ISSN: 2755-0176

Journal of Cancer Research Reviews & Reports

SCIENTIFIC Research and Community

Review Article

Open Access

Tumor Cell Behavior: Integrating Microbiome, Lifestyle, and Molecular Transformations in Cancer Development and Therapy Response

Melisa Hunis and Adrian Hunis*

School of Medicine Universidad de Buenos Aires Argentina (UBA)

***Corresponding author**
Adrian Hunis MD, School of Medicine Universidad de Buenos Aires Argentina (UBA).

Received: July 22, 2025; **Accepted:** July 24, 2025; **Published:** August 05, 2025

Introduction

Cancer remains a leading cause of morbidity and mortality worldwide. The transformation of a normal cell into a malignant one is a complex, multistep process influenced by a variety of intrinsic and extrinsic factors. While the genetic and molecular underpinnings of cancer have been extensively studied, there is increasing recognition of the importance of the tumor microenvironment, the human microbiome, and lifestyle factors in modulating tumor cell behavior and response to therapy [1,2]. This review aims to provide a comprehensive overview of the multifactorial nature of tumor cell behavior, integrating recent insights from molecular biology, microbiome research, and lifestyle medicine.

Molecular Transformations Preceding Clinically Detectable Cancer

The journey from a normal cell to a clinically detectable cancer involves a series of molecular events that often span years or even decades. These transformations can be categorized as follows:

Genetic Mutations and Chromosomal Aberrations

- **Oncogene Activation:** Protooncogenes such as KRAS, MYC, and EGFR become constitutively active, driving uncontrolled proliferation [3].
- **Tumor Suppressor Gene Inactivation:** Loss-of-function mutations in genes like TP53, RB1, and BRCA1/2 remove critical cell cycle checkpoints and DNA repair mechanisms [4].
- **Chromosomal Instability:** Structural and numerical chromosomal abnormalities contribute to genomic chaos and tumor heterogeneity [5].

Epigenetic Alterations

- **DNA Methylation:** Hypermethylation of promoter regions can silence tumor suppressor genes, while global hypomethylation may activate oncogenes [6].
- **Histone Modification:** Changes in histone acetylation and methylation alter chromatin structure and gene expression [7].
- **Non-coding RNAs:** Dysregulation of microRNAs and long non-coding RNAs influences gene networks involved in cell proliferation, apoptosis, and metastasis [8].

Preclinical Lesions and Field Cancerization

- **Pre-malignant Lesions:** Conditions such as adenomas, dysplasias, and carcinoma in situ represent stages where molecular alterations accumulate but invasive cancer has not yet developed [9].
- **Field Cancerization:** Widespread molecular changes in histologically normal tissue predispose to multifocal tumor development [10].

Table 1: Key Molecular Events in Early Tumorigenesis

Molecular Event	Examples	Functional Consequence
Oncogene activation	KRAS, EGFR mutations	Uncontrolled proliferation
Tumor suppressor loss	TP53, BRCA1/2 mutations	Impaired DNA repair, apoptosis
DNA methylation changes	MLH1 hypermethylation	Gene silencing
Chromosomal instability	Aneuploidy, translocations	Genomic diversity, heterogeneity
Non-coding RNA dysregulation	miR-21, HOTAIR	Altered gene expression

Adapted from references [3-8].

The Tumor Microenvironment and Microbiome

The tumor microenvironment (TME) is a dynamic ecosystem composed of cancer cells, stromal cells, immune cells, extracellular matrix components, and, as recent research has emphasized, the microbiome [11].

Cellular and Non-Cellular Components of the TME

- **Cancer-Associated Fibroblasts (CAFs):** Secrete growth factors, remodel the extracellular matrix, and promote angiogenesis [12].
- **Immune Cells:** Tumor-associated macrophages (TAMs), T cells, and myeloid-derived suppressor cells (MDSCs) can

either suppress or promote tumor progression, depending on their phenotype and activation state [13].

- **Extracellular Matrix (ECM):** Provides structural support and regulates cell signaling, migration, and invasion [14].

The Microbiome and Its Influence on Tumorigenesis

- **Gut Microbiota:** The gut harbors trillions of microbes that modulate systemic inflammation, metabolism, and immune responses [15].
- **Oncogenic vs. Protective Microbes:** Certain bacteria, such as Fusobacterium nucleatum, have been implicated in colorectal cancer progression, while others, like Lactobacillus spp., may have protective effects [16,17].
- **Microbial Metabolites:** Short-chain fatty acids (SCFAs), secondary bile acids, and other metabolites can influence epigenetic regulation, immune function, and cellular proliferation [18].
- **Tumor-Resident Microbiome:** Recent studies have identified unique microbial communities within tumor tissues, which may directly modulate tumor cell behavior and therapy response [19].

Microbiome and Therapy Response

- **Immunotherapy:** The gut microbiome modulates the efficacy of immune checkpoint inhibitors, with specific bacterial taxa associated with improved or diminished responses [20].
- **Chemotherapy and Toxicity:** Microbial enzymes can metabolize chemotherapeutic agents, affecting their efficacy and side effect profiles [21].

Table 2: Microbiome Influences on Cancer Development and Therapy

Microbiome Factor	Cancer Impact	Therapy Implication
Fusobacterium nucleatum	Promotes colorectal cancer	May reduce immunotherapy efficacy
Lactobacillus spp.	Anti-inflammatory, protective	Potentially enhances therapy
SCFA production	Regulates epigenetics, immunity	May sensitize to immunotherapy
Microbial β-glucuronidase	Reactivates drug metabolites	Increases chemotherapy toxicity

Adapted from references [16-21].

Lifestyle Factors Influencing Tumor Cell Behavior

Lifestyle factors are increasingly recognized as key modulators of cancer risk, tumor biology, and therapy outcomes.

Diet and Nutrition

- **Pro-carcinogenic Diets:** High intake of red and processed meats, saturated fats, and refined sugars is linked to increased cancer risk, partly through effects on inflammation and the microbiome [22].
- **Protective Diets:** Diets rich in fruits, vegetables, whole grains, and dietary fiber are associated with lower cancer incidence, likely due to antioxidant, anti-inflammatory, and microbiome-modulating effects [23].
- **Obesity:** Excess adiposity is a risk factor for multiple cancers, promoting chronic inflammation, insulin resistance, and altered hormone levels [24].

Physical Activity

- **Anti-Tumor Effects:** Regular exercise reduces systemic inflammation, improves immune surveillance, and may directly inhibit tumor growth via myokine secretion [25].
- **Improved Therapy Outcomes:** Physical activity is associated with better tolerance to chemotherapy and improved survival rates in several cancer types [26].

Tobacco and Alcohol Use

- **Carcinogenic Effects:** Tobacco smoke contains numerous carcinogens that induce DNA damage and mutations. Alcohol metabolism generates acetaldehyde, a toxic compound that can also damage DNA [27,28].
- **Synergistic Risk:** Combined use of tobacco and alcohol synergistically increases the risk of cancers of the upper aerodigestive tract [29].

Psychosocial Factors and Stress

- **Chronic Stress:** Sustained psychological stress can suppress immune function, promote inflammation, and potentially accelerate tumor progression [30].
- **Social Support:** Strong social networks and psychological resilience are associated with better cancer outcomes [31].

Tumor Cell Evolution and Heterogeneity

Tumors are not static entities but evolve dynamically under selective pressures from the host environment and therapeutic interventions.

Clonal Evolution and Selection

- **Genetic Diversity:** Tumors consist of multiple subclones with distinct genetic and epigenetic profiles, resulting from ongoing mutation and selection [32].
- **Selective Pressures:** Hypoxia, immune surveillance, and therapy act as selective forces, favoring the survival of resistant clones [33].

Intratumoral Heterogeneity

- **Phenotypic Diversity:** Subpopulations within a tumor may differ in proliferative capacity, metastatic potential, and drug sensitivity [34].
- **Implications for Therapy:** Heterogeneity underlies treatment resistance and disease relapse, as minor subclones can expand following therapy [35].

Tumor Evolution During Therapy

- **Acquired Resistance:** Tumors may develop new mutations or activate alternative signaling pathways in response to targeted therapies [36].
- **Adaptive Therapy:** Strategies that modulate treatment intensity based on tumor response may delay resistance and improve outcomes [37].

Integrated Perspective on Therapy Response

The interplay between molecular alterations, microbiome composition, and lifestyle factors shapes tumor cell behavior and therapeutic outcomes.

Microbiome-Therapy Interactions

- **Immunotherapy:** Specific gut microbiota compositions are associated with improved responses to PD-1/PD-L1 inhibitors in melanoma and other cancers [20,38].
- **Chemotherapy:** Microbial metabolism of drugs such as irinotecan can increase toxicity, highlighting the need for personalized approaches [21].

Lifestyle Interventions and Treatment Outcomes

- **Dietary Modification:** Nutritional interventions can modulate inflammation, immune function, and the microbiome, potentially enhancing therapy efficacy [39].
- **Exercise:** Physical activity during and after treatment is linked to improved quality of life, reduced recurrence, and better survival [40].

Personalized Oncology

- **Multi-omic Profiling:** Integrating genomic, epigenomic, microbiomic, and lifestyle data enables more precise risk stratification and therapy selection [41].
- **Holistic Patient Care:** Addressing lifestyle factors and the microbiome alongside molecular targets represents a paradigm shift in cancer management [42].

Conclusion

Tumor cell behavior is governed by a complex network of intrinsic and extrinsic influences, including molecular transformations, the microbiome, and lifestyle factors. Integrating these aspects into cancer research and clinical practice is vital for advancing precision oncology and improving patient outcomes. Future research should focus on unraveling the mechanistic links among these factors and translating this knowledge into personalized prevention and treatment strategies.

References

1. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144: 646-674.
2. Greaves M, Maley CC (2012) Clonal evolution in cancer. Nature 481: 306-313.
3. Kandoth C, McLellan MD, Vandin F, Ye K, Niu B, et al. (2013) Mutational landscape and significance across 12 major cancer types. Nature 502: 333-339.
4. Vogelstein B, Kinzler KW (1993) The multistep nature of cancer. Trends Genet 9: 138-141.
5. Negrini S, Gorgoulis VG, Halazonetis TD (2010) Genomic instability-an evolving hallmark of cancer. Nat Rev Mol Cell Biol 11: 220-228.
6. Baylin SB, Jones PA (2016) Epigenetic determinants of cancer. Cold Spring Harb Perspect Biol 8: a019505.
7. Dawson MA, Kouzarides T (2012) Cancer epigenetics: from mechanism to therapy. Cell 150: 12-27.
8. Esteller M (2011) Non-coding RNAs in human disease. Nat Rev Genet 12: 861-874.
9. Fearon ER (2011) Molecular genetics of colorectal cancer. Annu Rev Pathol 6: 479-507.
10. Slaughter DP, Southwick HW, Smejkal W (1953) Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer 6: 963-968.
11. Quail DF, Joyce JA (2013) Microenvironmental regulation of tumor progression and metastasis. Nat Med 19: 1423-1437.
12. Kalluri R (2016) The biology and function of fibroblasts in cancer. Nat Rev Cancer 16: 582-598.
13. Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P (2017) Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol 14: 399-416.
14. Lu P, Weaver VM, Werb Z (2012) The extracellular matrix: a dynamic niche in cancer progression. J Cell Biol 196: 395-406.
15. Garrett WS (2015) Cancer and the microbiota. Science 348: 80-86.
16. Kostic AD, Chun E, Robertson L, Glickman JN, Gallini CA, et al. (2013) Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host Microbe 14: 207-215.
17. Zitvogel L, Galluzzi L, Viaud S, Vetizou M, Daillere R, et al. (2015) Cancer and the gut microbiota: an unexpected link. Sci Transl Med. 2015;7(271):271ps1.
18. Louis P, Hold GL, Flint HJ (2014) The gut microbiota, bacterial metabolites and colorectal cancer. Nat Rev Microbiol 12: 661-672.
19. Nejman D, Livyatan I, Fuks G, Gavert N, Zwang Y et al. (2020) The human tumor microbiome is composed of tumor type-specific intracellular bacteria. Science 368: 973-980.
20. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, et al. (2018) Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science 359: 97-103.
21. Wallace BD, Wang H, Lane KT, Scott JE, Orans J, et al. (2010) Alleviating cancer drug toxicity by inhibiting a bacterial enzyme. Science 330: 831-835.
22. Schwingshackl L, Schwedhelm C, Hoffmann G, Knüppel S, Preterre AL, et al. (2018) Food groups and risk of colorectal cancer. Int J Cancer 142: 1748-1758.
23. Aune D, Giovannucci E, Boffetta P, Fadnes LT, Keum NN, et al. (2017) Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality-a systematic review and dose-response meta-analysis of prospective studies. Int J Epidemiol 46: 1029-1056.
24. Calle EE, Rodriguez C, WalkerThurmond K, Thun MJ (2003) Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 348: 1625-1638.
25. Friedenreich CM, Neilson HK, Farris MS, Courneya KS (2016) Physical activity and cancer outcomes: a precision medicine approach. Clin Cancer Res 22: 4766-4775.
26. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA (2005) Physical activity and survival after breast cancer diagnosis. JAMA 293: 2479-2486.
27. Boffetta P, Hashibe M (2006) Alcohol and cancer. Lancet Oncol. 2006;7: 149-156.
28. Hecht SS (1999) Tobacco smoke carcinogens and lung cancer. J Natl Cancer Inst 91: 1194-1210.
29. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, et al. (2007) Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. J Natl Cancer Inst 99: 777-789.
30. Antoni MH, Lutgendorf SK, Cole SW, Dhabhar FS, Sephton SE, et al. (2006) The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. Nat Rev Cancer 6: 240-248.
31. Pinquart M, Duberstein PR (2010) Associations of social networks with cancer mortality: a meta-analysis. Crit Rev Oncol Hematol 75: 122-137.
32. Marusyk A, Polyak K (2010) Tumor heterogeneity: causes and consequences. Biochim Biophys Acta 1805: 105-117.
33. Swanton C (2012) Intratumor heterogeneity: evolution through space and time. Cancer Res 72: 4875-4882.
34. Almendro V, Marusyk A, Polyak K (2013) Cellular heterogeneity and molecular evolution in cancer. Annu Rev Pathol 8: 277-302.
35. Holohan C, Schaeybroeck SV, Longley DB, Johnston PG (2013) Cancer drug resistance: an evolving paradigm. Nat Rev Cancer 13: 714-726.
36. Hata AN, Niederst MJ, Archibald HL, Gomez Caraballo M, Siddiqui FM, et al. (2016) Tumor cells can follow distinct

evolutionary paths to become resistant to epidermal growth factor receptor inhibition. Nat Med 22: 262-269.

37. Gatenby RA, Silva AS, Gillies RJ, Frieden BR (2009) Adaptive therapy. Cancer Res 69: 4894-4903.
38. Routy B, Chatelier EL, Derosa L, Duong CPM, Alou MT, et al. (2018) Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors. Science 359: 91-97.
39. Ligibel JA (2012) Impact of lifestyle factors on cancer outcomes. J Clin Oncol 30: 3697-3704.
40. Cormie P, Zopf EM, Zhang X, Schmitz KH (2017) The impact of exercise on cancer mortality, recurrence, and treatment-related adverse effects. Epidemiol Rev 39: 71-92.
41. Hasin Y, Seldin M, Lusis A (2017) Multi-omics approaches to disease. Genome Biol 18: 83.
42. Wild CP (2015) Cancer prevention: the role of science and society. Nat Rev Cancer 15: 113-118.