cell-Mediated Antigen Presentation

Lymph nodes serve as indispensable hubs for antigen presentation. Nevertheless, routine oncologic surgery often includes resection of peritumoral lymph nodes. This procedure disrupts dendritic-cell-mediated tumor antigen presentation and blocks key adaptive immune pathways[73–76], substantially impairing host immune competence and blunting the efficacy of immunotherapy. Accordingly, greater attention should be directed toward tumor staging, particularly the reliable identification of lymph-node metastatic disease, to refine surgical indications and foster innovation in local interventional techniques.

3.1.3. Tumor Resection Abolishes Secondary Antigen Stimulation of T Cells

Tumor immunology establishes that naïve T cells differentiate into effector T cells and a minor memory T-cell pool upon primary antigen encounter. Re-exposure to the same antigen drives accelerated proliferation and enhanced function of effector and memory T cells. Secondary antigen stimulation by tumor antigens is therefore essential for robust and durable adaptive anti-tumor immunity. Surgical resection removes the tumor mass and concurrently eliminates both primary and secondary antigenic stimulation of T-cell populations[77,78]. For immunotherapy-eligible tumors, surgical resection may therefore compromise adaptive immune responses and increase the risk of

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recurrence or metastasis. In this context, non-surgical local interventional therapies that preserve tumor antigens represent a core component of immunotherapeutic strategies.

While we emphasize the importance of "secondary stimulation" by tumor antigens, some literature indicates that persistent antigen exposure from viable tumors leads to T-cell exhaustion. In view of this apparent contradiction, four considerations merit discussion:

A. The requirement for secondary antigen stimulation to support effector T-cell function is undeniable.

B. Published work also demonstrates that T-cell exhaustion arises from combined effects of immunosuppressive molecules and complex TME-associated factors[79–84].

C. Several studies show that CD8+ T-cell exhaustion is not triggered by prolonged persistent antigen stimulation; instead, exhaustion emerges within hours after antigen encounter[78]. This finding supports the role of immunosuppressive molecular cues and suggests that the genuine mechanisms underlying T-cell exhaustion deserve deeper investigation.

D. Our advocacy for prudent surgical use aims to deploy interventional techniques to rapidly and completely ablate tumors while retaining tumor antigens, rather than preserving viable tumor tissue.

In summary, surgical resection should be selected more rationally in clinical oncology. Research and translation of simplified, safe, affordable and effective local tumor therapies are encouraged. Such approaches achieve rapid, complete tumor ablation while retaining tumor antigens to sustain secondary antigen stimulation of T cells [62–64], which may confer meaningful benefits for tumor immunotherapy.

3.2. Conflicts Between Systemic Chemotherapy and Immunotherapy

Systemic chemotherapy has long served as a mainstay of cancer treatment and has prolonged survival for numerous patients. Nevertheless, systemic chemotherapy impairs immune cells and host immune function[57,58], alongside rapidly dividing normal cells within the bone marrow, gastrointestinal tract and hair follicles. These toxic effects directly and indirectly blunt antitumor efficacy[85–89], while management of treatment-related adverse events increases overall healthcare expenditure. For hot tumors with favorable immunogenicity, systemic chemotherapy carries an unfavorable risk–benefit profile. An important limitation of prior head-to-head comparisons between systemic chemotherapy and immunotherapy is that many immunotherapy regimens lack systematic design and are rarely integrated with local non-surgical tumor ablation. Rigorous controlled studies should directly compare the widely adopted strategy of systemic chemotherapy plus immunotherapy versus local interventional ablation combined with immunotherapy. Such comparisons are essential to reliably distinguish the relative merits of the two strategies and constitute a responsible approach toward scientific inquiry and patient care.

Beyond these therapeutic conflicts, the clinical value of systemic chemotherapy also warrants careful scrutiny. A published analysis[2] reported that the monthly drug treatment costs in the USA were a median of 2.31 times as high as in the assessed European countries. There were no significant associations between monthly treatment costs for solid tumors and clinical benefit in all assessed countries, using the European Society for Medical Oncology Magnitude of Clinical Benefit Scale ($p = 0.16$ for the USA, $p = 0.98$ for England, $p = 0.54$ for Switzerland, $p = 0.52$ for Germany, and $p = 0.40$ for France), and for all assessed countries except France using the American Society of Clinical Oncology Value Framework ($p = 0.56$ for the USA, $p = 0.47$ for England, $p = 0.26$ for Switzerland, $p = 0.23$ for Germany, and $p = 0.037$ for France). Accordingly, systemic chemotherapy for hot tumors appears suboptimal from both scientific and practical standpoints.

4. How to Revise the Treatment Paradigms for Tumor Treatment

Given the substantial therapeutic conflicts widely observed in clinical oncology, which impair therapeutic efficacy while increasing patient morbidity and treatment expenditure, we need to explore ways to refine current tumor treatment paradigms. Guided by immunotherapeutic principles,

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surgery and systemic chemotherapy ought to be deployed with greater scientific rigor, to minimize patient distress, reduce costs and improve treatment outcomes.

Only a scientifically grounded tumor therapeutic strategy can maximize therapeutic efficacy and realize the integrated standards of therapeutic medicine, medical ethics and health economics. Accordingly, we must systematically evaluate the mechanisms, pros and cons of diverse cytoreductive modalities. Local interventional puncture cytoreductive techniques, capable of rapid, complete tumor ablation while preserving tumor antigens, should be actively and rationally adopted to replace surgery and systemic chemotherapy. These approaches enhance host immune competence and enable immunotherapy to achieve durable tumor control for more patients at an earlier time point. Even for cold tumors, if such interventional modalities can achieve rapid and complete tumor ablation as an alternative to surgery and systemic chemotherapy, this represents a meaningful advance for patient care and this is the core argument demonstrated in this review.

We need to evaluate tumor-related theories and technologies from a strategic perspective, compare the weighted net benefit of different therapeutic modalities comprehensively, follow the principles of tumor immunology, and actively develop more scientifically sound and efficient tumor therapeutic strategies.

4.1. Reflections on Tumor Therapeutic Strategy

When preparing grant proposals and designing research studies, investigators are generally required to describe the technical approach to justify scientific validity and feasibility. Nevertheless, within oncology—the research field with the largest scale, longest history and highest global investment—retrievable publications systematically addressing the therapeutic strategy for overall tumor management remain scarce. This constitutes a notable academic blind spot.

For decades, tumor treatment paradigms have been dominated predominantly by surgery and systemic chemotherapy, supplemented by radiotherapy, multiple local ablative approaches, transcatheter arterial chemoembolization (TACE), and immunotherapy. While the armamentarium of treatments is broad, clinical practice is heterogeneous, marked by pervasive therapeutic conflicts. There is a lack of head-to-head mechanistic comparison and rational selection of modalities framed by immunological principles. Clinical oncology is largely trapped within this established technical paradigm centered on surgery and systemic chemotherapy. Resources are disproportionately invested in refining surgical and chemotherapeutic techniques, whereas deep strategic re-evaluation of overarching tumor treatment technical approach rooted in fundamental oncological theory is uncommon. Much routine tumor care follows clinical practice guidelines in a formulaic manner, with insufficient attention to systemic immunological frameworks and patient-tailored treatment. Particularly over the past decade, with rapid advances in immunotherapy and wider availability of local ablative techniques, continued heavy reliance on surgery and systemic chemotherapy is a missed clinical opportunity.

Tumor immunology has undergone rapid conceptual and technical evolution. New insights into tumor antigen classification and presentation, the TME, and immune checkpoint inhibitors (ICIs) have expanded the therapeutic toolkit and also introduced new priorities for comparative research. Against this backdrop, universal reliance on surgery and systemic chemotherapy for all tumor subtypes is no longer justified. How can therapeutic modalities be rationally selected according to tumor subtype and disease stage? How should treatment pathways be standardized for different malignancies? These questions demand rigorous, mechanism-driven evaluation anchored in tumor immunology, to define therapeutic strategies that preserve immune function, minimize treatment-related injury and reduce healthcare costs.

4.2. Exploring a More Scientific Tumor Therapeutic Strategy

Current clinical regimens, although compliant with clinical practice guidelines, often fall short of optimal scientific and efficiency benchmarks, which limits improvements in clinical efficacy. Taken together, a rational therapeutic framework for most tumors—excluding early-stage tumors for which

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surgery alone yields durable survival as established by evidence-based medicine—should address the four domains outlined below. The first three domains are systematically interconnected, whereas the fourth merits especially careful consideration.

4.2.1. First, Characterize Tumor Immunogenicity

Immunogenicity is the foundational prerequisite for prioritizing immunotherapy. Therefore, immunogenicity stratification should be performed for every tumor using immunohistochemistry and genomic profiling of biopsy specimens. For instance, management of hot tumors with robust immunogenicity should be dominated by immunotherapy.

4.2.2. Rational Deployment of Local Interventional Puncture Techniques Is Paramount

A core prerequisite for displacing surgery and systemic chemotherapy and maximizing immunotherapeutic efficacy is achieving rapid, complete tumor ablation while retaining tumor antigens. Therefore, rational use of local interventional puncture techniques is central to this therapeutic paradigm, with distinct mechanistic advantages: A. Rapid and complete tumor ablation. B. Effective preservation of tumor antigens. C. Favorable remodeling of the TME. D. Enhanced immunogenicity of tumor lesions E. Elimination of surgical trauma, systemic chemotherapy-related toxicities and excessive costs. These cumulative benefits confer substantial advantages relative to surgery and systemic chemotherapy. After reviewing these therapeutic endpoints and biological effects, it becomes clear that local interventional puncture therapy is undoubtedly a tumor ablation modality with superior technical performance. It represents a priority strategy for tumor debulking and outperforms surgery and systemic chemotherapy in most clinical scenarios. At minimum, before immune and gene therapies can reliably achieve curative outcomes, these interventional approaches offer greater clinical benefit with reduced treatment-related morbidity.

The “local interventional techniques” discussed here mainly include ultrasound-guided puncture, CT- and MRI-guided puncture, and puncture-mediated technolgies under colonoscopy and other endoscopic platforms. This family of techniques aligns closely with tumor immunological principles and unlocks unique therapeutic opportunities.

4.2.3. Ensure Systemic Integrity of Immunotherapy

Foundational work by pioneers in tumor immunology has defined the building blocks of immunotherapy. A complete, systemic immunotherapeutic framework integrates multiple interdependent components: A. Identification of the MAGE-1 antigen by the Boon group, characterization of major histocompatibility complex (MHC)-eluted peptide epitopes, and discovery of dendritic cells by Ralph M. Steinman. These discoveries in antigen presentation and epitope profiling established the basis of adaptive anti-tumor immunity[90–92]. B. Discovery of PD-1 by Tasuku Honjo, PD-L1 by Lieping Chen, and CTLA-4 by Tak Wah Mak, Arlene H. Sharpe and James P. Allison, which collectively established the basis of immune checkpoint blockade (ICB) [93–98]. C. The concept of the TME formalized by Ioannides and Whiteside represents another core dimension of cancer immunotherapy[99–101]. D. The integrity and functional capacity of host immunity constitute an essential foundation for response to immunotherapy. These four sets of immune components act in sequential, coordinated fashion. Comparative studies between immunotherapy and conventional treatment must preserve the functional linkage of these immune components. Effective anti-tumor immunity depends on coordinated function across all these modules; deficiency in any single component compromises overall response—this is the “Liebig’s barrel effect” for immunotherapy. Studies that test isolated immunomodulatory agents as representative of “immunotherapy” against surgery or chemotherapy should be interpreted cautiously, as such designs produce incomplete, potentially misleading conclusions.

4.2.4. Management of Cold Tumors and Tumors with Weak Immunogenicity

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Cold tumors and lesions with low immunogenicity account for the majority of clinical cases and remain a major barrier for immunotherapy. Features including limited neoantigen abundance, impaired antigen presentation, MHC downregulation and strong immunosuppression lead to sparse intratumoral T-cell infiltration and poor immunotherapy response. This requires targeted investigation of each contributing factor and sequenced, weight-adjusted systemic intervention. Given the tight linkage between host immunity and tumor initiation, progression and disease resolution[20–33], and multiple ongoing strategies to boost the immunogenicity of cold and poorly immunogenic tumors[34–48], this review argues that even these tumors should be managed within an immunological framework guided by therapeutic, ethical and health-economic standards, in the absence of definitive supporting evidence from large prospective studies. Where local interventional puncture techniques can achieve equally rapid and complete tumor ablation, they should be preferred. This clearly constitutes a comparatively more beneficial and low-risk therapeutic pathway. Notably, interventional puncture may exert underappreciated advantages for TME remodeling and immunogenicity enhancement. For example, delivery barriers that limit many TME-targeted agents can be overcome by direct intralesional administration via interventional puncture[39,44], which is a promising direction for future investigation. Furthermore, cautious, rational substitution of surgery and systemic chemotherapy with rapid ablative interventional puncture first reduces patient suffering and treatment costs, representing a favorable therapeutic option. This approach merits further evaluation as an emerging therapeutic strategy for cold and weakly immunogenic tumors.

5. Conclusions

This review suggests that the therapeutic strategy for most tumors can be investigated as outlined below:

5.1. Tumor initiation, progression and curative outcomes depend predominantly on immune function. Accordingly, both clinical management and translational research in oncology should follow the principles of tumor immunology and immunotherapy, ensure the systemic integrity of immunotherapy, and avoid the "Liebig's barrel effect"—the weakest-link limitation—in immunotherapeutic regimens.

5.2. To preserve and augment host immunity, therapeutic conflicts between surgery, systemic chemotherapy and immunotherapy should be minimized. This requires rigorous and rational deployment of surgery and systemic chemotherapy, alongside systematic reappraisal of their clinical indications.

5.3. Reduced reliance on surgery and systemic chemotherapy requires reliable alternative modalities. Rational substitution of these conventional modalities with local interventional techniques therefore constitutes the core research priority for novel tumor therapeutic strategies. Local interventional puncture techniques carry distinctive theoretical and therapeutic advantages: they facilitate preservation of tumor antigens for hot tumors, enhance immunogenicity for cold tumors, and support remodeling of the TME. Compared with surgery and systemic chemotherapy, these techniques better satisfy the three core medical principles of therapeutics, medical ethics and health economics. For this reason, local interventional techniques represent the central focus for developing innovative tumor treatment strategies.

Nevertheless, therapeutic outcomes of local interventional puncture vary substantially depending on interventional modalities, equipment selection and operator performance. It is therefore critical to define its indications, standardized technical protocols, efficacy endpoints and evaluation frameworks.

5.4. Investigation into the selection of novel tumor therapeutic strategies carries substantial clinical significance. Efforts are needed to strengthen evidence-based development of tumor treatment paradigms. Only by exploring and implementing more scientifically grounded therapeutic strategies can clinical oncology achieve fewer therapeutic conflicts, lower treatment-related morbidity, reduced healthcare expenditure and improved long-term therapeutic outcomes.

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References

1. NATIONAL CANCER INSTITUTE n.d. [cited 2025 2025.04.18]. Available from: https://www.cancer.gov/about-nci/overview/history/national-cancer-act-1971.
2. Vokinger KN, Hwang TJ, Grischott T, Reichert S, Tibau A, Rosemann T, et al. Prices and clinical benefit of cancer drugs in the USA and Europe: a cost-benefit analysis. The Lancet Oncology. 2020 May;21(5):664-70. PubMed PMID: 32359489. Epub 2020/05/04. eng.
3. Khakwani A, Rich AL, Powell HA, Tata LJ, Stanley RA, Baldwin DR, et al. Lung cancer survival in England: trends in non-small-cell lung cancer survival over the duration of the National Lung Cancer Audit. British journal of cancer. 2013 Oct 15;109(8):2058-65. PubMed PMID: 24052044. Pubmed Central PMCID: PMC3798968. Epub 2013/09/21. eng.
4. Li Y, Yan B, He S. Advances and challenges in the treatment of lung cancer. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2023 Dec 31;169:115891. PubMed PMID: 37979378. Epub 2023/11/19. eng.
5. Bi JH, Tuo JY, Xiao YX, Tang DD, Zhou XH, Jiang YF, et al. Observed and relative survival trends of lung cancer: A systematic review of population-based cancer registration data. Thoracic cancer. 2024 Jan;15(2):142-51. PubMed PMID: 37986711. Pubmed Central PMCID: PMC10788469. Epub 2023/11/21. eng.
6. Chen JG, Zhu J, Zhang YH, Chen YS, Ding LL, Chen HZ, et al. Liver Cancer Survival: A Real World Observation of 45 Years with 32,556 Cases. Journal of hepatocellular carcinoma. 2021;8:1023-34. PubMed PMID: 34513745. Pubmed Central PMCID: PMC8418373. Epub 2021/09/14. eng.
7. The Basics of Cancer Immunotherapy. In: Haidong Dong SNM, editor. Springer Nature ed2019.
8. Aktar N, Yueting C, Abbas M, Zafar H, Paiva-Santos AC, Zhang Q, et al. Understanding of Immune Escape Mechanisms and Advances in Cancer Immunotherapy. Journal of oncology. 2022;2022:8901326. PubMed PMID: 35401745. Pubmed Central PMCID: PMC8989557. Epub 2022/04/12. eng.
9. Senft D. Programming immune escape. Nature reviews Cancer. 2024 May;24(5):294. PubMed PMID: 38609713. Epub 2024/04/13. eng.
10. Liu X, Song J, Zhang H, Liu X, Zuo F, Zhao Y, et al. Immune checkpoint HLA-E:CD94-NKG2A mediates evasion of circulating tumor cells from NK cell surveillance. Cancer cell. 2023 Feb 13;41(2):272-87 e9. PubMed PMID: 36706761. Epub 2023/01/28. eng.
11. Seliger B, Massa C. Immune Therapy Resistance and Immune Escape of Tumors. Cancers. 2021 Feb 1;13(3). PubMed PMID: 33535559. Pubmed Central PMCID: PMC7867077. Epub 2021/02/05. eng.
12. Galassi C, Musella M, Manduca N, Maccafeo E, Sistigu A. The Immune Privilege of Cancer Stem Cells: A Key to Understanding Tumor Immune Escape and Therapy Failure. Cells. 2021 Sep 8;10(9). PubMed PMID: 34572009. Pubmed Central PMCID: PMC8469208. Epub 2021/09/29. eng.
13. Dan L, Liu L, Sun Y, Song J, Yin Q, Zhang G, et al. The phosphatase PAC1 acts as a T cell suppressor and attenuates host antitumor immunity. Nature immunology. 2020 Mar;21(3):287-97. PubMed PMID: 31932812. Epub 2020/01/15. eng.
14. Onkar SS, Carleton NM, Lucas PC, Bruno TC, Lee AV, Vignali DAA, et al. The Great Immune Escape: Understanding the Divergent Immune Response in Breast Cancer Subtypes. Cancer discovery. 2023 Jan 9;13(1):23-40. PubMed PMID: 36620880. Pubmed Central PMCID: PMC9833841. Epub 2023/01/10. eng.
15. Zheng X, Hou Z, Qian Y, Zhang Y, Cui Q, Wang X, et al. Tumors evade immune cytotoxicity by altering the surface topology of NK cells. Nature immunology. 2023 May;24(5):802-13. PubMed PMID: 36959292. Epub 2023/03/25. eng.
16. Chen G, Huang AC, Zhang W, Zhang G, Wu M, Xu W, et al. Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response. Nature. 2018 Aug;560(7718):382-6. PubMed PMID: 30089911. Pubmed Central PMCID: PMC6095740. Epub 2018/08/10. eng.

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Preprints.org | NOT PEER-REVIEWED | Posted: 20 November 2026 https://doi.org/10.20944/preprints202611.2126.v1

17. Guan F, Wu X, Zhou J, Lin Y, He Y, Fan C, et al. Mitochondrial transfer in tunneling nanotubes-a new target for cancer therapy. Journal of experimental & clinical cancer research : CR. 2024 May 21;43(1):147. PubMed PMID: 38769583. Pubmed Central PMCID: PMC11106947. Epub 2024/05/21. eng.
18. Yang C, Dong X, Sun B, Cao T, Xie R, Zhang Y, et al. Physical immune escape: Weakened mechanical communication leads to escape of metastatic colorectal carcinoma cells from macrophages. Proceedings of the National Academy of Sciences of the United States of America. 2024 May 28;121(22):e2322479121. PubMed PMID: 38771871. Pubmed Central PMCID: PMC11145255. Epub 2024/05/21. eng.
19. Ganesh K, Massagué J. Targeting metastatic cancer. Nature medicine. 2021 Jan;27(1):34-44. PubMed PMID: 33442008. Pubmed Central PMCID: PMC7895475. Epub 2021/01/15. eng.
20. Wu X, Deng Z, Zhao Q. Immunotherapy improves disease prognosis by affecting the tumor microenvironment: A bibliometric study. Frontiers in immunology. 2022;13:967076. PubMed PMID: 36275770. Pubmed Central PMCID: PMC9582136. Epub 2022/10/25. eng.
21. Goel G, Sun W. Cancer immunotherapy in clinical practice -- the past, present, and future. Chinese journal of cancer. 2014 Sep;33(9):445-57. PubMed PMID: 25189717. Pubmed Central PMCID: PMC4190434. Epub 2014/09/06. eng.
22. Topalian SL, Sharpe AH. Balance and imbalance in the immune system: life on the edge. Immunity. 2014 Nov 20;41(5):682-4. PubMed PMID: 25517610. Pubmed Central PMCID: PMC4710093. Epub 2014/12/18. eng.
23. Yu H, Zhu W, Lin C, Jia M, Tan X, Yuan Z, et al. Stromal and tumor immune microenvironment reprogramming through multifunctional cisplatin-based liposomes boosts the efficacy of anti-PD-1 immunotherapy in pancreatic cancer. Biomaterials science. 2023 Dec 19;12(1):116-33. PubMed PMID: 37921708. Epub 2023/11/03. eng.
24. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013 Jul 25;39(1):1-10. PubMed PMID: 23890059. Epub 2013/07/31. eng.
25. Hiam-Galvez KJ, Allen BM, Spitzer MH. Systemic immunity in cancer. Nature reviews Cancer. 2021 Jun;21(6):345-59. PubMed PMID: 33837297. Pubmed Central PMCID: PMC8034277 from Roche/Genentech, Bristol-Myers Squibb and Valitor, and has been a paid consultant for Earli, Five Prime Therapeutics, Ono Pharmaceutical and January Inc. B.M.A. is currently an employee of Teiko Bio. K.J.H.-G. declares no competing interests. Epub 2021/04/11. eng.
26. Hussein A, Stamova S, Xydia M, Beckhove P. Hand in hand to successful immunotherapy: CD8(+) T cells and M1-like macrophages swap the baton. Cancer cell. 2024 Jun 10;42(6):938-41. PubMed PMID: 38861930. Epub 2024/06/12. eng.
27. Lin Y, Song Y, Zhang Y, Li X, Kan L, Han S. New insights on anti-tumor immunity of CD8(+) T cells: cancer stem cells, tumor immune microenvironment and immunotherapy. Journal of translational medicine. 2025 Mar 17;23(1):341. PubMed PMID: 40097979. Pubmed Central PMCID: PMC11912710. Epub 2025/03/18. eng.
28. Yan W, Li Y, Zou Y, Zhu R, Wu T, Sun X, et al. Breaking Tumor Immunosuppressive Network by Regulating Multiple Nodes with Triadic Drug Delivery Nanoparticles. ACS nano. 2023 Sep 26;17(18):17826-44. PubMed PMID: 37690028. Epub 2023/09/10. eng.
29. Saleh R, Elkord E. Acquired resistance to cancer immunotherapy: Role of tumor-mediated immunosuppression. Seminars in cancer biology. 2020 Oct;65:13-27. PubMed PMID: 31362073. Epub 2019/07/31. eng.
30. Fu Z, Mowday AM, Smaill JB, Hermans IF, Patterson AV. Tumour Hypoxia-Mediated Immunosuppression: Mechanisms and Therapeutic Approaches to Improve Cancer Immunotherapy. Cells. 2021 Apr 24;10(5). PubMed PMID: 33923305. Pubmed Central PMCID: PMC8146304. Epub 2021/05/01. eng.
31. Weber J, Dessureault S, Antonia S. Tumor Immunology and Immunotherapy. In: Chang AE, Hayes DF, Pass HI, Stone RM, Ganz PA, Kinsella TJ, et al., editors. Oncology: An Evidence-Based Approach. New York, NY: Springer New York; 2006. p. 254-68.
32. Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cellular & molecular immunology. 2020 Aug;17(8):807-21. PubMed PMID: 32612154. Pubmed Central PMCID: PMC7395159. Epub 2020/07/03. eng.

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Preprints.org | NOT PEER-REVIEWED | Posted: 20 November 2026 https://doi.org/10.20944/preprints202611.2126.v1

33. Zhang M, Liu C, Tu J, Tang M, Ashrafizadeh M, Nabavi N, et al. Advances in cancer immunotherapy: historical perspectives, current developments, and future directions. Molecular cancer. 2025 May 7;24(1):136. PubMed PMID: 40336045. Pubmed Central PMCID: PMC12057291. Epub 2025/05/08. eng.
34. Suffisseau A, Seguin J, Lemdani K, Diakhaby S, Capron C, El Hajjam M, et al. Revisiting the Immunological Landscape of Locoregional Therapies for Gastrointestinal Cancers: A Shift Toward Interventional Immuno-Oncology. Current oncology reports. 2026 Jul 3;28(1). PubMed PMID: 42397620. Pubmed Central PMCID: PMC13331855. Epub 2026/07/03. eng.
35. Ren E, Wang Y, Liang T, Zheng H, Shi J, Cheng Z, et al. Local Drug Delivery Techniques for Triggering Immunogenic Cell Death. Small methods. 2023 Sep;7(9):e2300347. PubMed PMID: 37259275. Epub 2023/06/01. eng.
36. Velez A, DeMaio A, Sterman D. Cryoablation and immunity in non-small cell lung cancer: a new era of cryo-immunotherapy. Frontiers in immunology. 2023;14:1203539. PubMed PMID: 37671163. Pubmed Central PMCID: PMC10475831. Epub 2023/09/06. eng.
37. Altun I, Demirlenk YM, Atar D, Cevik E, Gunduz S, Albadawi H, et al. Advances and Challenges in Interventional Immuno-Oncology Locoregional Therapies. Journal of vascular and interventional radiology : JVIR. 2024 Feb;35(2):164-72. PubMed PMID: 38272636. Epub 2024/01/26. eng.
38. Appleton E, Hassan J, Chan Wah Hak C, Sivamanoharan N, Wilkins A, Samson A, et al. Kickstarting Immunity in Cold Tumours: Localised Tumour Therapy Combinations With Immune Checkpoint Blockade. Frontiers in immunology. 2021;12:754436. PubMed PMID: 34733287. Pubmed Central PMCID: PMC8558396. Epub 2021/11/05. eng.
39. Zhao H, Dai S. Immunogenic cell death in cold tumors: transforming immune-excluded tumors into immunotherapy-sensitive lesions. Front Pharmacol. 2026;17:1732407. PubMed PMID: 42181899. Pubmed Central PMCID: PMC13190586. Epub 2026/05/25. eng.
40. Lyu L, Yi M, Chen J, Zhang J, Ma X, Zhang X, et al. Bispecific Antibody Targeting VEGF/TGF-β Synergizes with Local Radiotherapy: Turning Tumors from Cold to Inflamed and Amplifying Abscopal Effects. Advanced science (Weinheim, Baden-Wurttemberg, Germany). 2025 Aug;12(30):e01819. PubMed PMID: 40470716. Pubmed Central PMCID: PMC12376579. Epub 2025/06/05. eng.
41. Dotsu Y, Akagi K, Honda N, Matsuo M, Taniguchi H, Takemoto S, et al. Radiotherapy-Associated Systemic Antitumor Responses Beyond the Classical Abscopal Paradigm. Cancers. 2026 Jun 28;18(13). PubMed PMID: 42449641. Pubmed Central PMCID: PMC13359436. Epub 2026/07/15. eng.
42. Luke JJ, Davar D, Andtbacka RH, Bhardwaj N, Brody JD, Chesney J, et al. Society for Immunotherapy of Cancer (SITC) recommendations on intratumoral immunotherapy clinical trials (IICT): from premalignant to metastatic disease. Journal for immunotherapy of cancer. 2024 Apr 18;12(4). PubMed PMID: 38641350. Pubmed Central PMCID: PMC11029323. Epub 2024/04/20. eng.
43. Steffensen VG, Bratina M, Tsiavou C, Schmiegelow K, De Zio D. Turning cold tumors hot: Strategies to enhance antitumor immunity. The Journal of experimental medicine. 2026 Nov 2;223(11). PubMed PMID: 42878724. Epub 2026/10/15 23:30. eng.
44. Teiama MS, Gohar A, Amr M, El-Shinawi M, Elkhatib WF. Cold and hot tumors: immunological determinants, cancer-immunity cycle dysregulation, and nanotechnology-driven therapeutic approaches. Molecular biomedicine. 2026 Aug 18;7(1). PubMed PMID: 42608511. Pubmed Central PMCID: PMC13481959. Epub 2026/08/18. eng.
45. Tumor Immunogenicity Is Enhanced by Altering Mitochondrial Electron Flow. Cancer discovery. 2023;13(12):2498-.
46. Cui L, Wang Z, Guo Z, Zhang H, Liu Y, Zhang H, et al. Tryptophan Metabolite Indole-3-Aldehyde Induces AhR and c-MYC Degradation to Promote Tumor Immunogenicity. Advanced science (Weinheim, Baden-Wurttemberg, Germany). 2025 Sep;12(36):e09533. PubMed PMID: 40583248. Pubmed Central PMCID: PMC12463101. Epub 2025/07/01. eng.
47. Park H, Lee S, Son MK, Kang I, Surwase SS, Song YG, et al. Targeted Liposomal Co-delivery of an Immunogenic Cell Death Inducer and a Toll-Like Receptor 4 Agonist for Enhanced Cancer Chemo-immunotherapy. ACS applied materials & interfaces. 2024 Aug 14;16(32):41810-8. PubMed PMID: 39084852. Epub 2024/08/01. eng.

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Preprints.org | NOT PEER-REVIEWED | Posted: 20 November 2026 https://doi.org/10.20944/preprints202611.2126.v1

48. Zeng Q, Liu M, Wang Z, Zhou R, Ai K. Enhancing radiotherapy-induced anti-tumor immunity via nanoparticle-mediated STING agonist synergy. Molecular cancer. 2025 Jun 11;24(1):176. PubMed PMID: 40500702. Pubmed Central PMCID: PMC12153120. Epub 2025/06/12. eng.
49. Tang F, Tie Y, Tu C, Wei X. Surgical trauma-induced immunosuppression in cancer: Recent advances and the potential therapies. Clinical and translational medicine. 2020 Jan;10(1):199-223. PubMed PMID: 32508035. Pubmed Central PMCID: PMC7240866. Epub 2020/06/09. eng.
50. Bezu L, Rahmani LS, Buggy DJ. The effect of the type of anaesthesia on long-term outcomes after cancer resection surgery: a narrative review. Anaesthesia. 2025 Feb;80(2):179-87. PubMed PMID: 39777733. Epub 2025/01/09. eng.
51. Tohme S, Simmons RL, Tsung A. Surgery for Cancer: A Trigger for Metastases. Cancer research. 2017 Apr 1;77(7):1548-52. PubMed PMID: 28330928. Pubmed Central PMCID: PMC5380551. Epub 2017/03/24. eng.
52. Onuma AE, Zhang H, Gil L, Huang H, Tsung A. Surgical Stress Promotes Tumor Progression: A Focus on the Impact of the Immune Response. Journal of clinical medicine. 2020 Dec 18;9(12). PubMed PMID: 33353113. Pubmed Central PMCID: PMC7766515. Epub 2020/12/24. eng.
53. Cheng X, Zhang H, Hamad A, Huang H, Tsung A. Surgery-mediated tumor-promoting effects on the immune microenvironment. Seminars in cancer biology. 2022 Nov;86(Pt 3):408-19. PubMed PMID: 35066156. Pubmed Central PMCID: PMC11770836. Epub 2022/01/24. eng.
54. Bindea G, Mlecnik B, Tosolini M, Kirilovsky A, Waldner M, Obenauf AC, et al. Spatiotemporal dynamics of intratumoral immune cells reveal the immune landscape in human cancer. Immunity. 2013 Oct 17;39(4):782-95. PubMed PMID: 24138885. Epub 2013/10/22. eng.
55. Monteran L, Ershaid N, Doron H, Zait Y, Scharff Y, Ben-Yosef S, et al. Chemotherapy-induced complement signaling modulates immunosuppression and metastatic relapse in breast cancer. Nature communications. 2022 Oct 2;13(1):5797. PubMed PMID: 36184683. Pubmed Central PMCID: PMC9527249. Epub 2022/10/03. eng.
56. Karagiannis GS, Condeelis JS, Oktay MH. Chemotherapy-Induced Metastasis: Molecular Mechanisms, Clinical Manifestations, Therapeutic Interventions. Cancer research. 2019 Sep 15;79(18):4567-76. PubMed PMID: 31431464. Pubmed Central PMCID: PMC6744993. Epub 2019/08/23. eng.
57. Das RK, O'Connor RS, Grupp SA, Barrett DM. Lingering effects of chemotherapy on mature T cells impair proliferation. Blood advances. 2020 Oct 13;4(19):4653-64. PubMed PMID: 33002133. Pubmed Central PMCID: PMC7556159 support from Novartis, Servier and Kite; consulting, study steering committees, or scientific advisory boards: Novartis, Adaptimmune, Eureka, TCR2, Juno, GlaxoSmithKline, Cellectis, Janssen, Roche; and a toxicity management patent managed by University of Pennsylvania policies. D.M.B. discloses participation in a scientific advisory board for Eureka. The remaining authors declare no competing financial interests. Epub 2020/10/02. eng.
58. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. Cancer. 2004 Jan 15;100(2):228-37. PubMed PMID: 14716755. Epub 2004/01/13. eng.
59. Mackall CL, Fleisher TA, Brown MR, Magrath IT, Shad AT, Horowitz ME, et al. Lymphocyte depletion during treatment with intensive chemotherapy for cancer. Blood. 1994 Oct 1;84(7):2221-8. PubMed PMID: 7919339. Epub 1994/10/01. eng.
60. Sewell HF, Halbert CF, Robins RA, Galvin A, Chan S, Blamey RW. Chemotherapy-induced differential changes in lymphocyte subsets and natural-killer-cell function in patients with advanced breast cancer. International journal of cancer. 1993 Nov 11;55(5):735-8. PubMed PMID: 7902339. Epub 1993/11/11. eng.
61. Li Z, Lin A, Gao Z, Jiang A, Xiong M, Song J, et al. B-cell performance in chemotherapy: Unravelling the mystery of B-cell therapeutic potential. Clinical and translational medicine. 2024 Jul;14(7):e1761. PubMed PMID: 38997802. Pubmed Central PMCID: PMC11245406. Epub 2024/07/13. eng.
62. Wu Y, Cao F, Zhou D, Chen S, Qi H, Huang T, et al. Cryoablation reshapes the immune microenvironment in the distal tumor and enhances the anti-tumor immunity. Frontiers in immunology. 2022;13:930461. PubMed PMID: 36119081. Pubmed Central PMCID: PMC9470839. Epub 2022/09/20. eng.
63. Yakkala C, Denys A, Kandalaft L, Duran R. Cryoablation and immunotherapy of cancer. Current opinion in biotechnology. 2020 Oct;65:60-4. PubMed PMID: 32088576. Epub 2020/02/24. eng.

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Preprints.org | NOT PEER-REVIEWED | Posted: 20 November 2026 https://doi.org/10.20944/preprints202611.2126.v1

64. Sardela de Miranda F, Martinez-Marin D, Babcock RL, Castro M, Boligala GP, Khan SY, et al. Cryoablation of primary breast cancer tumors induces a systemic abscopal effect altering TIME (Tumor Immune Microenvironment) in distant tumors. Frontiers in immunology. 2024;15:1498942. PubMed PMID: 39703517. Pubmed Central PMCID: PMC11657241. Epub 2024/12/20. eng.
65. Zhang N, Li Z, Han X, Zhu Z, Li Z, Zhao Y, et al. Irreversible Electroporation: An Emerging Immunomodulatory Therapy on Solid Tumors. Frontiers in immunology. 2021;12:811726. PubMed PMID: 35069599. Pubmed Central PMCID: PMC8777104. Epub 2022/01/25. eng.
66. Kadosawa T, Watabe A. The effects of surgery-induced immunosuppression and angiogenesis on tumour growth. Veterinary journal (London, England : 1997). 2015 Aug;205(2):175-9. PubMed PMID: 25956342. Epub 2015/05/10. eng.
67. Vallejo R, Hord ED, Barna SA, Santiago-Palma J, Ahmed S. Perioperative immunosuppression in cancer patients. Journal of environmental pathology, toxicology and oncology : official organ of the International Society for Environmental Toxicology and Cancer. 2003;22(2):139-46. PubMed PMID: 14533877. Epub 2003/10/10. eng.
68. Tang F, Tie Y, Hong W, Wei Y, Tu C, Wei X. Targeting Myeloid-Derived Suppressor Cells for Premetastatic Niche Disruption After Tumor Resection. Annals of surgical oncology. 2021 Jul;28(7):4030-48. PubMed PMID: 33258011. Pubmed Central PMCID: PMC7703739. Epub 2020/12/02. eng.
69. Bezu L, Akçal Öksüz D, Bell M, Buggy D, Diaz-Cambronero O, Enlund M, et al. Perioperative Immunosuppressive Factors during Cancer Surgery: An Updated Review. Cancers. 2024 Jun 22;16(13). PubMed PMID: 39001366. Pubmed Central PMCID: PMC11240822. Epub 2024/07/13. eng.
70. Yang F, Hua Q, Zhu X, Xu P. Surgical stress induced tumor immune suppressive environment. Carcinogenesis. 2024 Apr 12;45(4):185-98. PubMed PMID: 38366618. Epub 2024/02/17. eng.
71. Ananth AA, Tai LH, Lansdell C, Alkayyal AA, Baxter KE, Angka L, et al. Surgical Stress Abrogates Pre-Existing Protective T Cell Mediated Anti-Tumor Immunity Leading to Postoperative Cancer Recurrence. PloS one. 2016;11(5):e0155947. PubMed PMID: 27196057. Pubmed Central PMCID: PMC4873120. Epub 2016/05/20. eng.
72. Market M, Tennakoon G, Auer RC. Postoperative Natural Killer Cell Dysfunction: The Prime Suspect in the Case of Metastasis Following Curative Cancer Surgery. International journal of molecular sciences. 2021 Oct 21;22(21). PubMed PMID: 34768810. Pubmed Central PMCID: PMC8583911. Epub 2021/11/14. eng.
73. Xu ZY, Li ZZ, Cao LM, Zhong NN, Liu XH, Wang GR, et al. Seizing the fate of lymph nodes in immunotherapy: To preserve or not? Cancer letters. 2024 Apr 28;588:216740. PubMed PMID: 38423247. Epub 2024/03/01. eng.
74. Saddawi-Konefka R, Schokrpur S, Gutkind JS. Let it be: Preserving tumor-draining lymph nodes in the era of immuno-oncology. Cancer cell. 2024 Jun 10;42(6):930-3. PubMed PMID: 38861928. Epub 2024/06/12. eng.
75. Grant SM, Lou M, Yao L, Germain RN, Radtke AJ. The lymph node at a glance - how spatial organization optimizes the immune response. Journal of cell science. 2020 Mar 6;133(5). PubMed PMID: 32144196. Pubmed Central PMCID: PMC7063836. Epub 2020/03/08. eng.
76. Dotta E, Maciola AK, Baccega T, Pasqual G. Dendritic cells steering antigen and leukocyte traffic in lymph nodes. FEBS letters. 2024 Jul 12. PubMed PMID: 38997244. Epub 2024/07/13. eng.
77. Wirth TC, Xue HH, Rai D, Sabel JT, Bair T, Harty JT, et al. Repetitive antigen stimulation induces stepwise transcriptome diversification but preserves a core signature of memory CD8(+) T cell differentiation. Immunity. 2010 Jul 23;33(1):128-40. PubMed PMID: 20619696. Pubmed Central PMCID: PMC2912220. Epub 2010/07/14. eng.
78. Rudloff MW, Zumbo P, Favret NR, Roetman JJ, Detrés Román CR, Erwin MM, et al. Hallmarks of CD8(+) T cell dysfunction are established within hours of tumor antigen encounter before cell division. Nature immunology. 2023 Sep;24(9):1527-39. PubMed PMID: 37537361. Pubmed Central PMCID: PMC10878719. Epub 2023/08/04. eng.
79. Cardenas MA, Prokhnevska N, Kissick HT. Organized immune cell interactions within tumors sustain a productive T-cell response. International immunology. 2021 Jan 1;33(1):27-37. PubMed PMID: 32827212. Pubmed Central PMCID: PMC7771196. Epub 2020/08/23. eng.

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Preprints.org | NOT PEER-REVIEWED | Posted: 20 November 2026 https://doi.org/10.20944/preprints202611.2126.v1

80. van der Heide V, Humblin E, Vaidya A, Kamphorst AO. Advancing beyond the twists and turns of T cell exhaustion in cancer. Science translational medicine. 2022 Nov 9;14(670):eabo4997. PubMed PMID: 36350991. Pubmed Central PMCID: PMC10000016. Epub 2022/11/10. eng.
81. Lamarche C, Novakovsky GE, Qi CN, Weber EW, Mackall CL, Levings MK. Repeated stimulation or tonic-signaling chimeric antigen receptors drive regulatory T cell exhaustion. bioRxiv. 2020 2020/6/28.
82. Baessler A, Vignali DAA. T Cell Exhaustion. Annual review of immunology. 2024 Jun;42(1):179-206. PubMed PMID: 38166256. Epub 2024/01/03. eng.
83. Belk JA, Daniel B, Satpathy AT. Epigenetic regulation of T cell exhaustion. Nature immunology. 2022 Jun;23(6):848-60. PubMed PMID: 35624210. Pubmed Central PMCID: PMC10439681. Epub 2022/05/28. eng.
84. Zhang B, Liu J, Mo Y, Zhang K, Huang B, Shang D. CD8(+) T cell exhaustion and its regulatory mechanisms in the tumor microenvironment: key to the success of immunotherapy. Frontiers in immunology. 2024;15:1476904. PubMed PMID: 39372416. Pubmed Central PMCID: PMC11452849. Epub 2024/10/07. eng.
85. Guo Y, Xue L, Tang W, Xiong J, Chen D, Dai Y, et al. Ovarian microenvironment: challenges and opportunities in protecting against chemotherapy-associated ovarian damage. Human reproduction update. 2024 Oct 1;30(5):614-47. PubMed PMID: 38942605. Pubmed Central PMCID: PMC11369228. Epub 2024/06/29. eng.
86. Karpov SM, Babenko DV, Tambieva HKC, Klimenko AI, Vyshlova IA. Nervous system damage in breast cancer patients receiving chemotherapy. Journal of Volgograd State Medical University. 2024 2024/1/27;20(4):22-7.
87. Alonso Domínguez T, Civera Andrés M, Santiago Crespo JA, García Malpartida K, Botella Romero F. Digestive toxicity in cancer treatments. Bibliographic review. Influence on nutritional status. Endocrinologia, diabetes y nutricion. 2023 Feb;70(2):136-50. PubMed PMID: 36868926. Epub 2023/03/04. eng.
88. Vera G, Nurgali K, Abalo R. Chemotherapy-Induced Neuropathy Affecting the Gastrointestinal Tract. Neurogastroenterology and motility. 2025 Aug;37(8):e14976. PubMed PMID: 39651634. Pubmed Central PMCID: PMC12287903. Epub 2024/12/09. eng.
89. Mansell E, van Tienhoven T, Sjoberg J, Lepland J, Rydstrom A, Bucakci A, et al. 3126 – PERSISTENT METABOLIC DEFLATION OF HEMATOPOIETIC STEM CELLS (HSCS) AFTER CHEMOTHERAPY CAUSES PREMATURE HEMATOPOIETIC AGEING. Experimental hematology. 2024 2024/8;137:104447.
90. Traversari C, van der Bruggen P, Luescher IF, Lurquin C, Chomez P, Van Pel A, et al. A nonapeptide encoded by human gene MAGE-1 is recognized on HLA-A1 by cytolytic T lymphocytes directed against tumor antigen MZ2-E. The Journal of experimental medicine. 1992 Nov 1;176(5):1453-7. PubMed PMID: 1402688. Pubmed Central PMCID: PMC2119413. Epub 1992/11/01. eng.
91. Szikora JP, Van Pel A, Boon T. Tum- mutation P35B generates the MHC-binding site of a new antigenic peptide. Immunogenetics. 1993;37(2):135-8. PubMed PMID: 8423052. Epub 1993/01/01. eng.
92. Steinman RM, Cohn ZA. Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution. The Journal of experimental medicine. 1973 May 1;137(5):1142-62. PubMed PMID: 4573839. Pubmed Central PMCID: PMC2139237. Epub 1973/05/01. eng.
93. Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. The EMBO journal. 1992 Nov;11(11):3887-95. PubMed PMID: 1396582. Pubmed Central PMCID: PMC556898. Epub 1992/11/01. eng.
94. Dong H, Zhu G, Tamada K, Chen L. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. Nature medicine. 1999 Dec;5(12):1365-9. PubMed PMID: 10581077. Epub 1999/12/02. eng.
95. Waterhouse P, Penninger JM, Timms E, Wakeham A, Shahinian A, Lee KP, et al. Lymphoproliferative disorders with early lethality in mice deficient in Ctla-4. Science (New York, NY). 1995 Nov 10;270(5238):985-8. PubMed PMID: 7481803. Epub 1995/11/10. eng.
96. Tivol EA, Borriello F, Schweitzer AN, Lynch WP, Bluestone JA, Sharpe AH. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. Immunity. 1995 Nov;3(5):541-7. PubMed PMID: 7584144. Epub 1995/11/01. eng.

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Preprints.org | NOT PEER-REVIEWED | Posted: 20 November 2026 https://doi.org/10.20944/preprints202611.2126.v1

97. Krummel MF, Allison JP. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. The Journal of experimental medicine. 1995 Aug 1;182(2):459-65. PubMed PMID: 7543139. Pubmed Central PMCID: PMC2192127. Epub 1995/08/01. eng.
98. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. Science (New York, NY). 1996 Mar 22;271(5256):1734-6. PubMed PMID: 8596936. Epub 1996/03/22. eng.
99. Ioannides CG, Whiteside TL. T cell recognition of human tumors: implications for molecular immunotherapy of cancer. Clinical immunology and immunopathology. 1993 Feb;66(2):91-106. PubMed PMID: 8453790. Epub 1993/02/01. eng.
100. Whiteside TL. Tumor microenvironment and immune effector cells. Introduction. Immunology series. 1994;61:133-6. PubMed PMID: 8011737. Epub 1994/01/01. eng.
101. Whiteside TL. The tumor microenvironment and its role in promoting tumor growth. Oncogene. 2008 Oct 6;27(45):5904-12. PubMed PMID: 18836471. Pubmed Central PMCID: PMC3689267. Epub 2008/10/07. eng.

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