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How Metastatic Cancer Cells Escape Immune System Detection Through EMT: A Review

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ABSTRACT

The global prevalence of cancer and its consequential mortality underscores the urgency of understanding the metastatic process, a primary cause of cancer-related deaths. Metastasis, characterized by the spread of cancer cells to distant sites, often involves immune evasion mechanisms facilitating uncontrolled growth. Epithelial-mesenchymal transition (EMT) is a pivotal process enabling metastatic cells to detach from the primary tumor and migrate. EMT induces alterations in surface molecule expression, impairing immune cell recognition. This transition also affects the tumor microenvironment, leading to immune-suppressive cytokine release. The need to investigate EMT-mediated immune evasion is immediate, as it is crucial for developing novel strategies to combat metastatic cancer by targeting these evasive mechanisms. This review aims to summarize molecular changes during EMT, evaluate its impact on surface molecules and the tumor microenvironment that helps it escape from the immune system, and offer insights for devising strategies to target EMT-driven metastatic cells.

Introduction

Cancer stands as a formidable health challenge, evolving from a dreaded 20th-century disease to an escalating 21st-century crisis, with a concerning one-in-four lifetime risk for individuals (Roy PS, Saikia BJ. 2016). The complexity of cancer is evident in its diverse manifestations, exhibiting spatial and temporal heterogeneity within and between entities and subtypes fueled by consecutive mutations and clonal evolution (McGranahan and Swanton 2017). Proliferation of cells, evading central control mechanisms, defines cancer, categorized by organ or tissue of origin and molecular characteristics.

Cancer's development involves intricate mechanisms with successive carcinogenic effects. Cancer can prevail despite defense mechanisms and immune responses due to ineffective defenses and immune system deficiencies, allowing carcinogenic cells to multiply excessively (X. Li et al. 2019).

Studies define several key factors contributing to a heightened cancer risk. External factors, constituting 85%, encompass smoking, environmental pollution, and a poor diet, each playing a significant role. Smoking is deemed the leading cause of global cancer deaths, emphasizing the absence of a safe exposure level (Dr. Otis Brawley, Commonwealth Club 2014). Environmental pollutants, such as asbestos and radon, also contribute, as highlighted by a former National Cancer Institute United States director. Congress. Senate. Committee on Environment and Public Works 1994). Dietary choices, obesity, and infectious agents like HPV and hepatitis further elevate risks (Dr. David Hunter, Times 2022; Prigge et al. 2015).

Internal factors, accounting for 15%, involve hereditary causes, changes, immune deficiencies, and hormonal/metabolic disorders (Henderson, Ponder and Ross, 2003). Overall, understanding these multifaceted aspects of cancer is crucial for developing effective prevention and treatment strategies in the ongoing battle against this pervasive disease.

Metastasis, a primary cause of cancer-related deaths globally, is driven by the transformative process of Epithelial-Mesenchymal Transition (EMT). EMT, a multi-step process altering cell characteristics, trans-

forms epithelial cells into mesenchymal cells, enhancing their migratory and invasive properties and contributing to cancer progression and mortality. This evasion mechanism impedes immune recognition by altering surface protein expression, potentially reducing MHC class I levels crucial for tumor antigen presentation. Furthermore, EMT-induced changes in the tumor microenvironment support immune evasion through pro-inflammatory cytokine production. Investigating EMT's role in immune evasion is vital for understanding cancer dynamics, necessitating research on molecular changes, effects on immune recognition, and microenvironment alterations. Developing strategies to target EMT-driven metastatic cancer cells is crucial for advancing cancer treatment.

Metastasis and Significance of EMT

Metastasis, the formation of secondary tumors in distant parts of the body originating from primary cancer, represents a significant challenge in cancer management and a primary cause of death for over 90% of cancer patients. The spread of cancer cells to remote organs gives rise to secondary tumors, presenting more formidable treatment challenges than the original tumor. Advanced stages of cancer with metastasis substantially decrease the likelihood of successful treatment, highlighting metastasis as a significant hurdle in cancer management (Steeg 2006).

The metastatic process is a dynamic and multifaceted journey wherein normal cells transform into oncogenic cells that uncontrollably proliferate. Throughout this process, metastatic cells demonstrate the ability to elude the immune system, resist programmed cell death, induce angiogenesis, gain invasive potential, survive in the bloodstream, and establish cancerous growths in distant organs (Welch and Hurst 2019; Hanahan and Weinberg 2011). Despite being a pivotal factor in the failure of cancer therapy and a leading cause of mortality, our understanding of metastasis remains incomplete. Studies indicate that, despite the release of a large number of cancer cells into circulation daily, a fraction as small as <0.1% of tumor cells metastasize, emphasizing the intricate challenges involved in the metastatic process (Luzzi et al. 1998; Halbrook et al. 2023; Massagué and Obenauf 2016).

Cancer, a major global cause of death with an annual toll of 8.2 million, is expected to rise further with an aging population. Carcinomas can be broadly classified into metastatic, the primary cause of cancer-related deaths, and nonmetastatic (Siegel et al. 2016). Traditionally, metastasis has been linked to later stages of cancer progression; however, emerging evidence suggests that metastatic dissemination can occur even in the early stages of tumor formation (Hosseini et al. 2016). During metastasis, cancer cells detach from primary tumors, acquiring traits that enable them to travel and colonize distant organs (Chambers and Werb 2015; Lambert et al. 2017; Gonzalez et al. 2018).

Cancer is inherently a systemic disease, and prolonged inflammation is a recognized hallmark. The role of inflammation in initiating tumorigenesis or supporting tumor growth is context-dependent. However, the global immune landscape beyond the tumor undergoes significant alterations during tumor progression (Coussens and Werb 2002). Understanding the intricate interplay between inflammation and cancer progression is crucial, as it contributes to the systemic nature of the disease.

Metastasis, a critical aspect of cancer research, remains a challenge marked by its complex and dynamic nature. Despite advancements, the intricate mechanisms of how cancer cells escape, travel, and establish themselves in distant organs remain elusive. Addressing these challenges is essential to improving cancer management and reducing mortality rates associated with this pervasive aspect of the disease. As research continues to unravel the intricacies of metastasis, it holds the potential to pave the way for more effective therapeutic interventions and a deeper understanding of cancer's systemic impact.

Cancer becomes an even more formidable challenge when it undergoes metastasis, spreading to distant sites within the body. This complex process involves the movement of primary tumor cells, prompting a crucial question about the predominant behavior of metastatic cancer cells—whether they primarily proliferate or adopt

migratory characteristics. In the normal cellular milieu, growth (proliferation), movement (migration), and differentiation into specialized cells are spatially and temporally distinct actions crucial for essential processes such as embryonic development, wound healing, and organ maintenance.

The concept of epithelial-mesenchymal transition (EMT), first elucidated by Elizabeth Hay in 1968 (Hay 1991), is at the forefront of understanding the metastatic journey. EMT is a fundamental process in organ development, wound healing, and fibrosis and continues to captivate researchers with its dynamic complexity. To fully appreciate EMT, one must delve into the phenotypic characteristics of epithelial and mesenchymal cells, the two extremes of the cellular spectrum.

Epithelial cells exhibit apicobasal polarity, cuboidal morphology, and strong adherence to the extracellular matrix. Tight cell-cell interactions define their spatial organization, forming colonies with a characteristic cuboidal shape *in vitro* culture. In early embryonic development, epithelial cells form polarized layers with extensive apicobasal cell surface polarity. On the contrary, mesenchymal cells arise during gastrulation through EMT, losing apicobasal polarity, redistributing their actin cytoskeleton, and connecting to the basal surface through focal adhesions and intercellular punctate adhesions.

The intricacies of organogenesis involve cycles of EMT and mesenchymal-epithelial transition (MET), a phenomenon observed in heart development. A striking example of EMT is witnessed in the formation and extensive migrations of cells of the neural crest during embryogenesis, properties believed to be exploited by cancer cells for initiating invasion and metastasis (Deugnier et al. 2002).

EMT is primarily driven by transcriptional repressors known as EMT transcription factors (EMT-TFs) (Figure 1), including SNAIL1/2 and ZEB1/2. These factors directly repress E-cadherin expression by binding to E-boxes on its proximal promoter. Other transcription factors, such as TWIST, FOXC2, E47 (TFC3), KLF8, and PRRX1, also induce EMT, though the direct regulation of E-cadherin expression remains unclear. MicroRNAs (miRs), such as the miR-200 family, play a critical role in maintaining the epithelial state through negatively regulated feedback loops with EMT-TFs. Beyond transcriptional and miR regulation, splicing mechanisms, posttranslational modifications, and epigenetic changes significantly contribute to the EMT phenotype (De Craene and Berx, 2013).

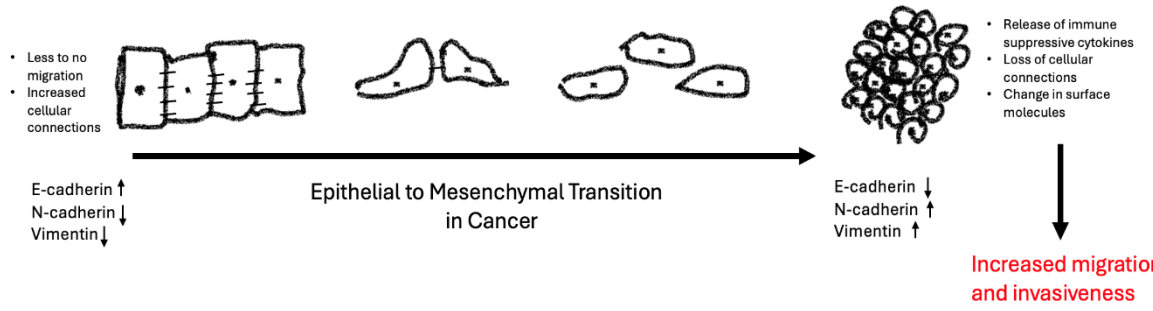

Figure 1. Epithelial to mesenchymal transition in cancer cells. Cellular connections, transcription factor expression profile and cell surface markers of epithelial state cells change drastically in the process to increase migration ability and invasiveness.

The frequency of cancers arising from mutations in EMT-associated genes varies widely across different cancer types. For instance, ZEB1 mutations are implicated in colorectal cancer, while SNAIL1 and SNAIL2 mutations are reported in breast and lung cancers. Epigenetic modifications, such as DNA methylation and histone repressive marks, ensure a more stable position in the EMT spectrum, whereas poised chromatin allows for a more plastic phenotype residing in the intermediate EMT stages (Tam and Weinberg, 2013).

Some transcription factors, like GRHL2, are originally shown to sustain E-cadherin gene expression and may also participate in maintaining the stability of the epithelial state. GRHL2 protects carcinoma cells from transitioning from the intermediate epithelial to the mesenchymal state. However, the forced expression of GRHL2 in mesenchymal ovarian carcinoma cells cannot revert the cells to an epithelial state (Chung et al., 2016).

The irreversibility of this transition is primarily attributed to the heterochromatization of GRHL2 target genes. Recent studies have emphasized that mesenchymal carcinoma cells acquire stem cell properties and a drug-resistant phenotype. However, several questions remain unanswered, such as when and how carcinoma cells acquire a mesenchymal phenotype, drug resistance, and stemness. Does this transformation occur before or during dissemination through the lymph and blood vessels?

Approximately 3% of luminal breast carcinoma cells express mesenchymal markers, with a significantly higher percentage detected in triple-negative breast tumors. A longitudinal analysis of patients with metastatic breast cancer undergoing several cycles of different targeted therapeutics revealed full refractoriness once their tumors reached a mesenchymal phenotype.

The local microenvironment and hypoxia may trigger the induction of EMT in carcinoma cells, priming specific cells for disseminating from the primary tumor. Stromal cells, including myofibroblast and inflammatory cells, could contribute as EMT inducers by secreting numerous growth factors and cytokines (Bai et al., 2015; Wyckoff et al., 2007). Overall, the intermediate epithelial and mesenchymal carcinoma phenotypes seem more conducive to tumor progression and distant dissemination, making EMT a promising target for therapeutic intervention to prevent or suppress these harmful effects.

A critical challenge lies in developing new therapeutic strategies based on the EMT concept. Additionally, the understanding that EMT confers invasion, metastasis, stemness, and drug resistance needs to be translated from murine models to the clinical setting. Such studies will pave the way for a more profound understanding of the essential properties conferred by EMT during dissemination.

Epithelial-mesenchymal transition (EMT) is a linchpin in cancer progression, influencing key steps such as invasion, migration, adhesion, and growth. Moreover, changes in surface molecules during EMT can hinder the immune system's recognition and targeting of cancer cells, contributing to immune evasion. The complex mechanisms involved in EMT encompass gene expression, proteins, the cytoskeleton, and intricate signaling pathways such as transforming growth factor-beta (TGF-β), Wnt, Notch, and Hedgehog.

The signaling pathways regulating EMT are complex and interconnected, allowing for crosstalk between them. Activation of these pathways involves various factors, including growth factors, cytokines, and extracellular matrix (ECM) proteins. The intricate crosstalk and interconnectedness of these pathways make targeting EMT challenging with a single therapy. Nevertheless, understanding these mechanisms provides the foundation for developing novel strategies to target and eliminate metastatic cancer cells.

In conclusion, the journey through the intricacies of EMT unfolds as a captivating saga in cancer biology. From normal cellular growth, movement, and differentiation to the orchestrated intricacies of EMT, the cellular landscape transforms in response to a complex interplay of genetic, molecular, and environmental factors. As we unravel the mysteries of EMT, the hope is that these insights will pave the way for innovative therapeutic interventions, ultimately tipping the balance in the ongoing battle against metastatic cancer.

Immune Detection of Cancer Cells

The immune system serves as a crucial guardian, protecting the body from pathogens and actively participating in cancer prevention, development, and defense. Rudolph Virchow first highlighted the link between the immune system and cancer over 150 years ago, recognizing the profound impact this intricate network has on the body's overall health (Adams et al. 2015).

Cancer, a major global cause of death with an annual toll of 8.2 million, is anticipated to rise further with an aging population (Ferlay et al. 2015). Carcinomas can be broadly categorized into two groups: metastatic, the principal cause of cancer-related deaths, and nonmetastatic (Siegel et al. 2016). Traditionally, metastasis has been considered to occur in later stages of cancer progression; however, accumulating evidence also describes metastatic dissemination during early tumor formation (Hosseini et al. 2016). Cancer, inherently a systemic disease, is marked by prolonged inflammation (Coussens and Werb 2002). Whether this inflammation initiates tumorigenesis or supports tumor growth is context-dependent, but the global immune landscape undergoes significant alterations during tumor progression.

The immune system comprises various cells, each with specific roles in defending the body against threats. T cells, a fundamental component, develop from stem cells in the bone marrow and play a vital role in protecting the body from infections and fighting cancer cells (D. Li et al. 2019). T cells include cytotoxic T cells (CD8+ cells) and helper T cells (CD4+ cells). Cytotoxic T cells directly kill cells infected with viruses, bacteria, and tumor cells, while helper T cells coordinate immune responses by signaling other cells, such as cytotoxic T cells, B cells, and macrophages (Yu et al. 2019; Chang et al. 2023).

Although not considered one of the main T-cell types, regulatory T cells play a crucial role in immune system regulation. These cells reduce the activity of other T cells when necessary, preventing them from attacking the body's healthy cells. Recent progress in cancer immunotherapy underscores the importance of understanding immune-regulatory pathways in tumors and identifying the molecular drivers of T-cell dysfunction, which is crucial for advancing cancer research and therapy.

Apart from T cells, other immune cells contribute to the body's defense mechanisms. B cells produce antibodies that neutralize foreign invaders, showcasing the collaborative effort of different immune cell types in maintaining overall health (den Haan, Arens, and van Zelm 2014).

The immune system can recognize cancer cells through various mechanisms. One approach involves the detection of cancer antigens, proteins or molecules found on the surface of cancer cells but not normal cells. When recognized by the immune system, these antigens trigger an immune response (Multhoff et al. 1995). Another recognition method involves changes in gene expression within cancer cells, producing abnormal proteins or molecules that signal the immune system to mount a response (Somensi et al. 2017).

The tumor microenvironment, the surroundings of tumor cells, can also signal the immune system about the presence of a tumor (Galli et al. 2020). Once the immune system recognizes cancer cells, it launches a response involving various immune cells, such as T cells, B cells, and natural killer cells, working together to eliminate or prevent the growth and spread of cancer cells.

Despite the immune system's pivotal role in cancer defense, challenges exist. Cancer cells can evade the immune system by altering surface proteins or suppressing immune cell activity. Additionally, the tumor microenvironment may create conditions unfavorable for an immune response.

Despite these challenges, the immune system offers a crucial avenue in the fight against cancer. New immunotherapies are developing, aiming to boost the immune system's ability to recognize and eliminate cancer cells. These promising therapies are currently undergoing clinical trials and hold the potential to introduce innovative treatment options for cancer patients (Gough and Crittenden 2012). The evolving landscape of cancer immunotherapy signifies a growing understanding of the immune system's intricate role in combating cancer and paves the way for improved therapeutic interventions.

Therapeutic Strategies to Overcome Metastasis

Cancer treatments, such as chemotherapy and radiation therapy, have long been the mainstay for combating cancer. Chemotherapy involves using drugs to target and eliminate rapidly dividing cancer cells throughout the body, while radiation therapy employs high-energy rays to damage cancer cells' DNA, hindering their growth

and division. Despite their effectiveness in localized cancers, these treatments encounter significant challenges with metastatic cancers, where cancer cells have spread to distant parts of the body.

Chemotherapy targets rapidly dividing cells, including cancer cells, but it also affects normal fast-dividing cells like those in the bone marrow and gastrointestinal tract, leading to side effects such as fatigue, nausea, and hair loss. In metastatic cancer, the spread of cancer cells to multiple locations makes it challenging for chemotherapy to effectively target all sites simultaneously. Additionally, cancer cells may develop resistance to chemotherapy over time, contributing to treatment failures.

Radiation therapy is successful in killing cancer cells by damaging their DNA. However, its effectiveness is highest when targeting a specific area, and metastatic cancers often involve multiple distant sites. Administering radiation to all these sites concurrently can increase toxicity in healthy tissues. Moreover, some metastatic lesions may be in sensitive areas where delivering adequate radiation doses without harming surrounding healthy tissues becomes difficult.

Metastatic cancers pose a unique challenge due to their ability to spread throughout the body via the bloodstream or lymphatic system, making it challenging to eradicate all cancer cells with localized treatments. These tumors may develop genetic variations that allow them to resist chemotherapy and radiation. The heterogeneity of metastatic tumors, in terms of their genetic makeup and microenvironment, further complicates treatment strategies.

Addressing metastatic cancer may require combination therapies, such as immunotherapy coupled with metabolic inhibitors. Nanomaterials and antibody-drug conjugates could enable targeted drug delivery to tumors, limiting the side effects of chemotherapies. Personalized therapies tailored to a patient's cancer-specific mutation status or immune system components, like T cells, may offer potential treatment options. However, utilizing personalized or targeted therapies for cancer metastasis presents challenges, including the lack of targetable mutations, logistical issues in genomic screening, and tumor heterogeneity.

A comprehensive understanding of cancer metastasis is essential to develop more effective therapies for metastatic cancer. It will be crucial to explore hybrid E/M cells, epithelial-mesenchymal transition (EMT), metabolic rewiring, immune reprogramming, and their interconnections. The future of cancer metastasis treatment relies on understanding the processes initiating metastasis, gaining EMP in specific cells, deciphering the causes of organ-specific metastatic homing, and comprehending how cancer cells exploit the immune system. A multi-targeted approach will likely be vital in combating cancer metastasis, as no single agent or treatment can provide a cure.

EMT emerges as a crucial process that contributes to immune resistance and activates an immunosuppressive network within the tumor microenvironment (TME). Targeting EMT may hold significant promise for enhancing current immunotherapy approaches for advanced tumors (Terry et al. 2017). Understanding the intricacies of EMT and its impact on the immune system could pave the way for innovative strategies in the ongoing battle against metastatic cancer.

Conclusion

In conclusion, the pivotal role of Epithelial-Mesenchymal Transition (EMT) in cancer metastasis cannot be understated, as it brings about changes in cellular characteristics and signaling pathways. The challenges in precisely and effectively targeting EMT necessitate a multi-pronged approach. Understanding the intricate processes involved, exploring combination therapies, and developing personalized treatments hold the potential for breakthroughs in managing metastatic cancer.

The pressing global challenge posed by cancer is significant, with incidence rates on the rise in the 20th and 21st centuries. The complexity of the disease, marked by genetic diversity and tumor heterogeneity,

emphasizes the imperative for precise diagnostics and personalized therapies. Cancer's evolution involves evading control mechanisms due to genetic mutations and clonal evolution, with various factors contributing to risk, including lifestyle choices, environmental pollutants, and genetic predisposition.

As the second leading cause of death worldwide, cancer's impact is significant, and the emphasis on metastasis, where cancer cells spread to distant organs, is crucial. The various steps in this process are outlined, shedding light on the intricate nature of cancer progression. The immune system's role in recognizing and eliminating cancer cells is explored, along with the potential for immunotherapy to enhance immune responses, aligning with recent advancements in cancer treatment.

The discussion on stem cells and differentiated cell types highlights their potential for regenerative therapies, providing a glimpse into innovative approaches. EMT is a complex process driving cancer metastasis through gene expression, proteins, and cytoskeletal reorganization changes. This understanding opens doors for targeted interventions in cancer progression.

Considering the rising incidence of cancer, genetic diversity, immune interactions, stem cells, and EMT-driven metastasis, the need for personalized therapies and diagnostics is emphasized to address the individual nature of cancer and its contributing factors.

Insights into immune interactions and stem cells offer valuable perspectives on potential therapeutic avenues, particularly in the context of evolving cancer treatments. The mention of immunotherapy and its potential to enhance immune responses aligns with recent advancements. Combination therapies and personalized treatments as potential strategies are relevant, though challenges posed by tumor heterogeneity and logistical barriers in genomic screening need addressing. Strategies should be designed to overcome challenges the immune system faces in defending against cancer, including cancer cells evading detection through alterations in surface proteins and suppression of immune cell activity. The tumor microenvironment can also create conditions unfavorable for an effective immune response.

Despite these obstacles, there is optimism in developing new immunotherapies to enhance the immune system's ability to recognize and eliminate cancer cells. These promising treatments are undergoing clinical trials, reflecting an evolving understanding of the immune system's role in cancer defense and offering potential innovative options for cancer patients (Gough and Crittenden 2012). A cancer vaccine is an immunotherapy that helps the body's immune system recognize and destroy cancer cells. Unlike vaccines that prevent infections from viruses or bacteria, cancer vaccines are used to treat existing cancer or prevent it from recurring after treatment.

There are two main types of cancer vaccines:

Therapeutic cancer vaccines: These vaccines treat people who already have cancer. They work by helping the immune system recognize and attack cancer cells.

Preventive cancer vaccines: These vaccines prevent cancer from developing. They work by exposing the body to weakened or inactivated forms of cancer cells or the viruses that cause cancer. The most well-known example is the HPV vaccine, which protects against human papillomavirus (HPV), a virus that can cause cervical cancer and other cancers.

In conclusion, navigating the intricate landscape of cancer demands a multifaceted approach, from understanding EMT-driven metastasis to exploring personalized therapies and harnessing the potential of immunotherapy. As we unravel the complexities of this pervasive disease, pursuing innovative strategies holds the promise of transforming the trajectory of cancer management and offering renewed hope to individuals facing its formidable challenges.

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References

Adams, Jerry L., James Smothers, Roopa Srinivasan, and Axel Hoos. 2015. "Big Opportunities for Small Molecules in Immuno-Oncology." *Nature Reviews. Drug Discovery* 14 (9): 603–22.

Arnedos, Monica, Cecile Vicier, Sherene Loi, Celine Lefebvre, Stefan Michiels, Herve Bonnefoi, and Fabrice Andre. 2015. "Precision Medicine for Metastatic Breast Cancer—limitations and Solutions." *Nature Reviews. Clinical Oncology* 12 (12): 693–704.

Babaei, Ghader, Shiva Gholizadeh-Ghaleh Aziz, and Nasrin Zare Zavieyh Jaghi. 2021. "EMT, Cancer Stem Cells and Autophagy; The Three Main Axes of Metastasis." *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 133 (January): 110909.

Chang, Xuechun, Kexin Jiao, Danjie Wang, Yufan Zhou, Zhao Zhao, Ying Xing, Jingzi Zhangbao, Chuanzhen Lu, Jun Wang, and Chao Quan. 2023. "The Immune Imbalance between Follicular Regulatory and Helper T Cells in Myelin Oligodendrocyte Glycoprotein IgG-Associated Disease." *Clinical Immunology* , August, 109734.

Coussens, Lisa M., and Zena Werb. 2002. "Inflammation and Cancer." *Nature* 420 (6917): 860–67.

Crystal, Ronald G., Scott H. Randell, John F. Engelhardt, Judith Voynow, and Mary E. Sunday. 2008. "Airway Epithelial Cells: Current Concepts and Challenges." *Proceedings of the American Thoracic Society* 5 (7): 772–77.

Deugnier, Marie-Ange, Jérôme Teulière, Marisa M. Faraldo, Jean Paul Thiery, and Marina A. Glukhova. 2002. "The Importance of Being a Myoepithelial Cell." *Breast Cancer Research: BCR* 4 (6): 224–30.

Dr. Otis Brawley: Fighting Patient Mistreatment in U.S. (Commonwealth Club). 2014. Kanopy Streaming.

Galli, Filippo, Jesus Vera Aguilera, Belinda Palermo, Svetomir N. Markovic, Paola Nisticò, and Alberto Signore. 2020. "Relevance of Immune Cell and Tumor Microenvironment Imaging in the New Era of Immunotherapy." *Journal of Experimental & Clinical Cancer Research: CR* 39 (1): 89.

Gough, Michael J., and Marka R. Crittenden. 2012. "Immune System Plays an Important Role in the Success and Failure of Conventional Cancer Therapy." *Immunotherapy* 4 (2): 125–28.

Haan, Joke M. M. den, Ramon Arens, and Menno C. van Zelm. 2014. "The Activation of the Adaptive Immune System: Cross-Talk between Antigen-Presenting Cells, T Cells and B Cells." *Immunology Letters* 162 (2 Pt B): 103–12.

Halbrook, Christopher J., Costas A. Lyssiotis, Marina Pasca di Magliano, and Anirban Maitra. 2023. "Pancreatic Cancer: Advances and Challenges." *Cell* 186 (8): 1729–54.

Hanahan, Douglas, and Robert A. Weinberg. 2011. "Hallmarks of Cancer: The next Generation." *Cell* 144 (5): 646–74.

Han, Joungho, Kyung Soo Lee, Chin A. Yi, Tae Sung Kim, Young Mog Shim, Jhingook Kim, Kwhanmien Kim, and O. Jung Kwon. 2003. "Thymic Epithelial Tumors Classified according to a Newly Established WHO Scheme: CT and MR Findings." *Korean Journal of Radiology: Official Journal of the Korean Radiological Society* 4 (1): 46–53.

Hay, E. D. 1991. *Cell Biology of Extracellular Matrix: Second Edition*. Springer Science & Business Media.

Henderson, Brian E., Bruce Ponder, and Ronald K. Ross. 2003. *Hormones, Genes, and Cancer*. Oxford University Press.

Hiemstra, Pieter S., Paul B. McCray Jr, and Robert Bals. 2015. "The Innate Immune Function of Airway Epithelial Cells in Inflammatory Lung Disease." *The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology* 45 (4): 1150–62.

Islam, Farhadul, and Alfred K. Lam. 2023. *Cancer Stem Cells: Basic Concept and Therapeutic Implications*. Springer Nature.

Krieghoff-Henning, Eva, Juliane Folkerts, Andrea Penzkofer, and Susanne Weg-Remers. 2017. "Cancer – an Overview." *Medizinische Monatsschrift Fur Pharmazeuten* 40 (2): 48–54.

Krzyszczyk, Paulina, Alison Acevedo, Erika J. Davidoff, Lauren M. Timmins, Ileana Marrero-Berrios, Misaal Patel, Corina White, et al. 2018. "The Growing Role of Precision and Personalized Medicine for Cancer Treatment." *Technology* 6 (3-4): 79–100.

Kurn, Heidi, and Daniel T. Daly. 2023. "Histology, Epithelial Cell." In *StatPearls*. Treasure Island (FL): StatPearls Publishing.

Liang, Chao, Ligeng Xu, Guosheng Song, and Zhuang Liu. 2016. "Emerging Nanomedicine Approaches Fighting Tumor Metastasis: Animal Models, Metastasis-Targeted Drug Delivery, Phototherapy, and Immunotherapy." *Chemical Society Reviews* 45 (22): 6250–69.

Li, Dan, Xue Li, Wei-Lin Zhou, Yong Huang, Xiao Liang, Lin Jiang, Xiao Yang, et al. 2019. "Genetically Engineered T Cells for Cancer Immunotherapy." *Signal Transduction and Targeted Therapy* 4 (September): 35.

Lim, Jormay, and Jean Paul Thiery. 2012. "Epithelial-Mesenchymal Transitions: Insights from Development." *Development* 139 (19): 3471–86.

Li, Xiaoyun, Mathias Wenes, Pedro Romero, Stanley Ching-Cheng Huang, Sarah-Maria Fendt, and Ping-Chih Ho. 2019. "Navigating Metabolic Pathways to Enhance Antitumour Immunity and Immunotherapy." *Nature Reviews. Clinical Oncology* 16 (7): 425–41.

Li, Yan-Ruide, Zachary Spencer Dunn, Yang Zhou, Derek Lee, and Lili Yang. 2021. "Development of Stem Cell-Derived Immune Cells for Off-the-Shelf Cancer Immunotherapies." *Cells* 10 (12). https://doi.org/10.3390/cells10123497.

Luzzi, K. J., I. C. MacDonald, E. E. Schmidt, N. Kerkvliet, V. L. Morris, A. F. Chambers, and A. C. Groom. 1998. "Multistep Nature of Metastatic Inefficiency: Dormancy of Solitary Cells after Successful Extravasation and Limited Survival of Early Micrometastases." *The American Journal of Pathology* 153 (3): 865–73.

Maclean, Norman. 1977. *The Differentiation of Cells*. E. Arnold.

Mason, Chris, and Peter Dunnill. 2008. "A Brief Definition of Regenerative Medicine." *Regenerative Medicine* 3 (1): 1–5.

Massagué, Joan, and Anna C. Obenauf. 2016. "Metastatic Colonization by Circulating Tumour Cells." *Nature* 529 (7586): 298–306.

McGranahan, Nicholas, and Charles Swanton. 2017. "Clonal Heterogeneity and Tumor Evolution: Past, Present, and the Future." *Cell* 168 (4): 613–28.

Mulholland, David J., Naoko Kobayashi, Marcus Ruscetti, Allen Zhi, Linh M. Tran, Jiaoti Huang, Martin Gleave, and Hong Wu. 2012. "Pten Loss and RAS/MAPK Activation Cooperate to Promote EMT and Metastasis Initiated from Prostate Cancer Stem/progenitor Cells." *Cancer Research* 72 (7): 1878–89.

Multhoff, G., C. Botzler, M. Wiesnet, E. Müller, T. Meier, W. Wilmanns, and R. D. Issels. 1995. "A Stress-Inducible 72-kDa Heat-Shock Protein (HSP72) Is Expressed on the Surface of Human Tumor Cells, but Not on Normal Cells." *International Journal of Cancer. Journal International Du Cancer* 61 (2): 272–79.

Niederman, M. S., T. D. Rafferty, C. T. Sasaki, W. W. Merrill, R. A. Matthay, and H. Y. Reynolds. 1983. "Comparison of Bacterial Adherence to Ciliated and Squamous Epithelial Cells Obtained from the Human Respiratory Tract." *The American Review of Respiratory Disease* 127 (1): 85–90.

Prigge, Justin R., Teri R. Hoyt, Erin Dobrinen, Mario R. Capecchi, Edward E. Schmidt, and Nicole Meissner. 2015. "Type I IFNs Act upon Hematopoietic Progenitors To Protect and Maintain Hematopoiesis during Pneumocystis Lung Infection in Mice." *Journal of Immunology* 195 (11): 5347–57.

Riva, Gabriele, Simona Baronchelli, Laura Paoletta, Valentina Butta, Ida Biunno, Marialuisa Lavitrano, Leda Dalprà, and Angela Bentivegna. 2014. "In Vitro Anticancer Drug Test: A New Method Emerges from the Model of Glioma Stem Cells." *Toxicology Reports* 1 (May): 188–99.

Roy, P. S., and B. J. Saikia. 2016. "Cancer and Cure: A Critical Analysis." *Indian Journal of Cancer* 53 (3):

441–42.

Sathananthan, Professor Arunachalam Henry. 2015. *HUMAN CELL AND TISSUE FINE STRUCTURE FOR TEACHING AND RESEARCH IN STEM CELLS*. Professor Arunachalam Henry Sathananthan.

Somensi, Nauana, Pedro Ozorio Brum, Vitor de Miranda Ramos, Juciano Gasparotto, Alfeu Zanotto-Filho, Diana Carolina Rostirolla, Maurilio da Silva Morrone, José Claudio Fonseca Moreira, and Daniel Pens Gelain. 2017. "Extracellular HSP70 Activates ERK1/2, NF-kB and Pro-Inflammatory Gene Transcription Through Binding with RAGE in A549 Human Lung Cancer Cells." *Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology* 42 (6): 2507–22.

Steeg, Patricia S. 2006. "Tumor Metastasis: Mechanistic Insights and Clinical Challenges." *Nature Medicine* 12 (8): 895–904.

Terry, Stéphane, Pierre Savagner, Sandra Ortiz-Cuaran, Linda Mahjoubi, Pierre Saintigny, Jean-Paul Thiery, and Salem Chouaib. 2017. "New Insights into the Role of EMT in Tumor Immune Escape." *Molecular Oncology* 11 (7): 824–46.

Times, O. 2022. "Shop Talk." *Oncology Times* 44 (11): 36–37.

Uchinomiya, Kouki, and Masanori Tomita. 2023. "A Mathematical Model for Cancer Risk and Accumulation of Mutations Caused by Replication Errors and External Factors." *PloS One* 18 (6): e0286499.

United States. Congress. Senate. Committee on Environment and Public Works. 1994. *Nominations of Frederic J. Hansen, Paul L. Hill, Devra Lee Davis, Gerald V. Poje, Anne J. Udall, Ronald K. Burton, and David M. Rappoport: Hearing Before the Committee on Environment and Public Works, United States Senate, One Hundred Third Congress, Second Session, on the Nominations of Frederic J. Hansen, to Be Deputy Administrator, Environmental Protection Agency; Paul L. Hill ... the Chemical Safety Board, and Anne J. Udall ... the Board of Directors, Morris K. Udall Foundation, September 27, 1994*. U.S. Government Printing Office.

Weigelt, B., L. F. A. Wessels, A. J. Bosma, A. M. Glas, D. S. A. Nuyten, Y. D. He, H. Dai, J. L. Peterse, and L. J. van't Veer. 2005. "No Common Denominator for Breast Cancer Lymph Node Metastasis." *British Journal of Cancer* 93 (8): 924–32.

Welch, Danny R., and Douglas R. Hurst. 2019. "Defining the Hallmarks of Metastasis." *Cancer Research* 79 (12): 3011–27.

Wilkerson, Amy, Kathaliya Wongsatittham, and Josephine Johnston. 2013. "The NIH Stem Cell Registry: An Absence of Gamete Donor Consent." *Cell Stem Cell* 12 (2): 147–48.

Yu, Wenqi, Xueqin He, Zhihang Yang, Xiaotong Yang, Wei Xiao, Rui Liu, Rou Xie, Lin Qin, and Huile Gao. 2019. "Sequentially Responsive Biomimetic Nanoparticles with Optimal Size in Combination with Checkpoint Blockade for Cascade Synergetic Treatment of Breast Cancer and Lung Metastasis." *Biomaterials* 217 (October): 119309.

Zhang, Pengcheng, Yihui Zhai, Ying Cai, Yuliang Zhao, and Yaping Li. 2019. "Nanomedicine-Based Immunotherapy for the Treatment of Cancer Metastasis." *Advanced Materials* 31 (49): e1904156.