Hallmarks of Cancer

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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.
The Hallmarks of Cancer

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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 con-
crete by a large body of work indicating that the gen-
omes of tumor cells are invariably altered at multiple
sites, having suffered disruption through lesions as sub-
tle as point mutations and as obvious as changes in
chromosome complement (e.g., Kinzler and Vogelstein,
1996). Transformation of cultured cells is itself a
multistep process; rodent cells require at least two intra-

Hallmarks of Cancer: The Next Generation

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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 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
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: Gatekeeper of cell cycle progression
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)
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
Inducing Angiogenesis

- Tumors require oxygen, nutrients, and the ability to evacuate metabolic wastes and CO$_2$
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

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?