



Hallmarks Of Cancer and Its Oral Implications

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Abstract

Cancer is a multifaceted disease driven by genetic and molecular alterations that lead to uncontrolled cell proliferation and invasion. Hanahan and Weinberg identified fundamental traits of cancer, termed the "Hallmarks of Cancer," which include sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, reprogramming energy metabolism, evading immune destruction, tumor-promoting inflammation, and genome instability. These hallmarks are highly relevant in oral malignancies, particularly oral squamous cell carcinoma (OSCC). Oral cancer progression is influenced by genetic mutations, chronic inflammation, immune evasion, and metabolic reprogramming. Factors such as tobacco use, alcohol consumption, and viral infections (e.g., HPV) exacerbate these processes. Understanding the hallmarks of cancer aids in early detection, targeted therapies, and improved management of oral cancers. This review explores these hallmarks and their implications in the oral cavity, emphasizing their role in diagnosis, treatment, and prevention.

Keywords: Cancer, tobacco, hallmarks, growth suppressors

Introduction

Carcinogenesis is a general term used to denote the development of neoplasia. One many consider this process an active phenomenon induced by any one or several of a variety of agents-chemical, physical, biological, or genetic. Passive carcinogenesis may be equated with carcinogenesis occurring in organisms without any active introduction of a carcinogenic agent into the system under study 1,2. Passive carcinogenesis is the result of uncontrolled variables in a given experiment. Mechanistically, a distinction between active and passive carcinogenesis does not exist; however, in experimentally determining the mechanism of action of some carcinogenic agents, uncontrolled (spontaneous) events during the carcinogenic process can play a major role.

Carcinogenesis may be actively induced in living organisms by a variety of different agents that are generally chemical or physical in nature but have been grouped into four relatively distinct categories: chemical, physical, biological, and genetic 3. On the other hand, radiation carcinogenesis may result not from the action of informational macromolecules, but rather from the direct or indirect action of high-energy photons or particles with existing DNA. Carcinogenesis by many small molecular weight chemicals involves either a direct action of the chemical on cellular DNA or metabolism of the parent chemical to an active or ultimate form, which can then react with cellular DNA to produce a permanent chemical change in the DNA structure4.

Cancer develops in discrete stages, at least three in number, with defined differences at the molecular and biologic level. The three stages of carcinogenesis include:

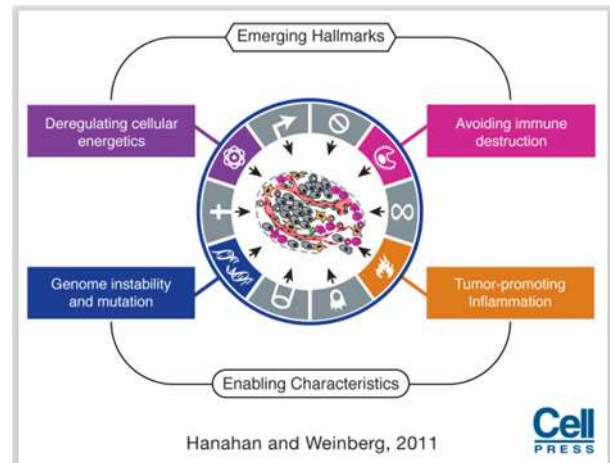
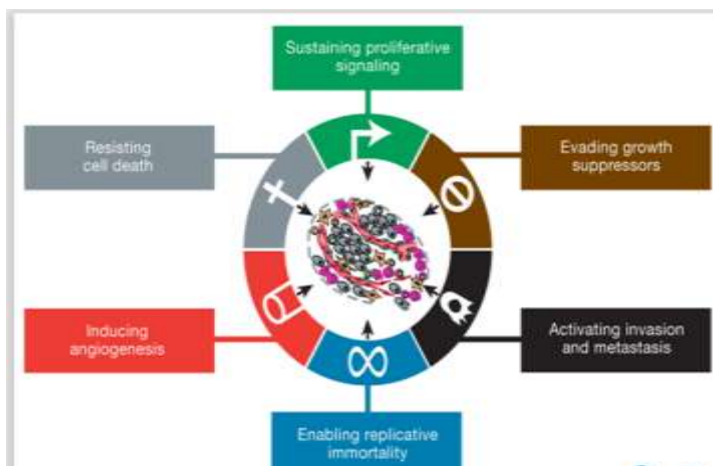
1. Initiation
2. Promotion
3. Progression

In the first and last stages of cancer development (initiation and progression) involve heritable, genetic changes within cells. The intermediate stage of promotion does not involve direct structural changes in the genome of the cell but, generally speaking, is characterized by an altered expression of the genome of the initiated cell, such alterations presumably resulting from an interaction of the genetic alterations that induced initiation and environmental factors

termed “promoting agents.” Unlike initiation and progression, the stage of promotion requires extended treatment with the promoting agent for the stage not only to be developed but also to traverse into the stage of progression. Such alterations in genetic expression involve not only genes and sets of genes, but also a selective enhancement of the replication of initiated cells in the presence of the promoting agent⁵.

Hannahan & Weinberg (2000) has proposed six hallmarks of cancer⁶:

1. Sustaining proliferative signalling.
2. Evading growth suppressor.
3. Resisting cell death.
4. Inducing angiogenesis.
5. Enabling replicative immortality.
6. Activating invasion and metastasis.



In 2010, two new emerging hallmarks were included⁷:

Deregulating cellular metabolism.

Avoiding immune destruction.

The 2011 sequel further incorporated two hallmarks as a second enabling characteristic, which were fundamentally involved in activating the eight hallmark (functional) capabilities necessary for tumor growth and progression⁸.

1. Tumor-promoting inflammation
2. Genome instability and mutation

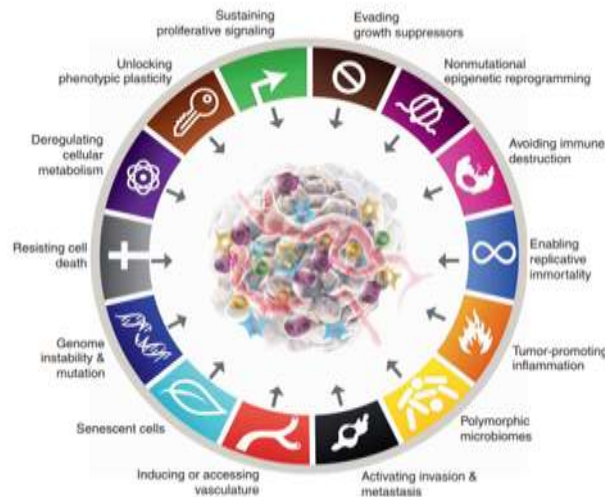
Accordingly, Hanahan and Weinberg (2022) added another concept to the discussion, portrayed as “enabling characteristics,” consequences of the aberrant condition of neoplasia that provide means by which cancer cells and tumors can adopt these functional traits⁸

These parameters included:

1. Unlocking phenotypic plasticity

2. Non-mutational epigenetic reprogramming
3. Polymorphic microbiomes
4. Senescent cells

Hallmarks of cancer 2022: new dimensions



The Hallmarks of Cancer: A Detailed Overview

Cancer is a complex disease that arises due to genetic and environmental factors leading to uncontrolled cell growth. In their seminal work, Hanahan and Weinberg identified key biological capabilities, known as the Hallmarks of Cancer, that enable cancer cells to survive, proliferate, and spread^{6,7}. These hallmarks are essential for understanding cancer progression and developing targeted therapies.

1. **Sustaining Proliferative Signalling**
Normal cells require external growth signals to divide, but cancer cells bypass this control by producing their own growth signals or manipulating cellular pathways to remain in a constant proliferative state⁹.
2. **Evading Growth Suppressors**
Tumor suppressor genes (e.g., TP53 and RB1) regulate cell division and prevent uncontrolled growth. Cancer cells inactivate these genes through mutations or deletions, allowing unchecked proliferation¹⁰.
3. **Resisting Cell Death (Apoptosis Evasion)**
Programmed cell death, or apoptosis, is a defense mechanism that eliminates damaged or dangerous cells. Cancer cells resist apoptosis by altering pathways involving proteins like Bcl-2 and p53, enabling their survival despite genetic damage¹¹.

4. **Enabling Replicative Immortality**
Normal cells have a limited lifespan due to telomere shortening with each division. Cancer cells activate telomerase, an enzyme that maintains telomere length, allowing them to divide indefinitely¹².

5. **Inducing Angiogenesis**
To sustain rapid growth, tumors require a continuous supply of oxygen and nutrients. Cancer cells stimulate new blood vessel formation (angiogenesis) by producing factors like VEGF (vascular endothelial growth factor)¹³.

6. **Activating Invasion and Metastasis**
Cancer becomes deadly when it spreads beyond its original site. Tumor cells acquire the ability to invade surrounding tissues, enter the bloodstream or lymphatic system, and establish new tumors in distant organs¹⁴.

Emerging Hallmarks and Enabling Characteristics

In addition to the core hallmarks, two emerging hallmarks and two enabling characteristics have been identified:

7. **Deregulating Cellular Energetics**
Cancer cells reprogram their metabolism to prioritize energy production pathways that support rapid growth, often favoring glycolysis

(the Warburg effect) even in oxygen-rich environments⁷.

8. Avoiding Immune Destruction
The immune system recognizes and eliminates abnormal cells, but cancer cells evade detection by suppressing immune responses through mechanisms like PD-L1 expression, which inhibits T-cell activation¹⁵.
9. Genomic Instability and Mutation: Cancer cells acquire mutations at an accelerated rate, promoting further evolution and adaptation¹⁶
10. Tumor-Promoting Inflammation: Chronic inflammation creates an environment rich in growth signals and mutagenic factors that support tumor development¹⁷.
11. Unlocking phenotypic plasticity: Cancer cells exhibit remarkable plasticity, allowing them to switch between different cellular states, such as epithelial-to-mesenchymal transition (EMT) and mesenchymal-to-epithelial transition (MET), enabling adaptation, resistance to therapy, and metastasis¹⁸
12. Nonmutational Epigenetic Reprogramming: genetic changes, such as DNA methylation, histone modifications, and chromatin remodeling, regulate gene expression without altering the DNA sequence. These changes can drive cancer progression by silencing tumor suppressor genes and activating oncogenes, contributing to cellular plasticity and drug resistance¹⁹
13. Polymorphic Microbiomes: An expansive frontier in biomedicine is unfolding via illumination of the diversity and variability of the plethora of microorganisms, collectively termed the microbiota⁸
14. Senescent Cells: Cellular senescence is a typically irreversible form of proliferative arrest, likely evolved as a protective mechanism for maintaining tissue homeostasis, ostensibly as a complementary mechanism to programmed cell death that serves to inactivate and in due course remove diseased, dysfunctional, or otherwise unnecessary cells⁸.

Oral Implications of the Hallmarks of Cancer

Cancer is a complex disease characterized by a series of biological alterations that enable uncontrolled cell growth and tumor progression. Hanahan and Weinberg's concept of the hallmarks of cancer provides a framework for understanding the fundamental mechanisms that drive malignancy⁶. These hallmarks have significant implications for oral cancer, particularly oral squamous cell carcinoma (OSCC), which is the most common malignancy affecting the oral cavity⁷. By examining these hallmarks in the context of oral pathology, we can gain insight into the development, progression, and potential therapeutic interventions for oral cancers.

One of the key hallmarks of cancer is **sustaining proliferative signaling**, which allows cancer cells to divide without regulatory control continuously. In oral cancers, this is often driven by the overexpression of growth factors such as the epidermal growth factor receptor (EGFR), leading to the formation of aggressive lesions that grow rapidly. Clinically, this uncontrolled proliferation manifests as non-healing ulcers, leukoplakic or erythroplakic patches, and exophytic growths within the oral cavity^{7,20}.

Equally significant is the ability of cancer cells to **evade growth suppressors**, which normally act as brakes on cell division. Tumor suppressor genes like TP53 and RB1 are frequently mutated in oral cancers, allowing unchecked cellular proliferation. As a result, oral lesions persist and progress unchecked, increasing the risk of malignancy. This also explains why precancerous conditions, such as oral leukoplakia and erythroplakia, can transition into invasive cancer when these regulatory pathways are disrupted²¹.

Another critical hallmark is **resisting cell death**, or the ability of cancer cells to avoid apoptosis. Normally, cells undergo programmed cell death when they become damaged or dysfunctional, but oral cancer cells often evade this fate through genetic alterations in apoptotic pathways. Mutations in the TP53 gene and overexpression of anti-apoptotic proteins like Bcl-2 contribute to the survival of malignant cells, leading to the persistence of oral tumors²².

To sustain their growth, cancer cells must achieve **replicative immortality**, which they accomplish by upregulating telomerase, an enzyme that maintains the length of telomeres and prevents cellular aging. In the oral cavity, this mechanism enables cancer cells to undergo unlimited divisions, contributing to

aggressive tumor growth and resistance to conventional therapies.

A further hallmark is **inducing angiogenesis**, the process of forming new blood vessels to supply oxygen and nutrients to tumors. In oral cancer, this is facilitated by the overexpression of vascular endothelial growth factor (VEGF), leading to increased vascularization within tumors. This process not only supports tumor expansion but also makes oral cancers prone to excessive bleeding and ulceration, complicating surgical intervention²³.

For cancer to become invasive and metastatic, it must acquire the ability to **invade and metastasize** to other tissues. Oral cancers frequently invade nearby structures such as the tongue, jawbone, and lymph nodes. The epithelial-to-mesenchymal transition (EMT) plays a crucial role in this process, allowing tumor cells to migrate and establish secondary tumors. This hallmark is particularly concerning in OSCC, as metastasis to cervical lymph nodes significantly reduces survival rates²⁴.

Cancer cells also undergo **metabolic reprogramming** to meet the high energy demands of rapid growth. Oral cancer cells often shift to aerobic glycolysis, known as the Warburg effect, even in the presence of oxygen. This metabolic adaptation allows tumors to thrive in diverse microenvironments, contributing to their resilience against treatment. Clinically, this can be detected using imaging techniques such as PET scans, which highlight increased glucose uptake by malignant cells.

To avoid destruction by the immune system, cancer cells develop mechanisms for **immune evasion**. In oral cancer, tumors can create an immunosuppressive microenvironment by recruiting regulatory T cells and secreting inhibitory cytokines. This allows them to escape immune surveillance, making immunotherapy an important emerging treatment strategy in oral oncology.

Chronic inflammation is another factor that promotes tumor progression. **Tumor-promoting inflammation** is often seen in individuals with risk factors such as tobacco use, alcohol consumption, and viral infections like HPV. Chronic inflammatory conditions such as oral lichen planus and periodontitis have been linked to an increased risk of malignant transformation. The inflammatory microenvironment supports tumor

growth by releasing pro-inflammatory cytokines that enhance proliferation and survival²⁵.

Beyond genetic mutations, **non-mutational epigenetics** plays a crucial role in oral cancer progression. Epigenetic modifications, such as DNA methylation and histone modifications, regulate gene expression without altering the DNA sequence. In oral malignancies, aberrant methylation of tumor suppressor genes can silence their expression, leading to unchecked tumor growth. Epigenetic therapies, such as DNA methyltransferase inhibitors, are being explored as potential treatments for oral cancers¹⁹.

Another contributing factor is the presence of **polymorphic microbes** in the oral microbiome. Certain bacterial species, including *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, have been linked to oral carcinogenesis by promoting inflammation and immune evasion. These bacteria can alter host cell signaling pathways, contributing to the progression of precancerous lesions to malignancy²⁶.

Cellular senescence, the irreversible growth arrest of damaged cells, plays a dual role in oral cancer. While senescence can act as a protective mechanism against tumorigenesis by preventing damaged cells from proliferating, cancer cells can also exploit senescent cells to create a pro-tumorigenic microenvironment. Senescent cells secrete inflammatory factors known as the senescence-associated secretory phenotype (SASP), which can enhance tumor growth and resistance to therapy²⁷.

Lastly, **phenotypic plasticity**, the ability of cancer cells to change their identity in response to environmental cues, is a critical factor in oral cancer progression. This plasticity allows tumor cells to switch between epithelial and mesenchymal states, aiding in invasion, metastasis, and resistance to treatment. Targeting pathways that regulate phenotypic plasticity, such as the Wnt and Notch signaling pathways, is being investigated as a potential strategy for limiting oral cancer spread²⁸.

Understanding these hallmarks in the context of oral cancer is essential for improving early detection, prevention, and treatment strategies. Regular dental check-ups, lifestyle modifications, and advancements in targeted therapy and immunotherapy offer hope for better patient outcomes. As research continues to uncover new insights into these hallmarks, novel

therapeutic approaches will further refine the management of oral malignancies, ultimately improving survival rates and quality of life for affected individuals.

References:

- Ward, J. M. (1983) Background data and variations in tumor rates of control rats and mice. *Prog. Exp. Tumor Res.* 26, 241-258
- Enomoto, M., Kobayashi, K., and Inoue, H. (1990) Significance of naturally occurring tumors in evaluating the carcinogenicity of a test compound: a review and an improved carcinogenicity bioassay for chemicals. *J Toxicol. Pathol.* 3, 1-17
- Pitot, H. C. (1987) The molecular determinants of carcinogenesis: a symposium sketch. *Symp. Fund. Cancer Res.* 39, 187-196
- Henry C. Pitot And Yvonne P. Dragan, Facts and theories concerning the mechanisms of carcinogenesis; *The FASEB Journal* Vol. `${article.issue.getVolume()}`, N
- The Molecular Biology of Carcinogenesis Henry C. Pitot, M, *CANCER Supplement* August 2, 2993, Volume 72, No.3;962-70
- Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000;100: 57–70.
- Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646–74.
- Hanahan D. Hallmarks of Cancer: New Dimensions. *Cancer Discov.* 2022 Jan;12(1):31-46.
- Lemmon, M. A., & Schlessinger, J. (2010). Cell signaling by receptor tyrosine kinases. *Cell*, 141(7), 1117-1134.
- Sherr, C. J. (2004). Principles of tumor suppression. *Cell*, 116(2), 235-246.
- Adams, J. M., & Cory, S. (2007). The Bcl-2 apoptotic switch in cancer development and therapy. *Oncogene*, 26(9), 1324-1337.
- Shay, J. W., & Wright, W. E. (2010). Telomeres and telomerase in normal and cancer stem cells. *FEBS Letters*, 584(17), 3819-3825.
- Carmeliet, P., & Jain, R. K. (2000). Angiogenesis in cancer and other diseases. *Nature*, 407(6801), 249-257.
- Friedl, P., & Alexander, S. (2011). Cancer invasion and the microenvironment: plasticity and reciprocity. *Cell*, 147(5), 992-1009.
- Pardoll, D. M. (2012). The blockade of immune checkpoints in cancer immunotherapy. *Nature Reviews Cancer*, 12(4), 252-264.
- Negrini, S., Gorgoulis, V. G., & Halazonetis, T. D. (2010). Genomic instability—an evolving hallmark of cancer. *Nature Reviews Molecular Cell Biology*, 11(3), 220-228.
- Grivennikov, S. I., Greten, F. R., & Karin, M. (2010). Immunity, inflammation, and cancer. *Cell*, 140(6), 883-899.
- Thiery JP, Acloque H, Huang RY, Nieto MA. Epithelial-mesenchymal transitions in development and disease. *Cell*. 2009;139(5):871-90. doi:10.1016/j.cell.2009.11.007.
- Baylin SB, Jones PA. A decade of exploring the cancer epigenome – biological and translational implications. *Nat Rev Cancer*. 2011;11(10):726-34. doi:10.1038/nrc3130.
- Grandis, J. R., & Sok, J. C. (2004). Signaling through the epidermal growth factor receptor during the development of malignancy. *Pharmacology & Therapeutics*, 102(1), 37-46. <https://doi.org/10.1016/j.pharmthera.2004.02.007>
- Poeta, M. L., Manola, J., Goldwasser, M. A., et al. (2007). TP53 mutations and survival in squamous-cell carcinoma of the head and neck. *New England Journal of Medicine*, 357(25), 2552-2561. <https://doi.org/10.1056/NEJMoa073770>
- Gopalakrishnan, A., Xu, C. J., Nair, S., & Chen, Z. (2022). Bcl-2 family proteins in oral cancer: Molecular mechanisms and therapeutic potential. *Cancers*, 14(3), 741.
- Aksu, A. E., Rubinstein, J. T., & Hohberger, T. C. (2021). Vascular endothelial growth factor (VEGF) expression and angiogenesis in oral squamous cell carcinoma. *Head & Neck*, 43(8), 2504-2515.
- Agarwal, E., Chaudhary, A., Gupta, S., & Ghosh, S. (2020). Role of epithelial-mesenchymal transition in oral squamous cell carcinoma progression and metastasis: An update. *Translational Oncology*, 13(5), 100845.
- Amaral, R. R., Bueno, A. G., & Thomaz, M. C. (2022). Association between chronic inflammation and oral squamous cell carcinoma: A review of molecular and cellular mechanisms. *Cancers*, 14(6), 1496.

26. Guo, T., & Zhang, T. (2022). Oral microbiome and oral cancer—The possible mechanisms and potential therapeutic strategies. *Frontiers in Microbiology*, 13, 843695.
27. Gorgoulis, V., Adams, P. D., Alimonti, A., et al. (2019). Cellular senescence: Defining a path forward. *Cell*, 179(4), 813-827.
28. Kaufhold, S., & Bonavida, B. (2014). Notch signaling in cancer: A double-edged sword. *Cell Death & Disease*, 5(6), e1499. <https://doi.org/10.1038/cddis.2014.428>.