

UNDERSTANDING CANCER: Hallmarks of Cancer

This PIP Digest describes the ten “hallmarks of cancer” — the crucial features and functions that distinguish cancer cells from the body’s normal cells.

Key concepts

- Distinct biology of cancer

Related PIP Digests

- Understanding Cancer: What is Cancer and Types of Cancer
- Understanding Cancer: Genetics 101
- Understanding Cancer: Tumour Heterogeneity

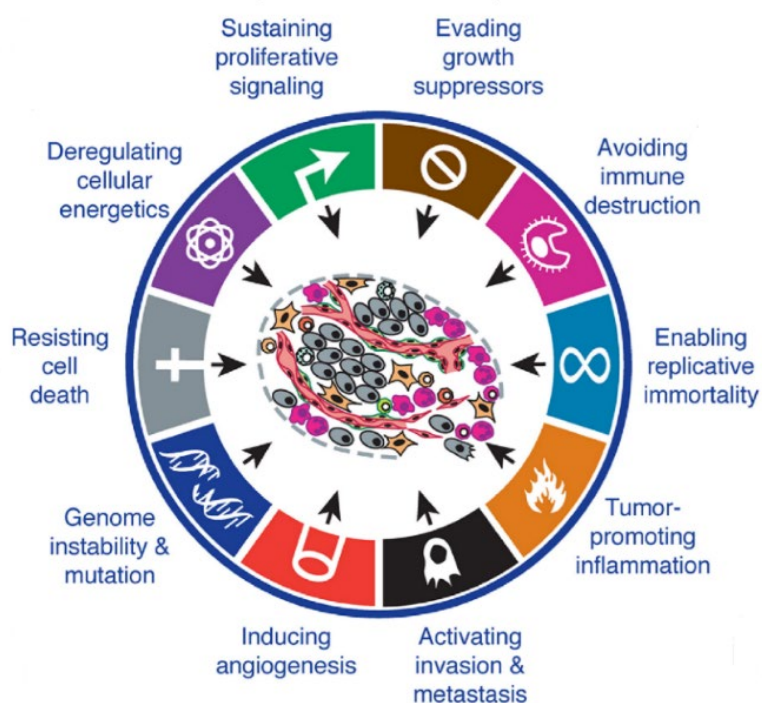
In 2000, cancer researchers Douglas Hanahan (https://en.wikipedia.org/wiki/Douglas_Hanahan) and Robert Weinberg (https://en.wikipedia.org/wiki/Robert_Weinberg) published a review article in the journal *Cell*, which identified six “hallmarks” or rules of how cancers behave. Their huge undertaking synthesized much of what was known at the time about the distinct biology of cancer.

In an update in the same journal in 2011, the authors added four more hallmarks. These ten hallmarks (see diagram on the next page) are key to understanding and advancing cancer research.

Hallmarks refer to **acquired functional capabilities** or properties of cancer. They activate tumours to do things normal cells do not do, to behave chronically, and to disrupt the normally well-regulated activities of the body’s cells and organs.

Therapies have been developed to target each hallmark and its enablers. Often, these therapies yield dramatic results, but only for short periods. Cancer cells are very adaptable, and variants quickly emerge that resist the therapy.

Attacking all hallmarks simultaneously would stop tumours in their tracks, but such an approach would likely be too toxic to be useful. Strategically combining therapies to target limited combinations of hallmarks, though, can reduce a tumour’s ability to adapt and resist.



Source: Hanahan D & Weinberg RA. (2011). Hallmarks of cancer: the next generation. *Cell*, 144(5):646-74.

The ten major hallmarks fall into groups: those that occur inside the cell, those “enabling characteristics” that allow cancers to grow, and those that operate outside in the tumour microenvironment (outside the tumour itself).

Inside the Cell



1. Sustaining proliferative signaling

Normal cells have a controlled and time-limited cycle of cell division, growth, and death. In healthy tissue, certain signaling proteins called “growth factors” regulate cell proliferation.

Growth factors work by binding to receptor proteins located on the surface of the plasma membrane that forms the outer boundary of all cells. Different cell types have different plasma membrane receptors and thus respond to different growth factors. When a growth factor binds to its receptor, it triggers a multi-step process — proteins relay signals that trigger molecular changes that stimulate cell growth and division. In normal cells, this growth is well regulated.

Cancer is often called a “disease of expansive proliferation” because it involves cells that divide and grow out of control. The signals from growth factors become deregulated, and cancer cells produce molecules that stimulate their own proliferation. Many factors, including mutated genes known as “oncogenes” contribute to this process, which researchers continue to work to understand.



2. Evading growth suppressors

Many genes categorized as “tumour suppressors” operate to prevent or inhibit cells from proliferating — their function is the opposite of growth factors. Cancer cells, though, evade or inactivate these tumour suppressor genes, allowing them to continue dividing uncontrollably.



3. Resisting cell death

Tumour growth is affected by the rate not just of cell proliferation but also of cell death. Healthy cells have an inborn capability for “assisted suicide” or programmed cell death (called **apoptosis**). If cells start to behave abnormally, signals are sent that cause the cells to die.

Apoptosis is the body’s natural defense mechanism against cancer. Typically, cells that become damaged from radiation, trauma, or oxidative damage — which often cause the kinds of DNA mutations that give rise to cancer — will initiate apoptosis preemptively. Cancer cells, though, limit or sometimes entirely override this protective mechanism. Evading apoptosis is crucial to the survival of cancer cells. Almost half of human cancers involve mutations to the *p53* gene, a key protein in the apoptotic pathway known as the “Guardian of the Genome.”



4. Enabling replicative immortality

As normal cells get older, the tips of their chromosomes (called **telomeres**) start to break down and shorten, which is a signal for the cell to die. This seems to be part of the normal cell aging process. However, cancer cells have developed a way to divide indefinitely — effectively achieving immortality — by maintaining telomere length above a critical threshold.

Cancer cells circumvent telomere deterioration in a variety of ways but most commonly by inducing an enzyme called telomerase, which protects the ends of the chromosomes. The long life of cancer cells is part of what allows them to grow and spread throughout the body.

Enabling Characteristics



5. Tumour-promoted inflammation

While the immune system works to contain cancer cells, it can also increase inflammatory responses that make cancer cells grow. Cells in our immune system can misdiagnose tumours as “wounds that don’t heal,” and inadvertently help them survive, repair themselves, and grow more aggressively.



6. Genome instability and mutation

Cancer cells lose genomic integrity, disrupting the very program encoded in our DNA. In cancer cells, crucial proteins that normally protect our DNA from being corrupted, become rearranged, and damaged.

As cancer cells increase their rate of mutation, they evade the body’s system for maintaining an intact genome. Genomic instability is an inherent part of many cancer cells. This instability leads to enormous heterogeneity not just between tumours, but also within a single tumour.

Tumour Microenvironment (Outside the Tumour)



7. Inducing angiogenesis

Cancer cells acquire the capacity to draw their own supply of blood and blood vessels, through a process known as tumour angiogenesis. By triggering a network of blood vessels to supply a tumour with nutrients and oxygen and remove waste products, a localized mass of tumour cells becomes invasive and metastatic.



8. Activating invasion and metastasis

Cancer cells coopt normal development and homeostasis functions, subverting them for their own purposes. Tumours are composed of an assortment of corrupted and recruited cells operating in a complex microenvironment.

Cancer cells acquire the capacity to invade other tissues and colonize other organs. They can spread throughout the body and disrupt the function of normal tissues and organs. It is this hallmark that makes cancer so difficult to successfully treat.



9. Deregulating cellular energetics

Cells need energy to carry out functions such as absorbing nutrients, reacting to changes in their environment, and maintaining a stable internal environment (homeostasis). Cancer cells energize their proliferation differently from normal cells. Their chronic proliferation is driven by “glucose fueling,” in which cancer cells seem to reprogram their metabolism, mobilizing transporters on their cell membrane to increase the uptake and use of energy-rich glucose.



10. Avoiding immune destruction

Usually, the body’s “ever-alert” immune system searches for and destroys abnormal and damaged cells before they develop into cancerous tumours. However, cancer cells can adapt to evade and disable the very components of the immune system that are dispatched to eliminate them.

References:

- Hanahan D & Weinberg RA. (2000). The hallmarks of cancer. *Cell*, 100(1):57-70.
- Hanahan D & Weinberg RA. (2011). Hallmarks of cancer: the next generation. *Cell*, 144(5):646-74.

Hear about the Hallmarks from Weinberg and Hanahan themselves:

- National Cancer Research Institute (NCRI). *Robert Weinberg - Hallmarks of Cancer. (YouTube)* November 8, 2010 [3:43 minutes] <https://www.youtube.com/watch?v=RP4js-yYK2U>
- Technion. *Douglas Hanahan Hallmarks of Cancer – Applications. (YouTube)* December 1, 2016 [24:39 minutes] <https://www.youtube.com/watch?v=NWcv1r2cgll>

This additional video provides a good overview of cancer biology that will help to further your understanding about the Hallmarks.

- CancerQuest – EmoryUniversity. *Animated Introduction to Cancer Biology (Full Documentary)*. Oct 2, 2013 [12:07 minutes] <https://www.youtube.com/watch?v=46Xh7OFkkCE>

Reviewer: Louisa Salemi, PhD
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