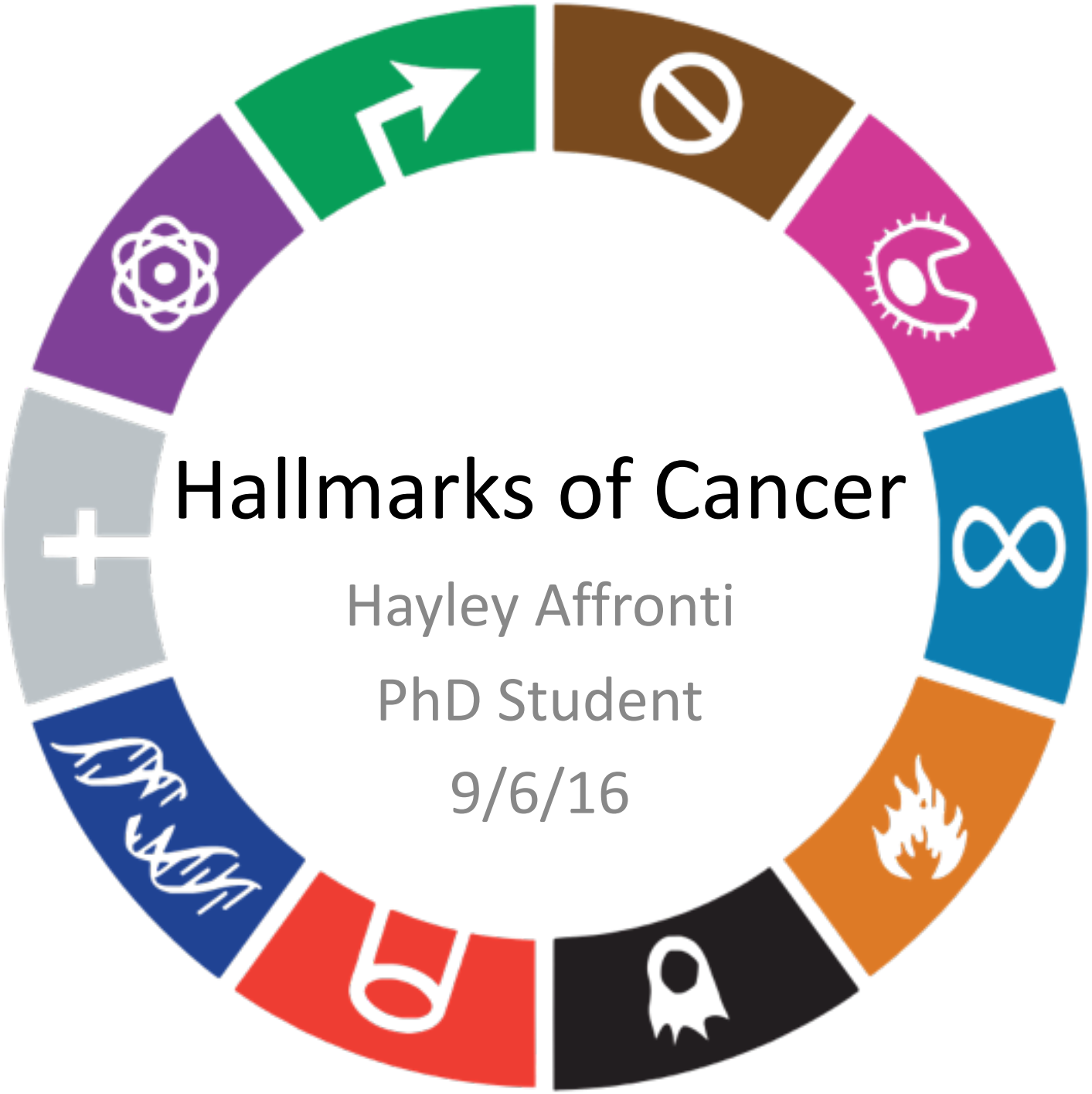


Hallmarks of Cancer

Hayley Affronti

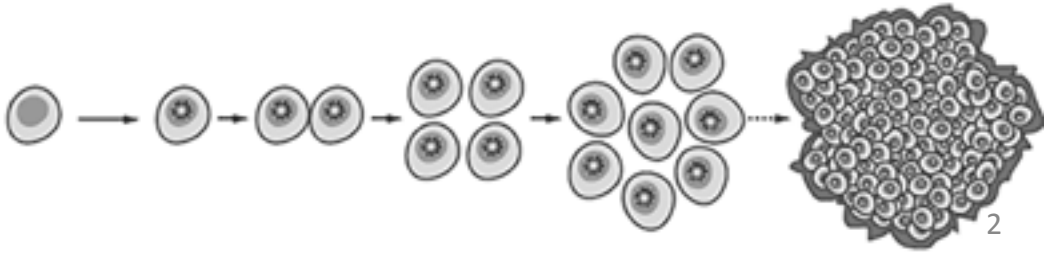
PhD Student

9/6/16

What is Cancer? What are the Hallmarks?

- Normal body cells which begin to divide without stopping and can spread into surrounding tissues
- The hallmarks of cancer are the distinctive and complementary capabilities that enable tumor growth and metastatic dissemination

- In other words… The characteristics that make cancer, cancer.



Cell, Vol. 100, 57–70, January 7, 2000, Copyright ©2000 by Cell Press

The Hallmarks of Cancer

Review

Douglas Hanahan* and Robert A. Weinberg†
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evolve progressively from normalcy via a series of pre-malignant states into invasive cancers (Foulds, 1954).

These observations have been rendered more concrete by a large body of work indicating that the genomes of tumor cells are invariably altered at multiple sites, having suffered disruption through lesions as subtle as point mutations and as obvious as changes in chromosome complement (e.g., Kinzler and Vogelstein, 1996). Transformation of cultured cells is itself a

Cell

Leading Edge
Review

Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
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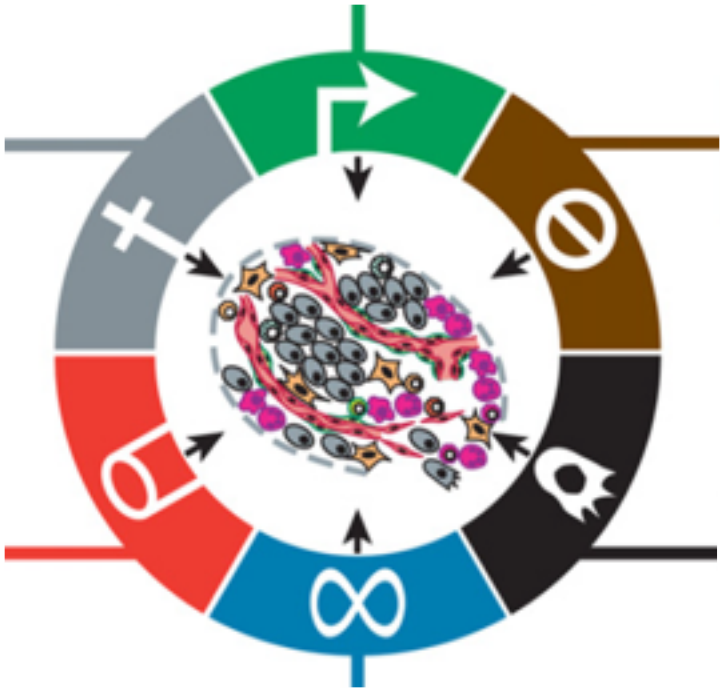
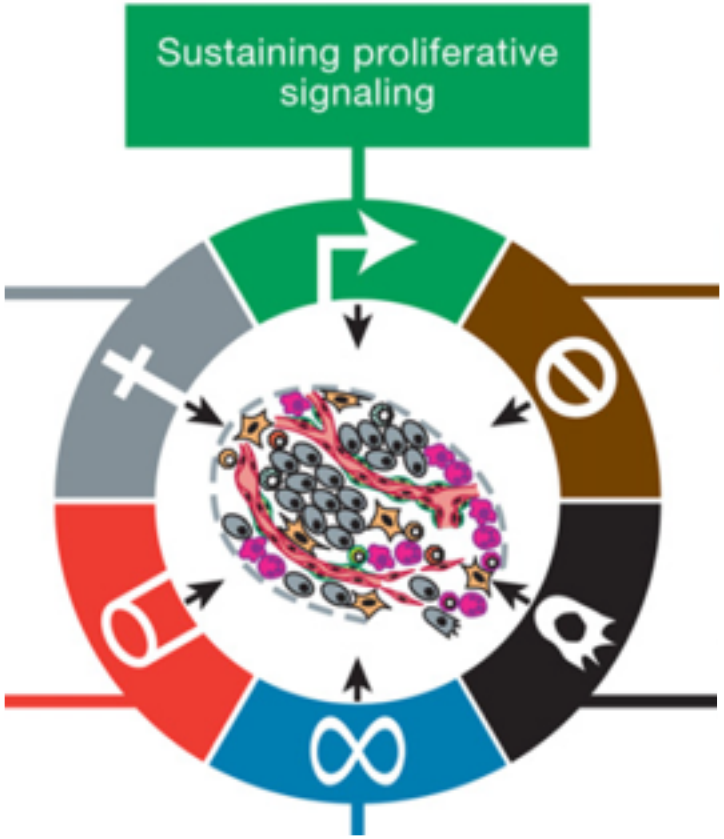
DOI 10.1016/j.cell.2011.02.013

Oncogene and Tumor Suppressor Genes

- **Oncogene**: mutated forms of normal cellular genes generally involved in promoting cell proliferation. These mutations result in dominant gain of function.
- **Tumor suppressor**: genes whose normal function in regulating proliferation is to stop it. Mutation results in recessive loss of function.

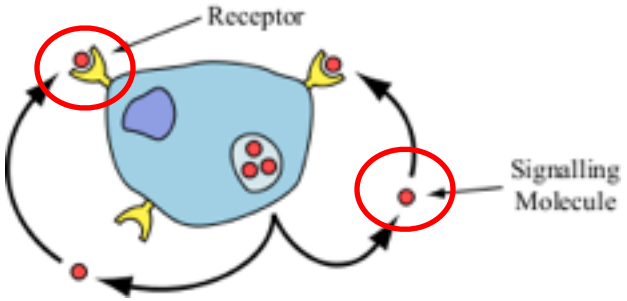
Tumor Heterogeneity



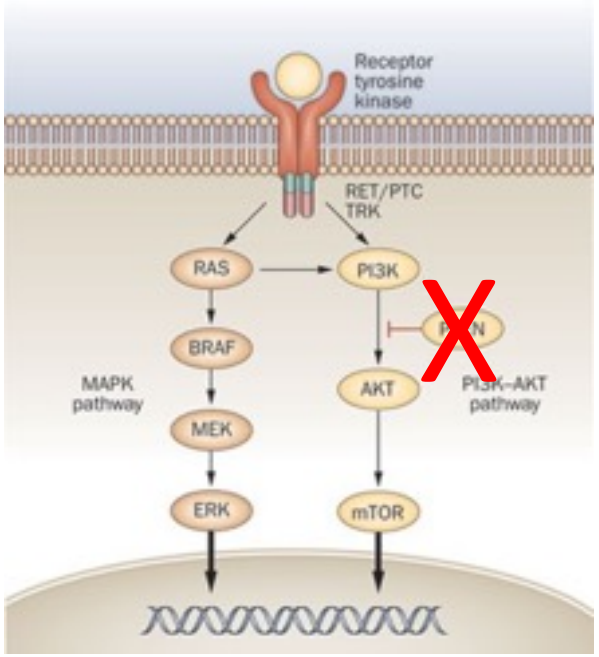

Sustaining proliferative signaling

Sustaining Proliferative Signalling: Masters of their Own Destinies!

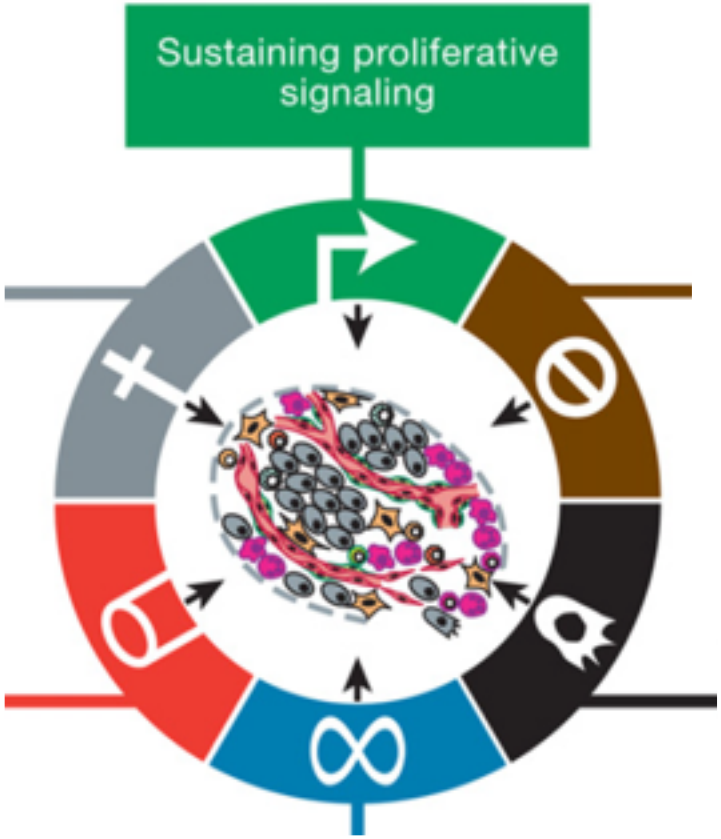
- Normal cells carefully control growth and division
- Cancer cells deregulate these signals
- How do tumors deregulate this?



http://www.labbookpages.co.uk/research/bioNode.html



Nikiforov Y., Nature Endocrinology 2011

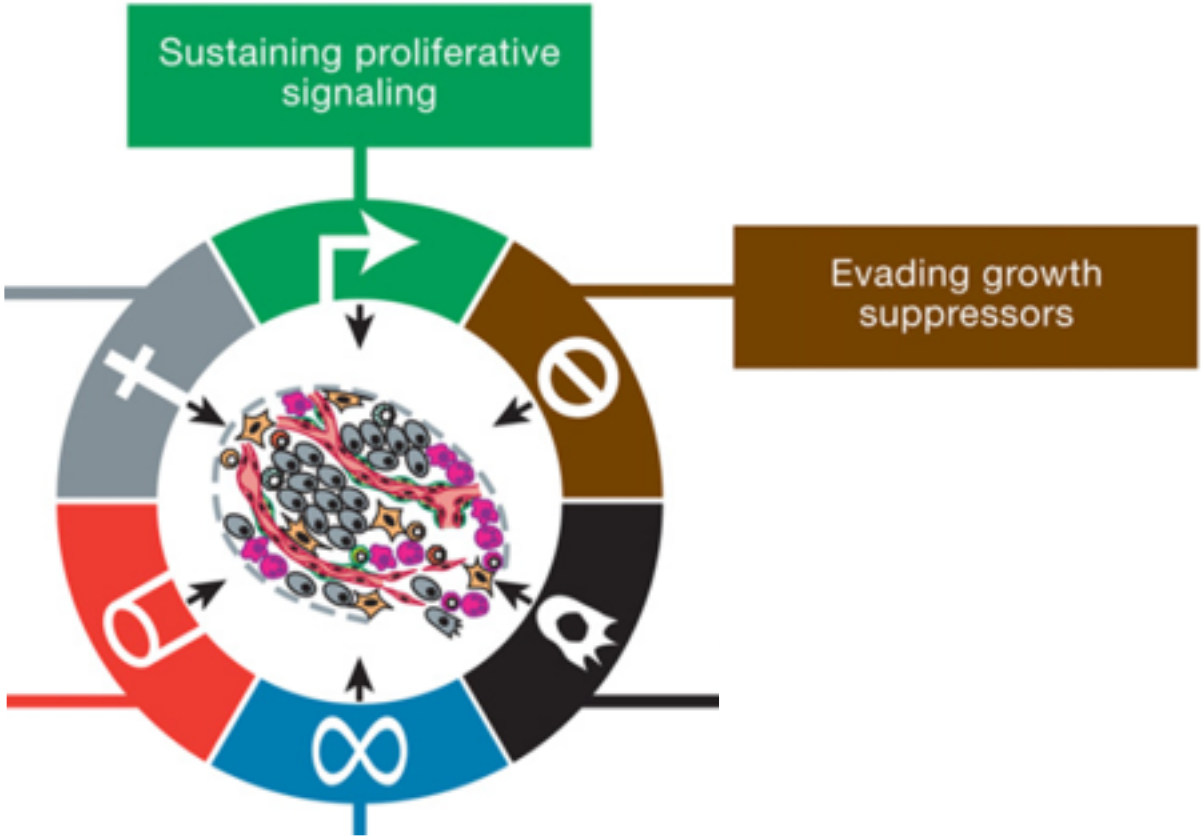

Sustaining proliferative signaling

Evading Growth Suppressors

- Circumventing programs which negatively regulate cell proliferation
- What are these programs?
  - Apoptosis
  - Senescence
  - DNA damage response
  - Cell cycle inhibition
  - Contact inhibition

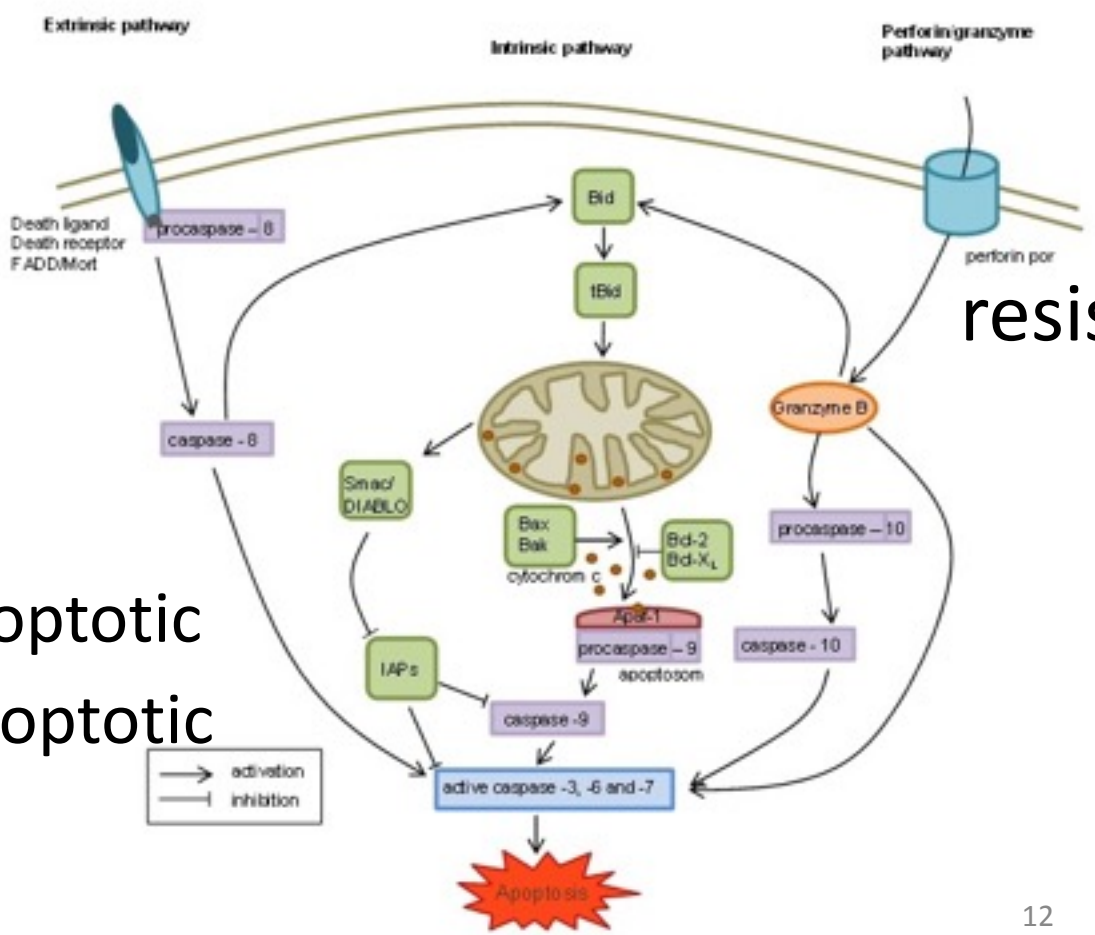
Key Players in Growth Suppression

- TP53: Senses the need to halt cell cycle progression and can trigger apoptosis
  - >50% of tumors have mutation
  - Li-Fraumeni Syndrome: ~50% chance of developing cancer by age 30
- RB: Gate keeper of cell cycle progression


Sustaining proliferative signaling
Evading growth suppressors

Resisting Cell Death

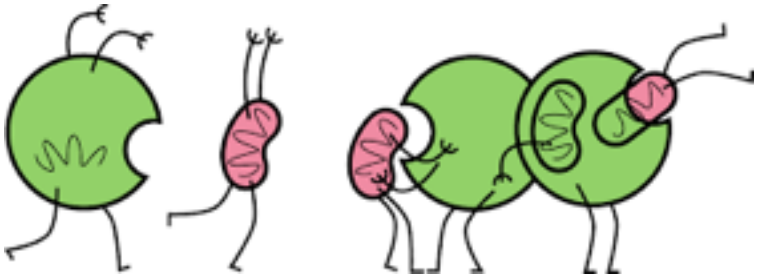
- What are forms of cell death?
  - Apoptosis
  - Autophagy
  - Necrosis
- How do tumors resist cell death?
  - Loss of p53
  - Increase anti-apoptotic
  - Decrease pro-apoptotic



Kulbacka J., *Intech* 2012

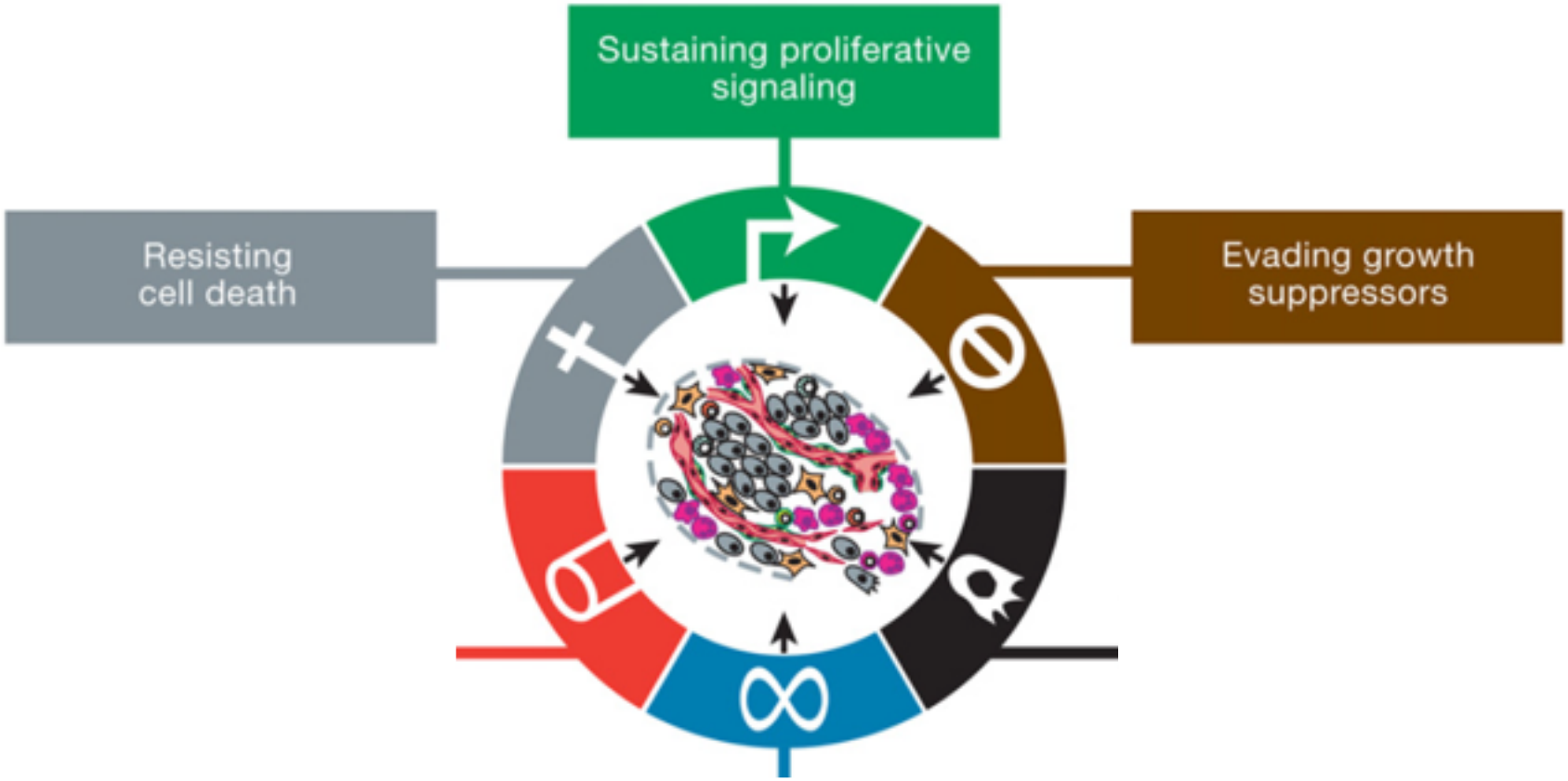
Autophagy and Necrosis

- Autophagy: Enables cells to break down cellular organelles, and recycle them for biosynthesis and energy metabolism



- Necrosis: Release contents into local tissue microenvironment (including proinflammatory signals)

http://ds9.botanik.uni-bonn.de/zellbio/AG-Baluska-Volkmann/pdf/PCDU/09%20-%20Autophagy.pdf

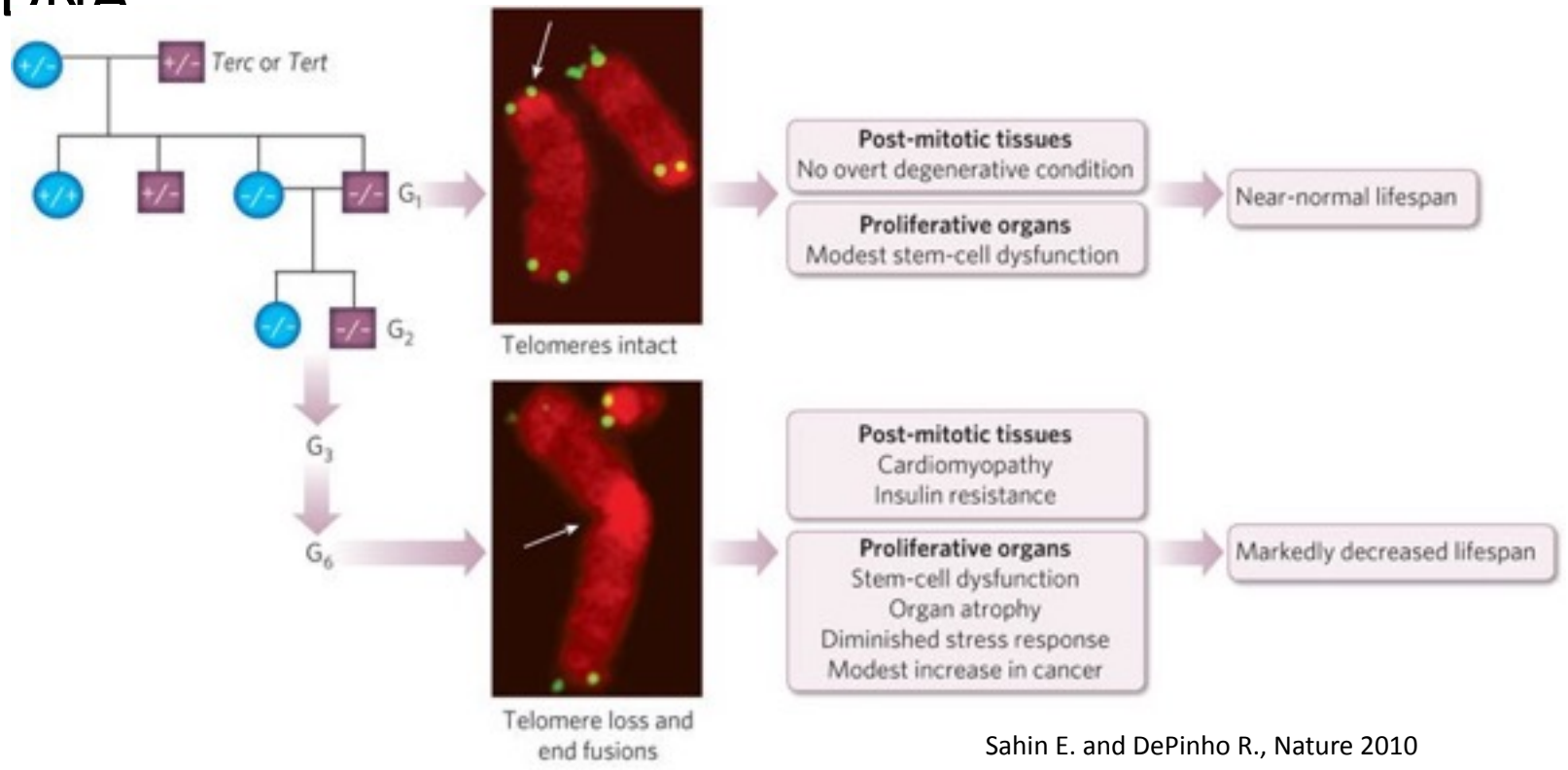

Sustaining proliferative signaling
Resisting cell death
Evading growth suppressors

Enabling Replicative Immortality

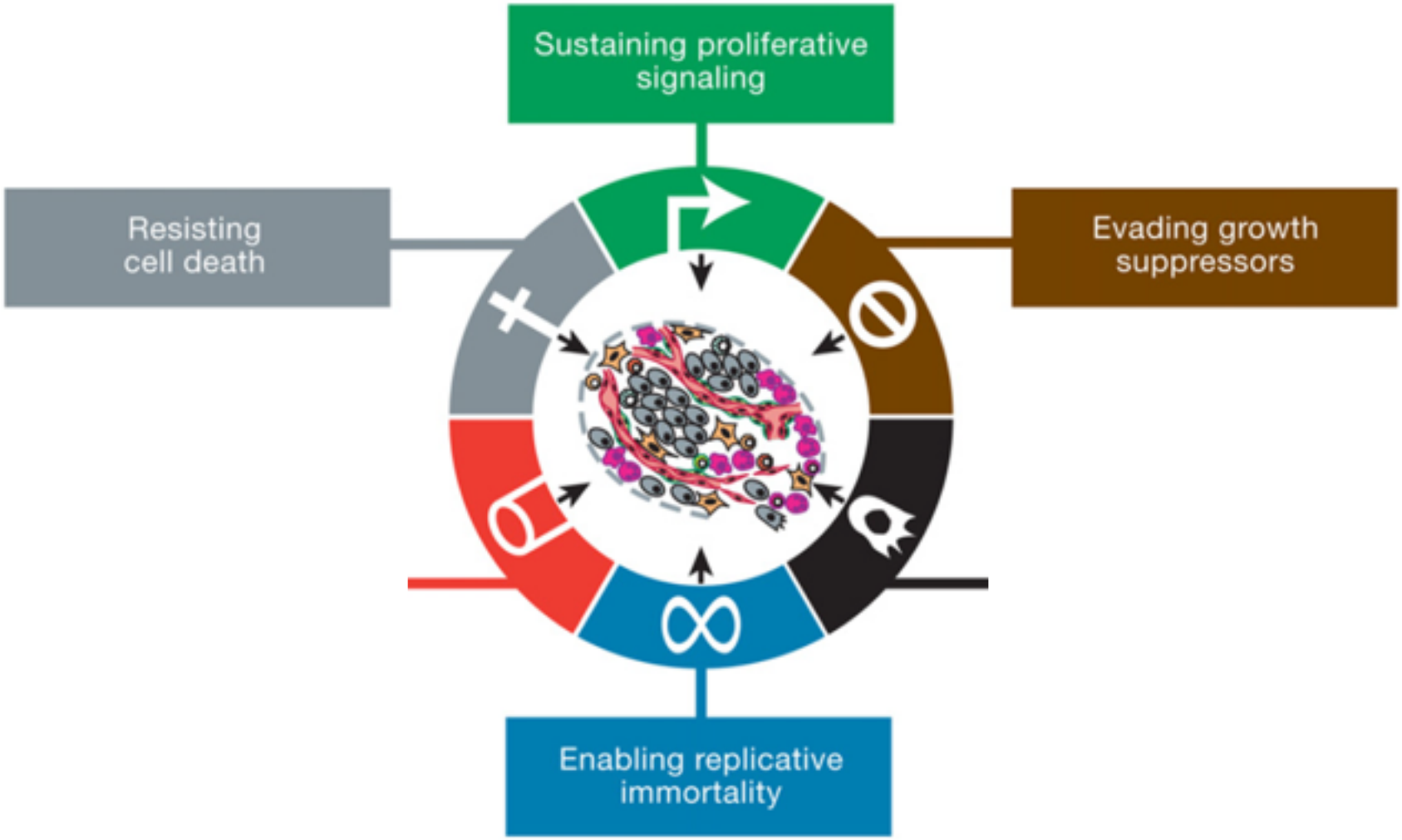
- Cancer cells must have unlimited replicative potential
- Normal cells pass through a limited number of successive cell growth-and-division cycles
- Cells must overcome senescence and crisis

Telomeres: the good and the bad

- Short tandem repeats which protect the ends of chromosomes, and are shortened upon cell division
- Telomerase adds telomeres to the ends of telomeric DNA

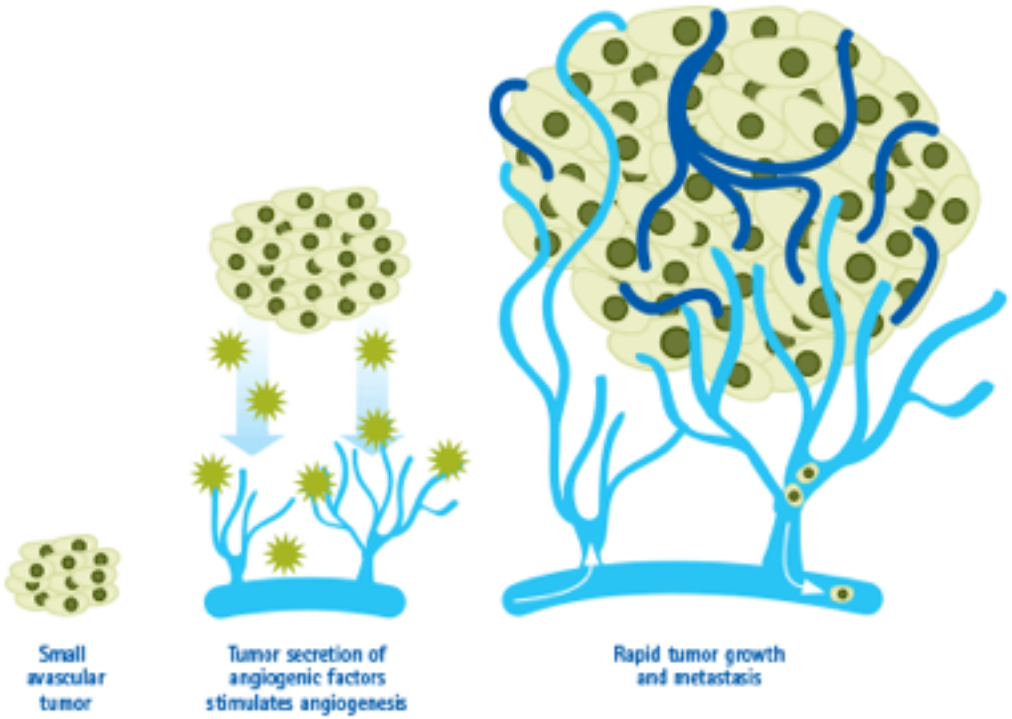


Sahin E. and DePinho R., Nature 2010

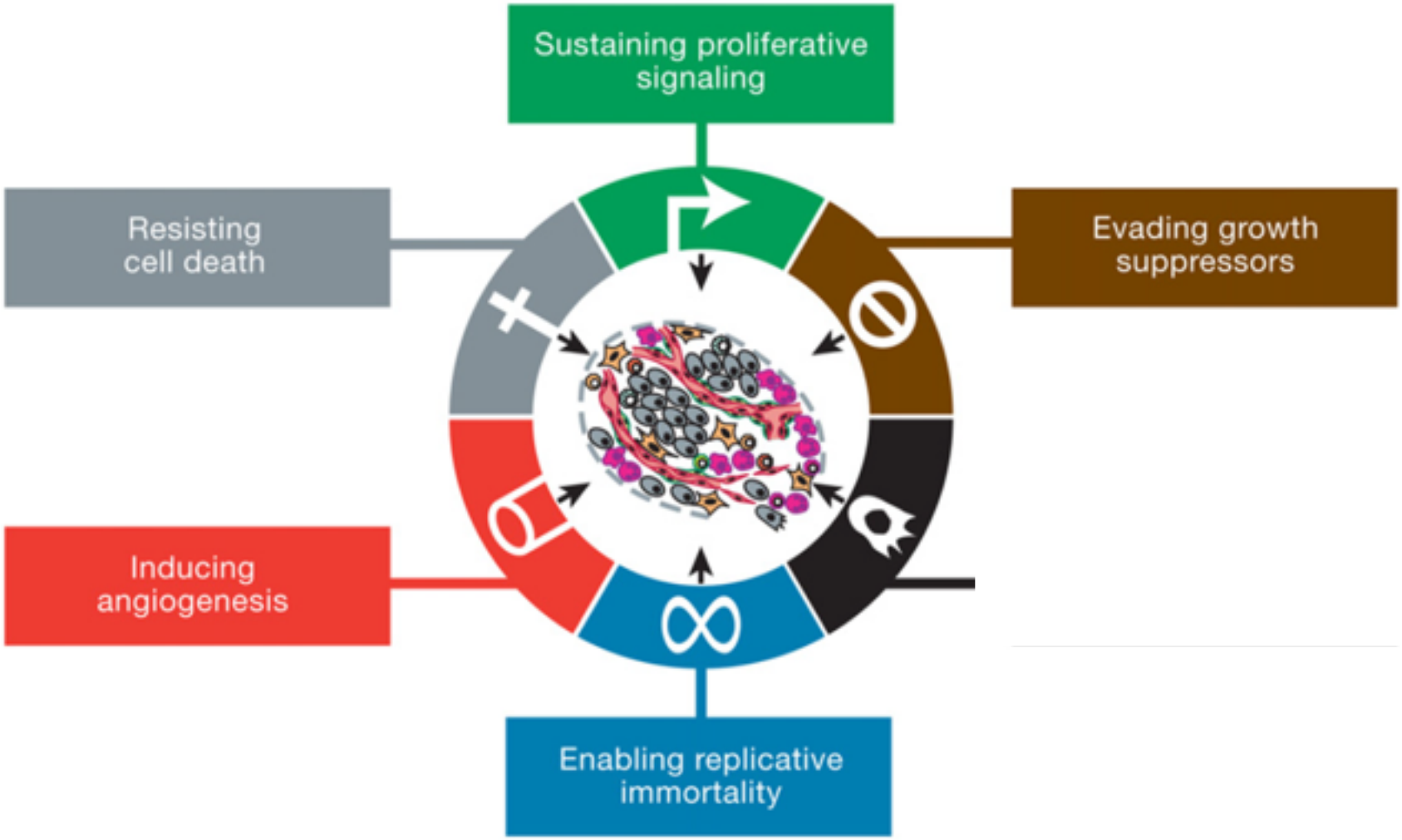

Sustaining proliferative signaling
Resisting cell death
Evading growth suppressors
Enabling replicative immortality

Inducing Angiogenesis

- Tumors require oxygen, nutrients, and the ability to evacuate metabolic wastes and CO_2



EMD Millipore

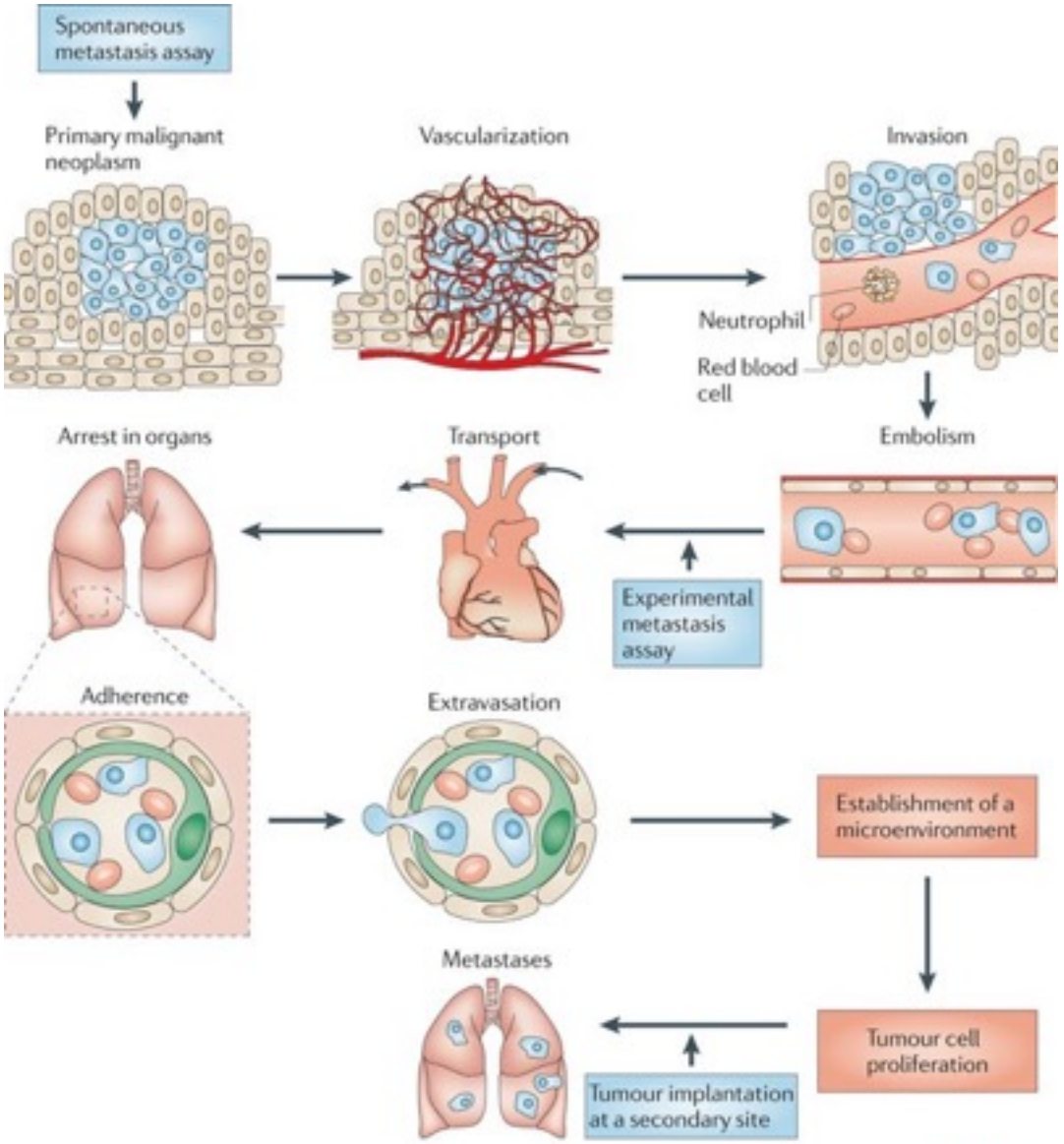

Sustaining proliferative signaling
Resisting cell death
Evading growth suppressors
Inducing angiogenesis
Enabling replicative immortality

Activating Invasion and Metastasis

Step 1: Physical Dissemination of cancer cells from primary tumor to Distant Tissues

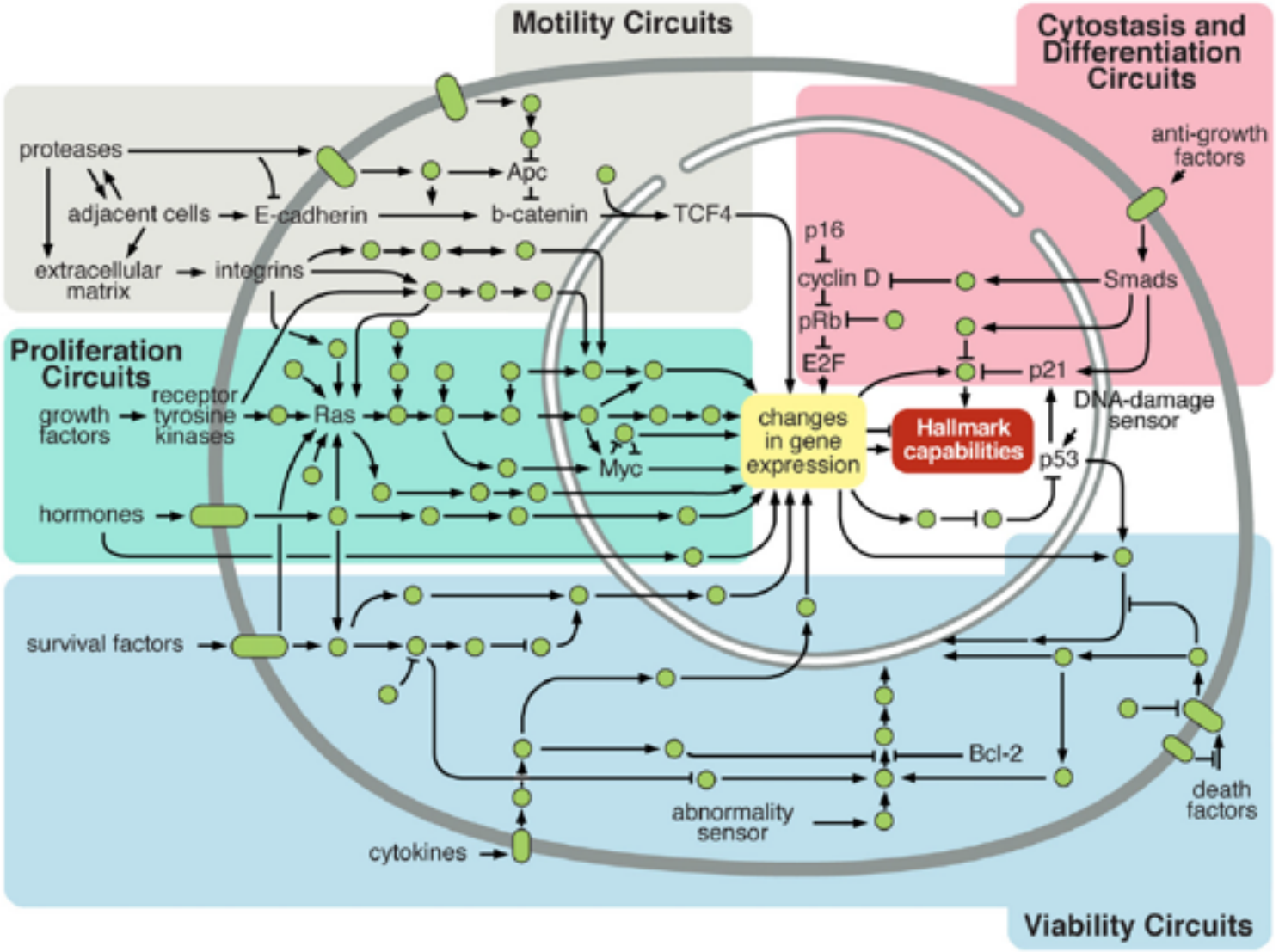
Step 2: Adaptation of these cells to foreign tissue microenvironments, successful colonization

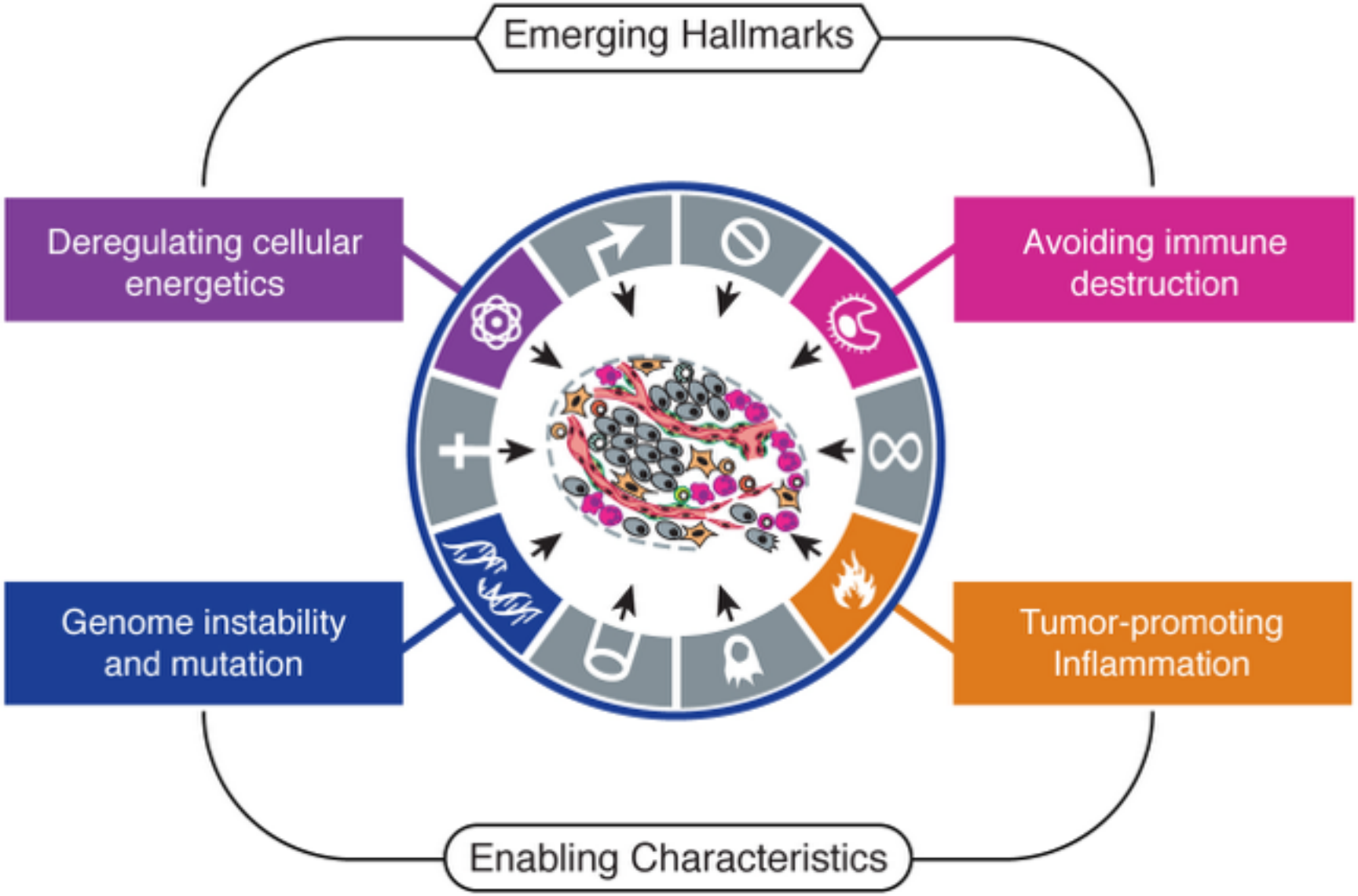
Activating Invasion and Metastasis



Francia G. et al, *Nature Reviews Cancer* 2011

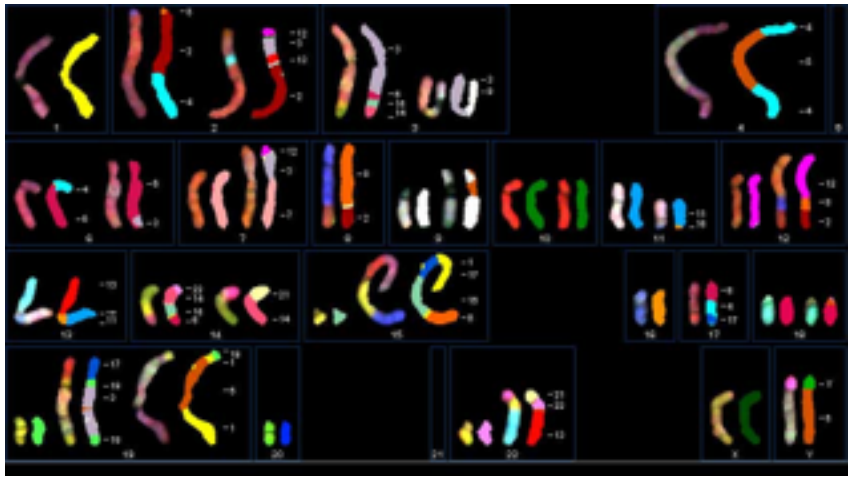
Interconnection of the Hallmarks




Emerging Hallmarks
Deregulating cellular energetics
Avoiding immune destruction
Genome instability and mutation
Tumor-promoting Inflammation
Enabling Characteristics

Genome Instability and Mutation

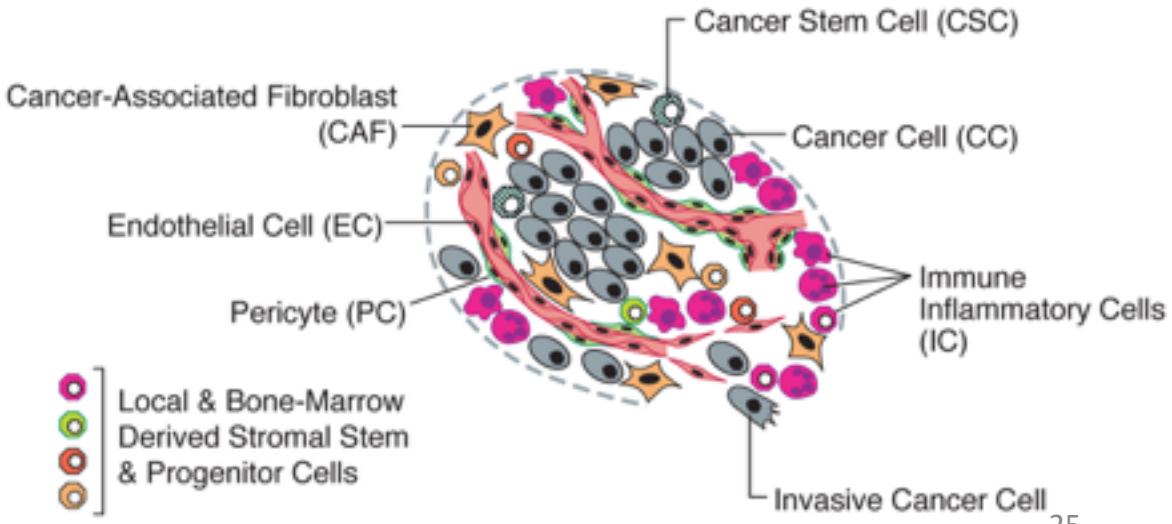
- Acquisition of the hallmarks in part depends on genomic alterations
- This may be acquired through…
  - Clonal selection
  - DNA methylation
  - Histone modifications



- Alterations in DNA maintenance machinery

Tumor Promoting Inflammation

- Immune cells are present in tumors at various densities
- Inflammation can contribute to multiple hallmarks by supplying bioactive molecules to the tumor microenvironment, including growth factors and survival factors



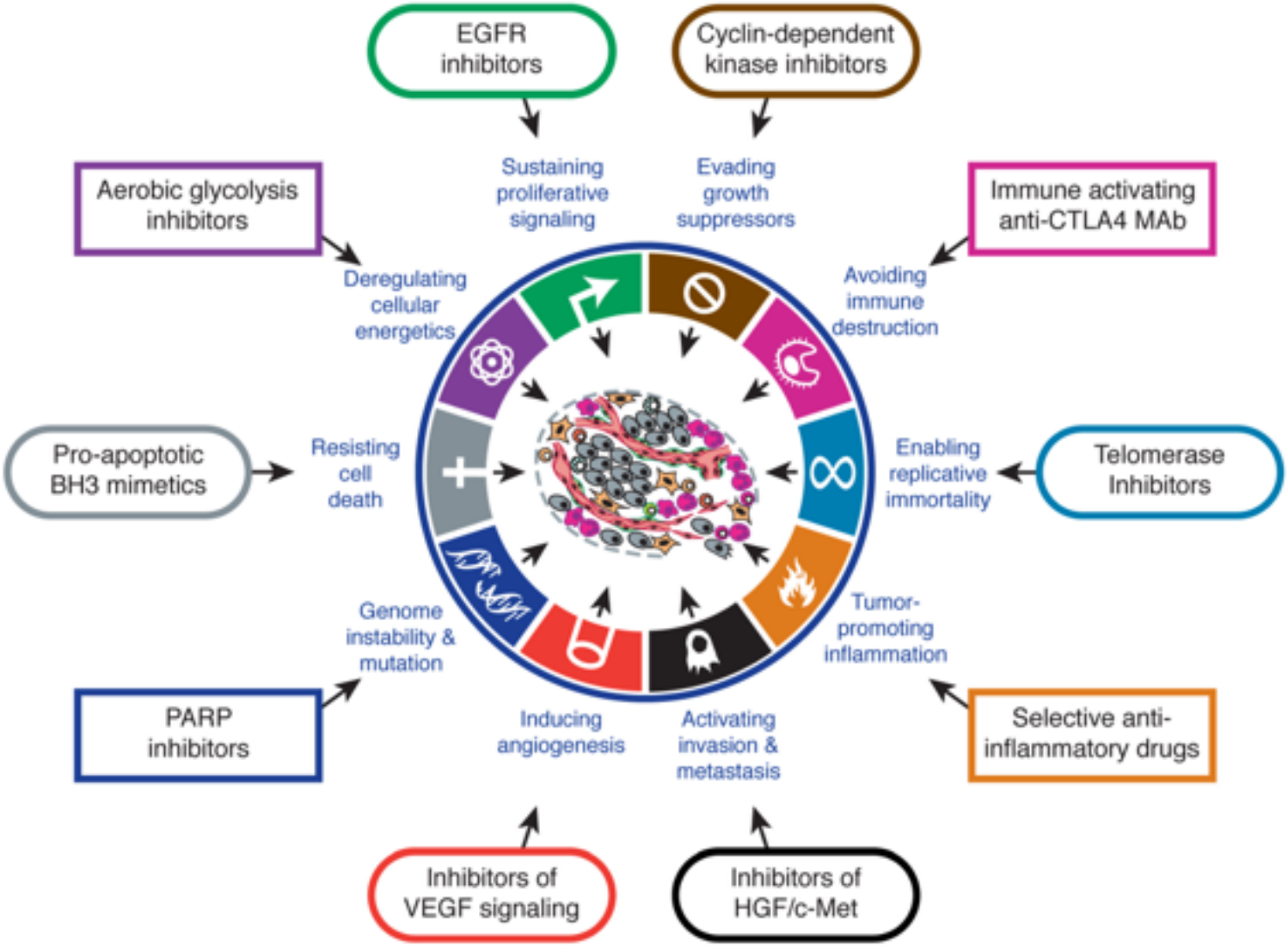
Reprogramming Energy Metabolism

- The Warburg Effect: Cancer cells reprogram their glucose metabolism, by limiting their energy production largely to glycolysis
- Divert glycolytic intermediates to other biosynthetic pathways to make macromolecules and organelles

Evading Immune Destruction

- Cells and tissues are under constant surveillance by the immune system
- Mice lacking NK and T cells were more susceptible to cancer development
- Patients with higher CTLs and NK cells have a better prognosis

The Hallmarks and Therapies



Do you feel that one hallmark is more important than the other?

Thank you!
Comments/Questions?