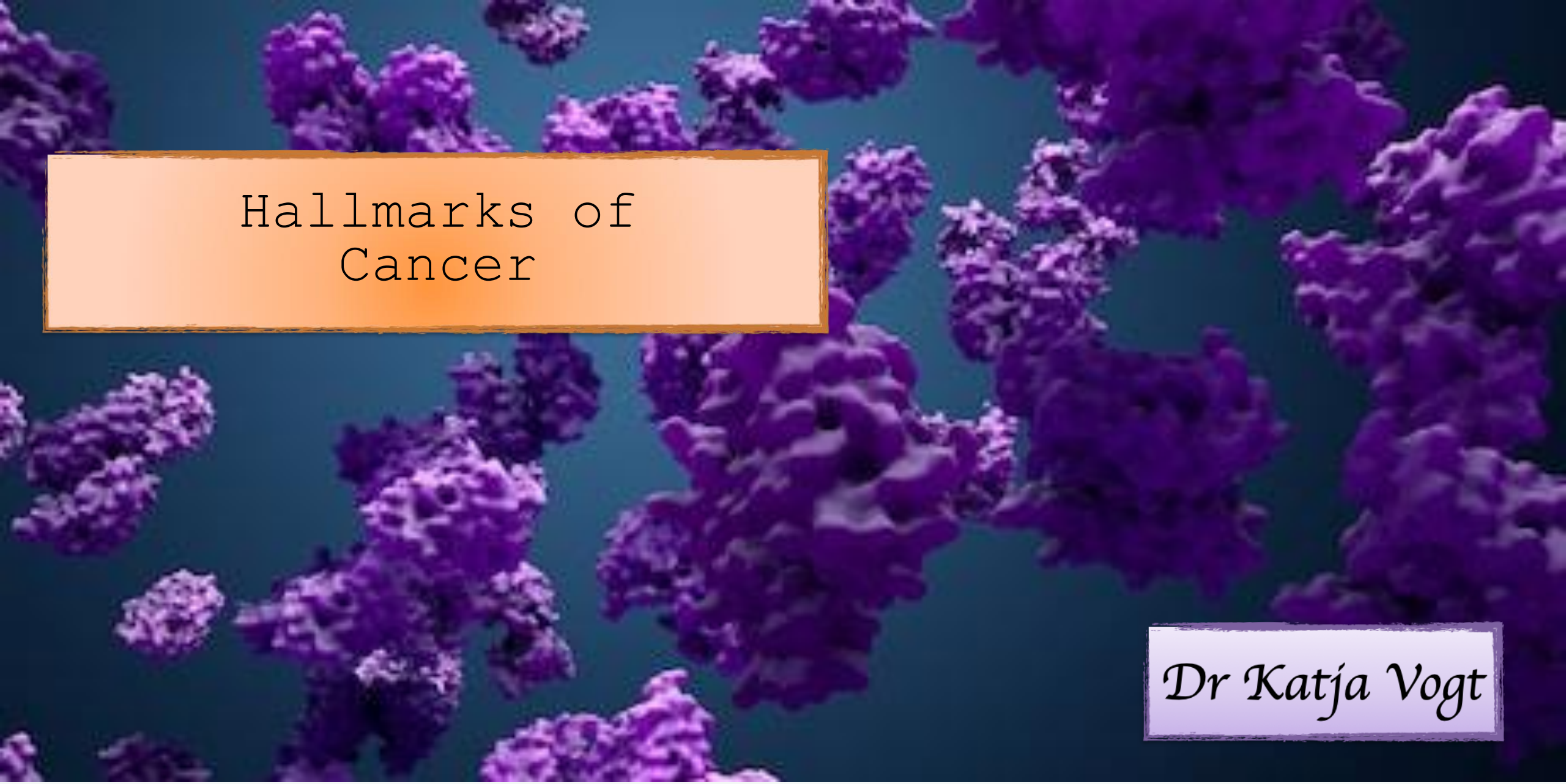


Hallmarks of Cancer

Dr Katja Vogt

University of Lancashire

Today we are going to…

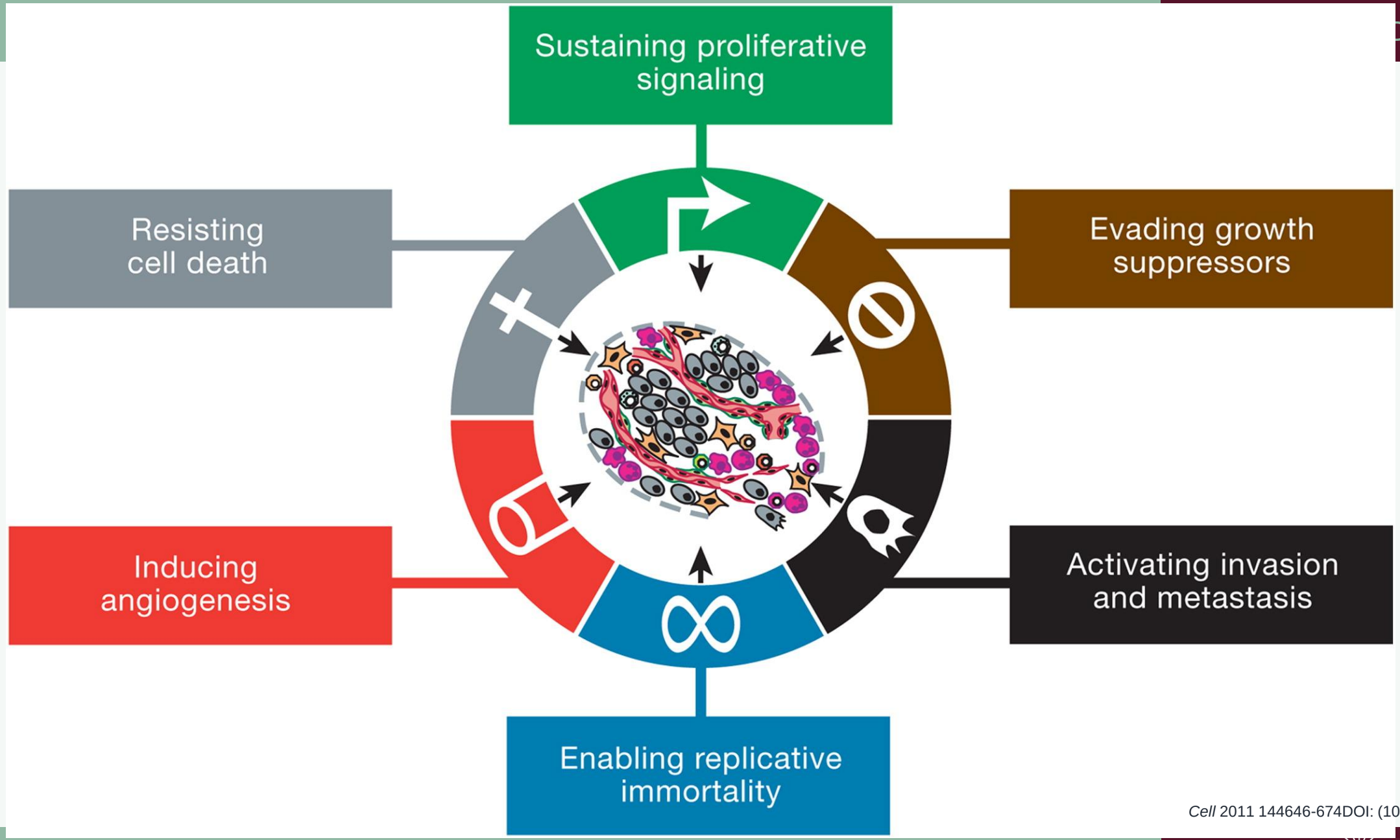
- … define the hallmarks of cancer
- … investigate the overarching concepts of the hallmarks of cancers
- … explore different nomenclature
- … identify the underlying principles of cells developing into cancer

MBBS learning outcomes

- Recognise the basic concepts of cancer, including the Hallmarks of cancer, cell cycle checkpoints, oncogenes and tumour suppressor genes
- Apply the concepts of cancer to the use of biomarkers in the aetiology and diagnosis of cancer.

Hallmarks

⭐ Distinctive capabilities that are acquired by cells progressing towards a neoplastic state



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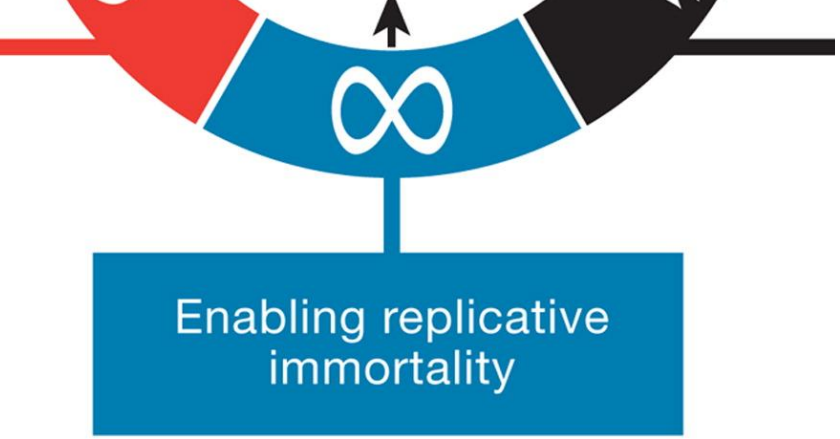

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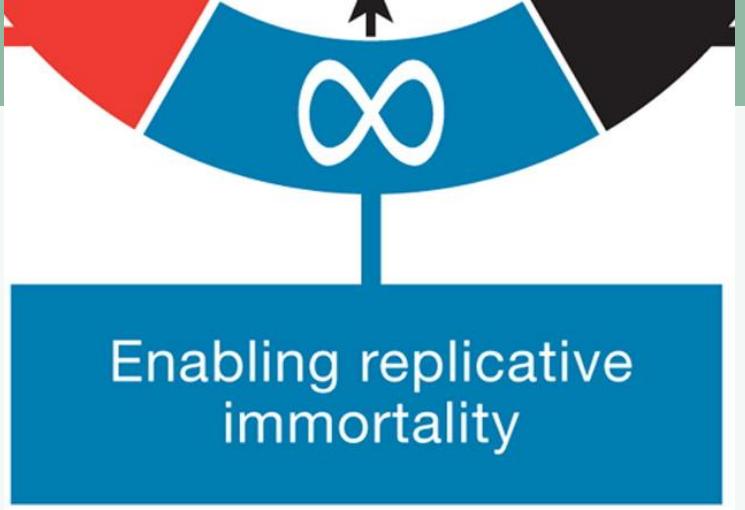
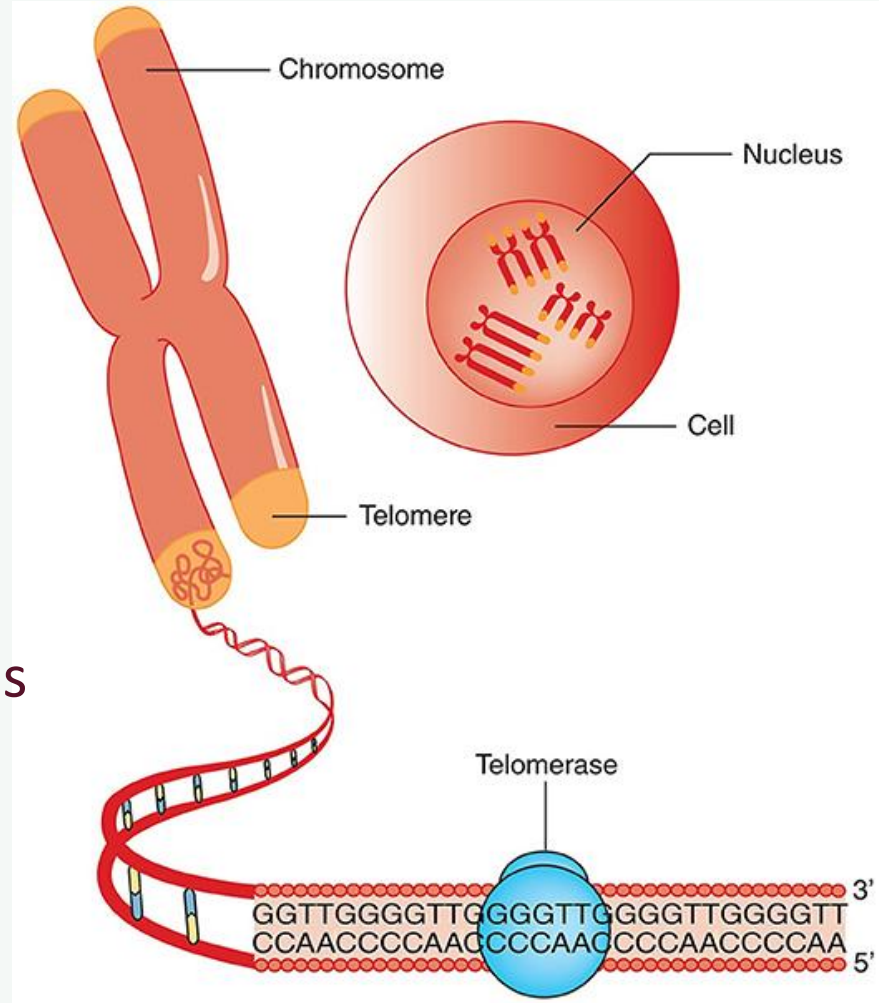
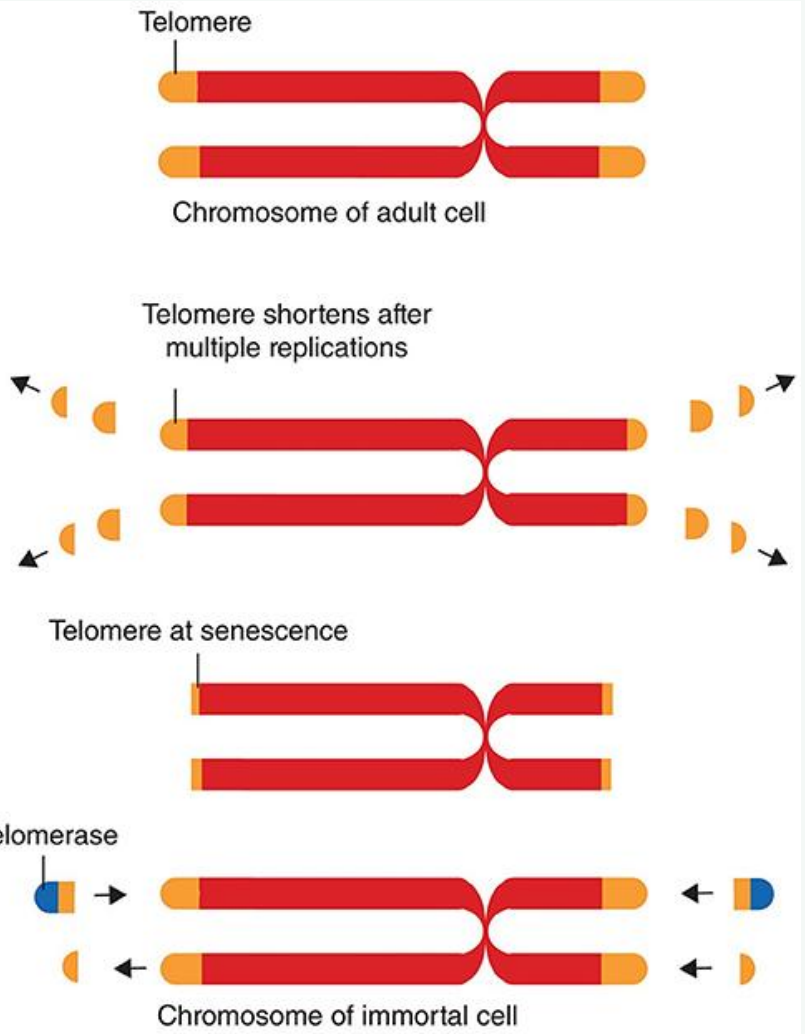


Telomeres

- Protect the ends of chromosome
  - Enhancing of cell proliferation and/or resistance to apoptosis
  - DNA-damage repair
  - RNA-dependent RNA polymerase function





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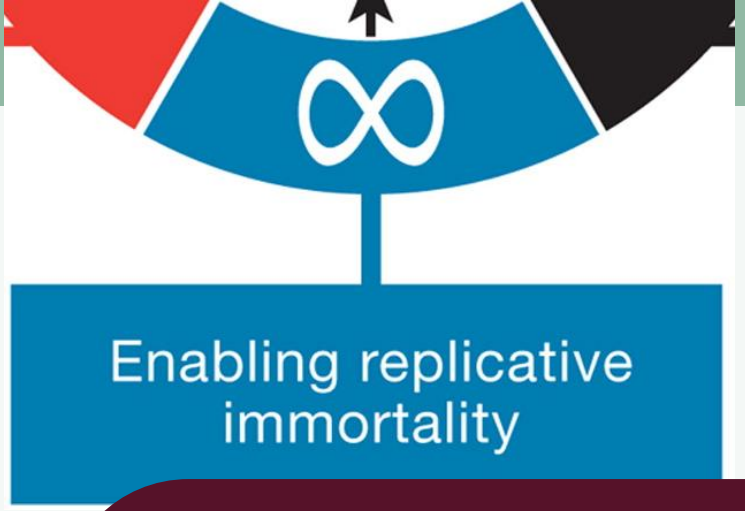
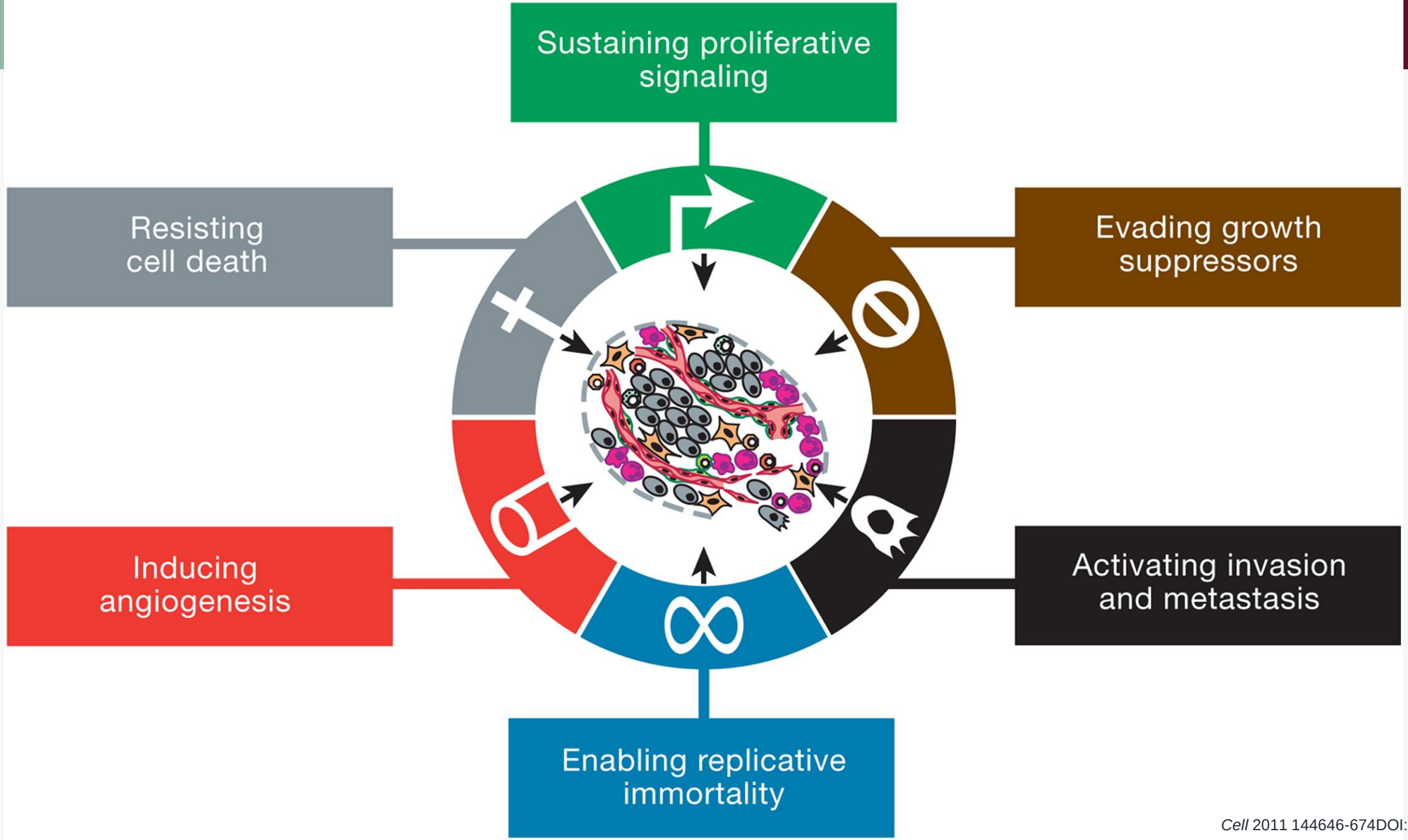


Telomerase on neoplastic cells

- Telomerase expressed at functionally significant levels in the vast majority (90%) of spontaneously immortalised cells
- Maintain telomeric DNA at lengths sufficient to **avoid** triggering senescence or apoptosis
- Impaired telomere function can actually foster tumour progression → to generate tumour-promoting mutations

Senescence can be induced by high levels of oncogenic signalling and subcritical shortening of telomeres



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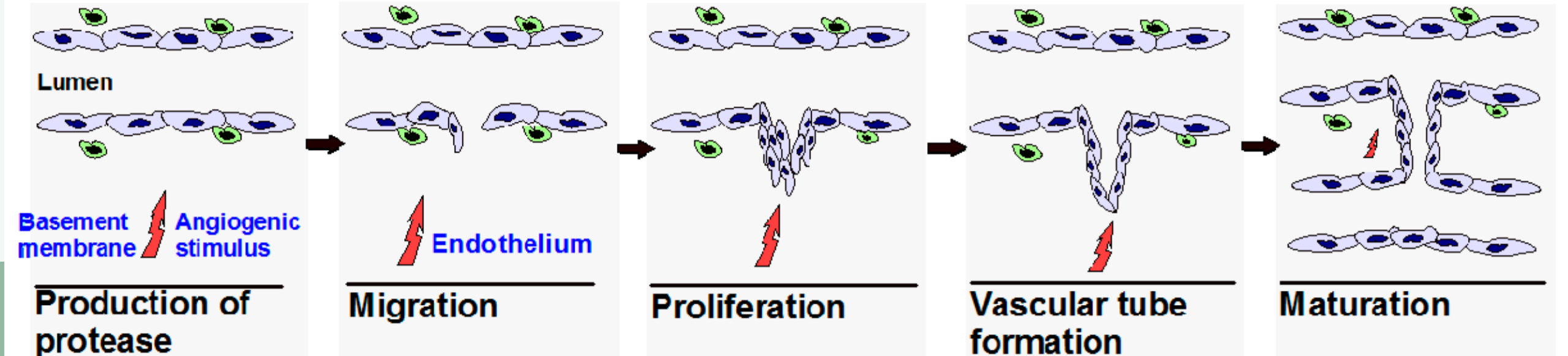
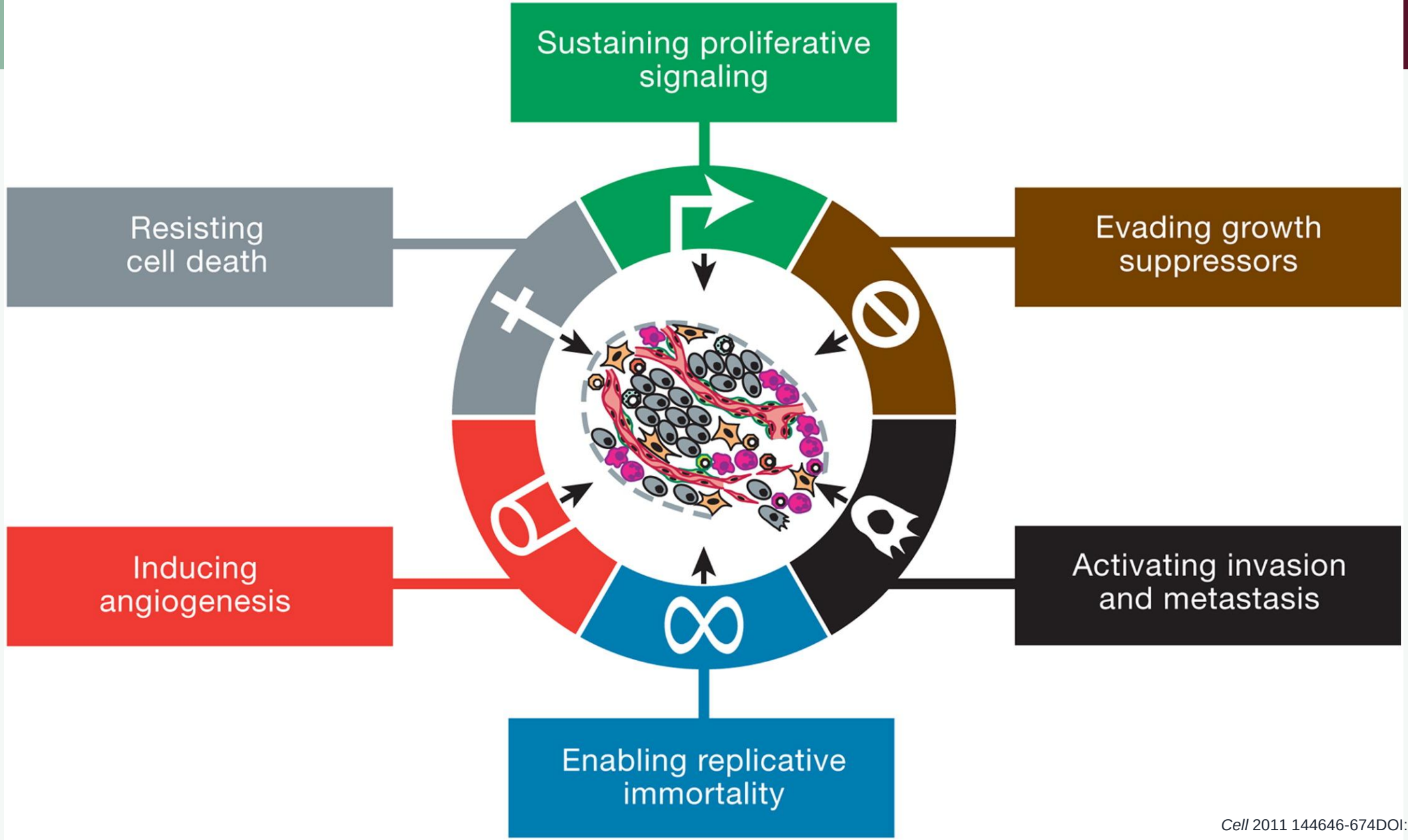
Angiogenesis

- Vasculogenesis and angiogenesis as part of development
- Normal vasculature is largely quiescent
- Angiogenesis inducer: vascular endothelial growth factor-A (VEGF-A)
- Angiogenesis inhibitor: thrombospondin-1 (TSP-1)



Angiogenesis in cancer

- Angiogenic switch is activated
- Tumour neovasculature is typically aberrant
  - Precocious capillary sprouting
  - Convoluted and excessive vessel branching
  - Distorted and enlarged vessels
  - Erratic blood flow
  - Microhemorrhaging
  - Leakiness
  - Abnormal levels of endothelial cell proliferation and apoptosis
- Induced early in development of cancer
- Pericytes and bone marrow-derived cells maintain and contribute to tumour angiogenesis



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Sequence of discrete steps → the invasion-metastasis cascade

- Cell-biological changes
- Local invasion
- Intravasation into nearby blood and lymphatic vessels
- Transit through the lymphatic and hematogenous systems
- Escape from the lumina into the parenchyma of distant tissues (extravasation)

- Loss of E-cadherin (adhesion molecule)
- Adhesion favouring molecules downregulated
- Cell migration promoting proteins upregulated

Forms of invasion and metastasis

1. **Epithelial-mesenchymal transition** (EMT), prominently by epithelial cells
2. **Collective Invasion**
3. **Amoeboid invasion**: individual cancer cells slither through existing interstices in the extracellular matrix

- **Facilitation of invasion by inflammatory cells** that assemble at the boundaries of tumours

EMT epithelial-mesenchymal transition

Down to a number of transcription factors

- Transition from polygonal/epithelial to a spindly/fibroblastic morphology
- Loss of adherens junctions
- Expression of matrix-degrading enzymes
- Increased motility
- Heightened resistance to apoptosis

- Transcription factors also:
  - Can directly repress E-cadherin gene expression
  - Regulate one another as well as overlapping sets of target genes
- Crosstalk between cancer cells and neoplastic stroma are also involved
- Cells that have undergone an EMT can go through the reverse process, termed the mesenchymal-epithelial transition (MET)

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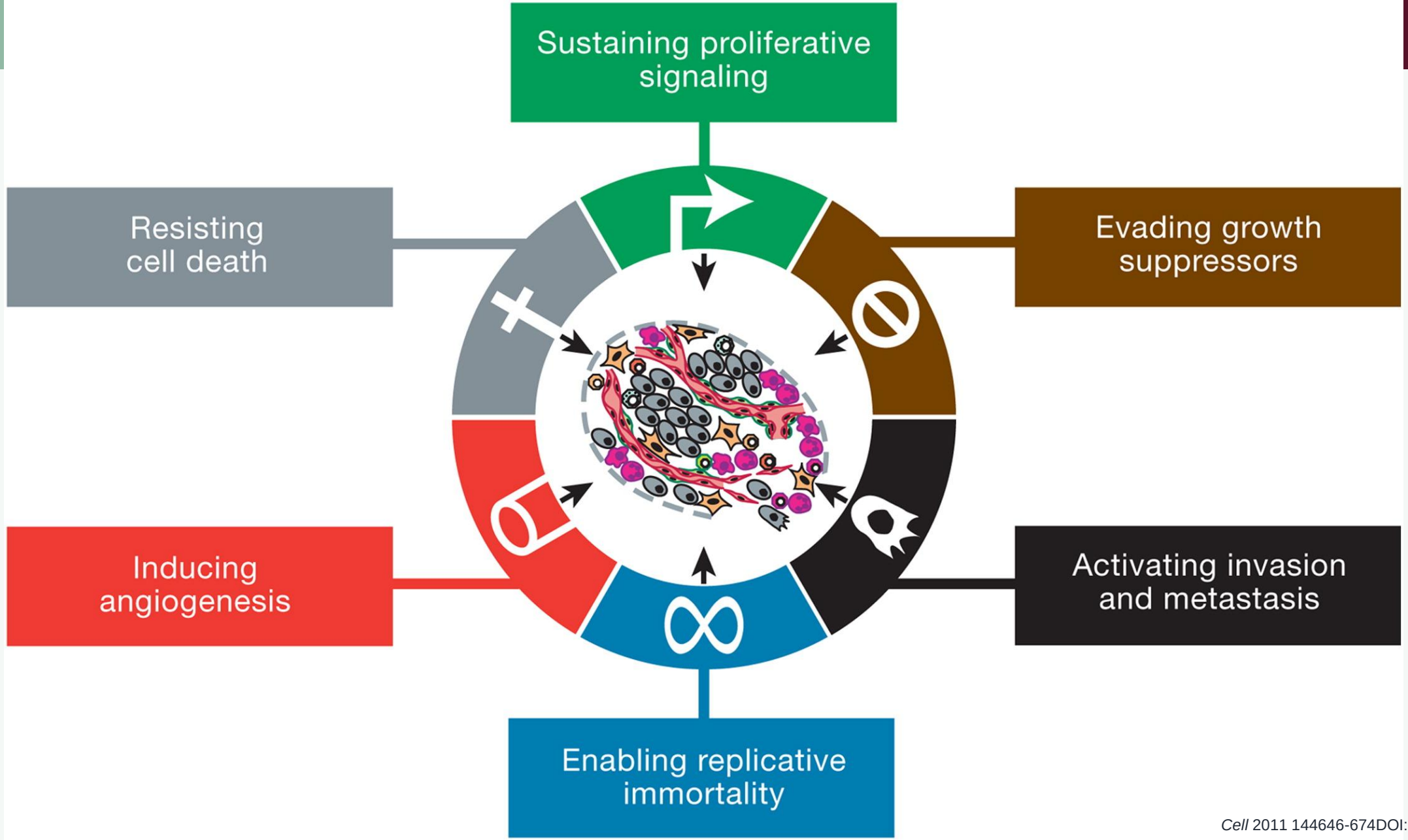
Micrometastases

- Many patients have micrometastases but never show macroscopic metastatic tumours
- Primary tumour may release systemic suppressor factors to make micrometastases dormant,
  - When primary tumour is removed, micrometastases start growing
- In breast cancer and melanoma, macroscopic metastases may erupt decades after a primary tumour has been removed → dormant micrometastases
- Micrometastases may lack other hallmark capabilities

Having developed such tissue-specific colonising ability, the cells in metastatic colonies may proceed to disseminate further, not only to new sites in the body but also back to the primary tumours



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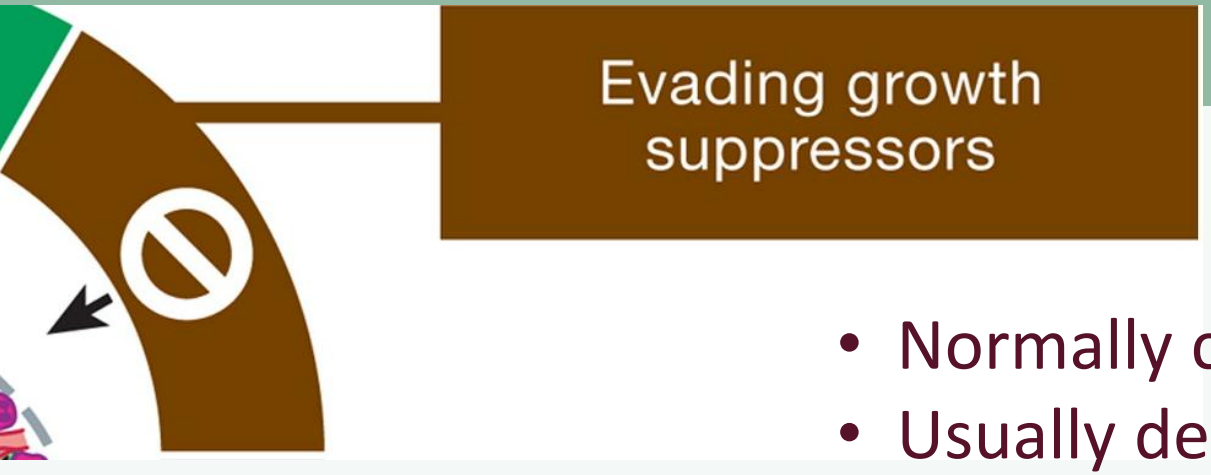

- Normally cell proliferation is negatively regulated
- Usually depend on tumour suppressor genes

- Two prototypical tumor suppressors encode the RB (retinoblastoma-associated) and TP53 proteins
- Are part of a larger network with functional redundancy
- Contact inhibition is evaded due to mutation of specific tumour suppressors
- Corruption of the TGF-b pathway promotes malignancy, termed the epithelial to mesenchymal transition (EMT)

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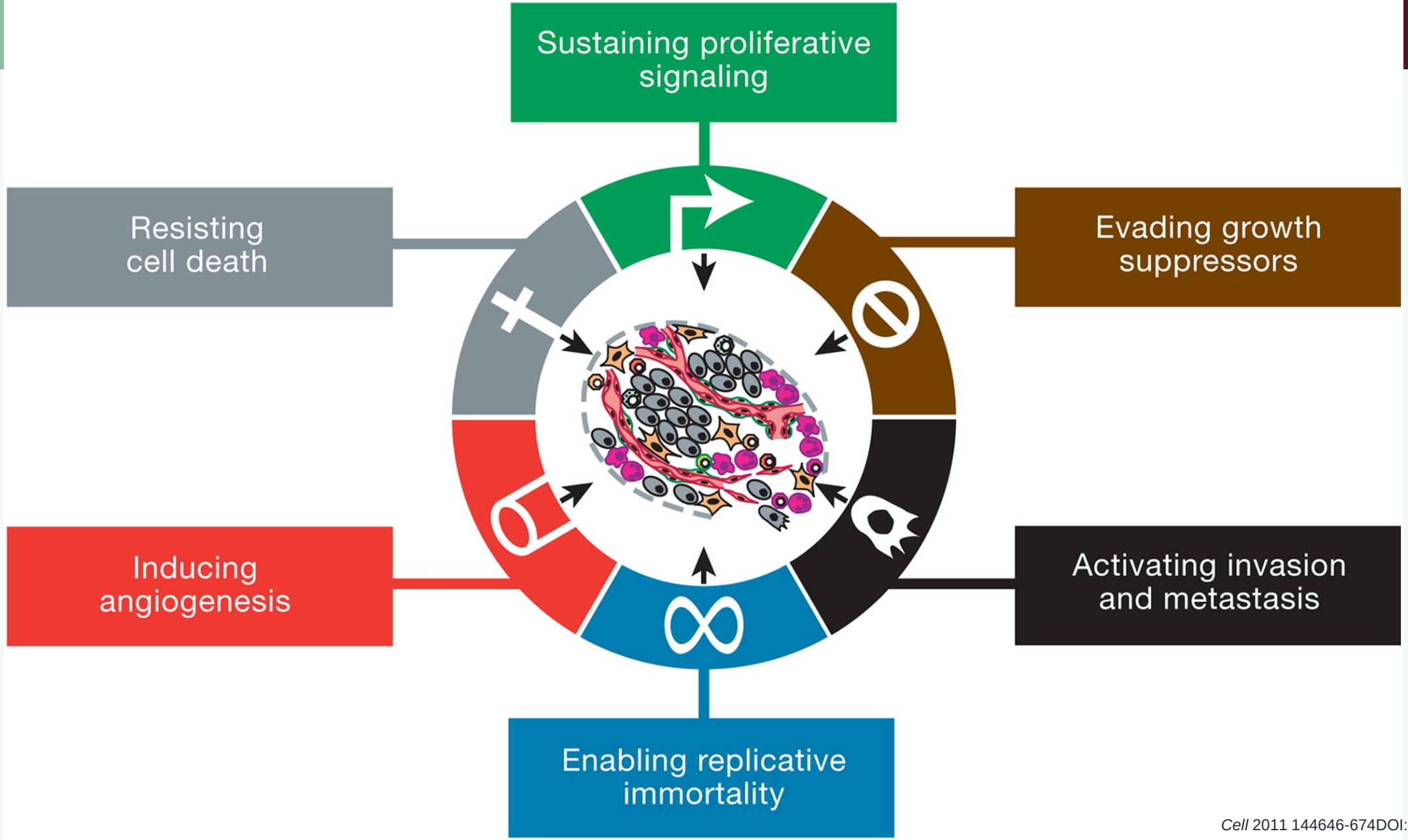

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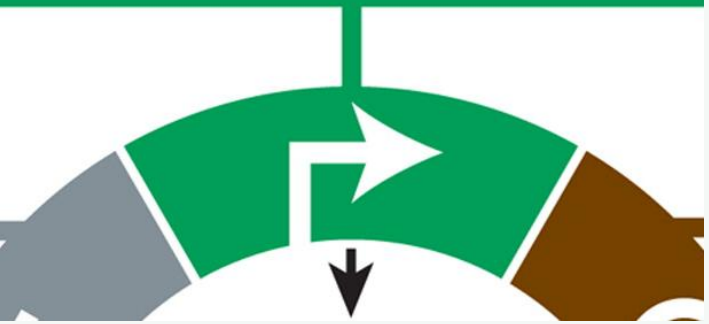
Sustaining proliferative signaling

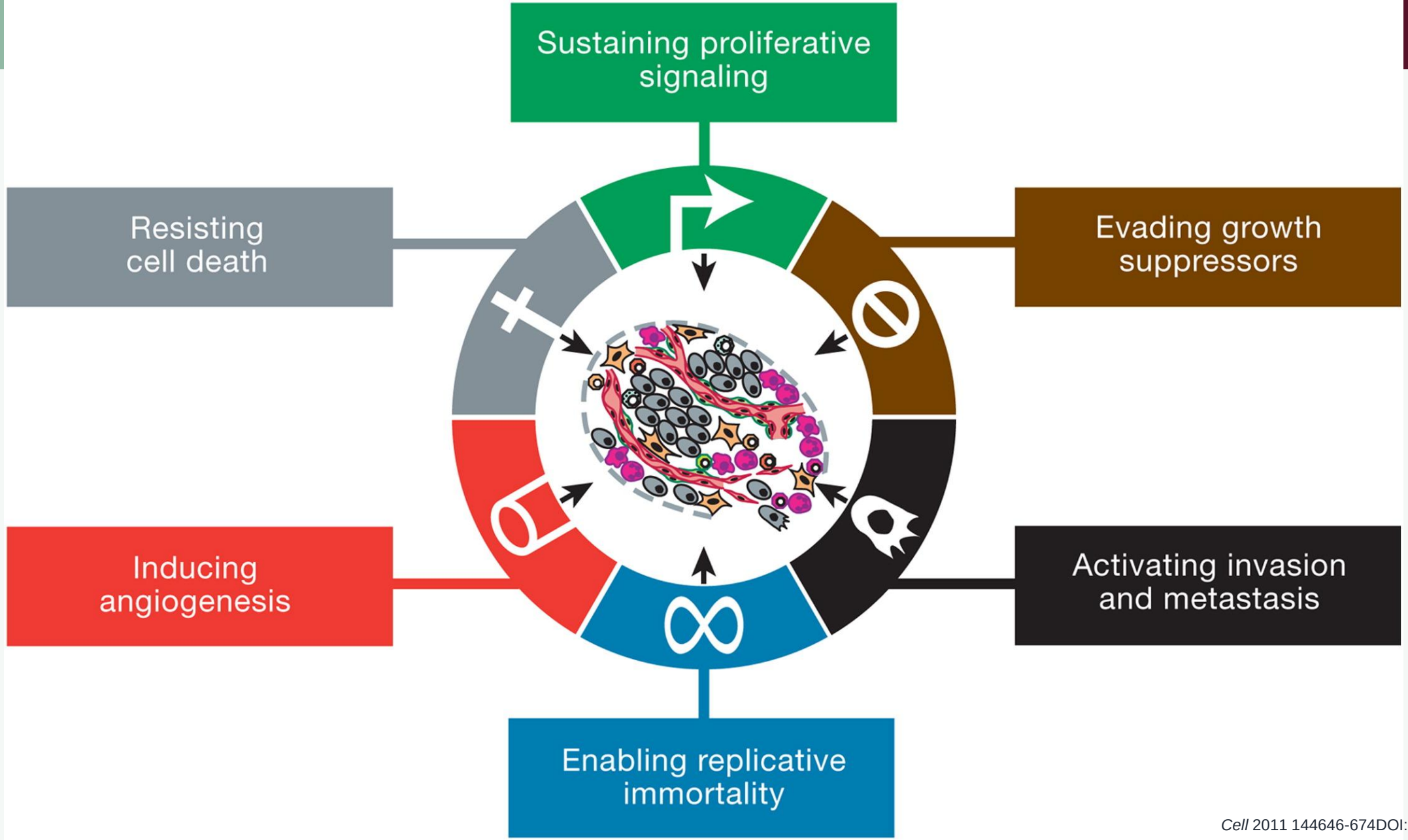


- Normally proliferation is carefully controlled, including the production and release of growth inducing signals
- The release of mitogens and growth factor signals is still poorly understood

Normal cells

- Autocrine proliferative stimulation
- Stimulation of associated stroma
- Hyperresponsive by increasing receptor numbers / binding
- Constitutive activation of downstream signalling cascades
  - Somatic mutations activate downstream pathways
  - Disruptions of negative-feedback mechanisms that attenuate proliferative signalling
  - Excessive proliferative signalling can trigger cell senescence

Neoplastic cells



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- Apoptosis is a natural barrier to cancer development
- TP53 induces apoptosis by upregulating expression of BH3- containing protein, which interfere with the anti-apoptosis Bcl-2 proteins
- Hyperactive signaling by certain oncoproteins, such as Myc, can also trigger apoptosis

Normal cells

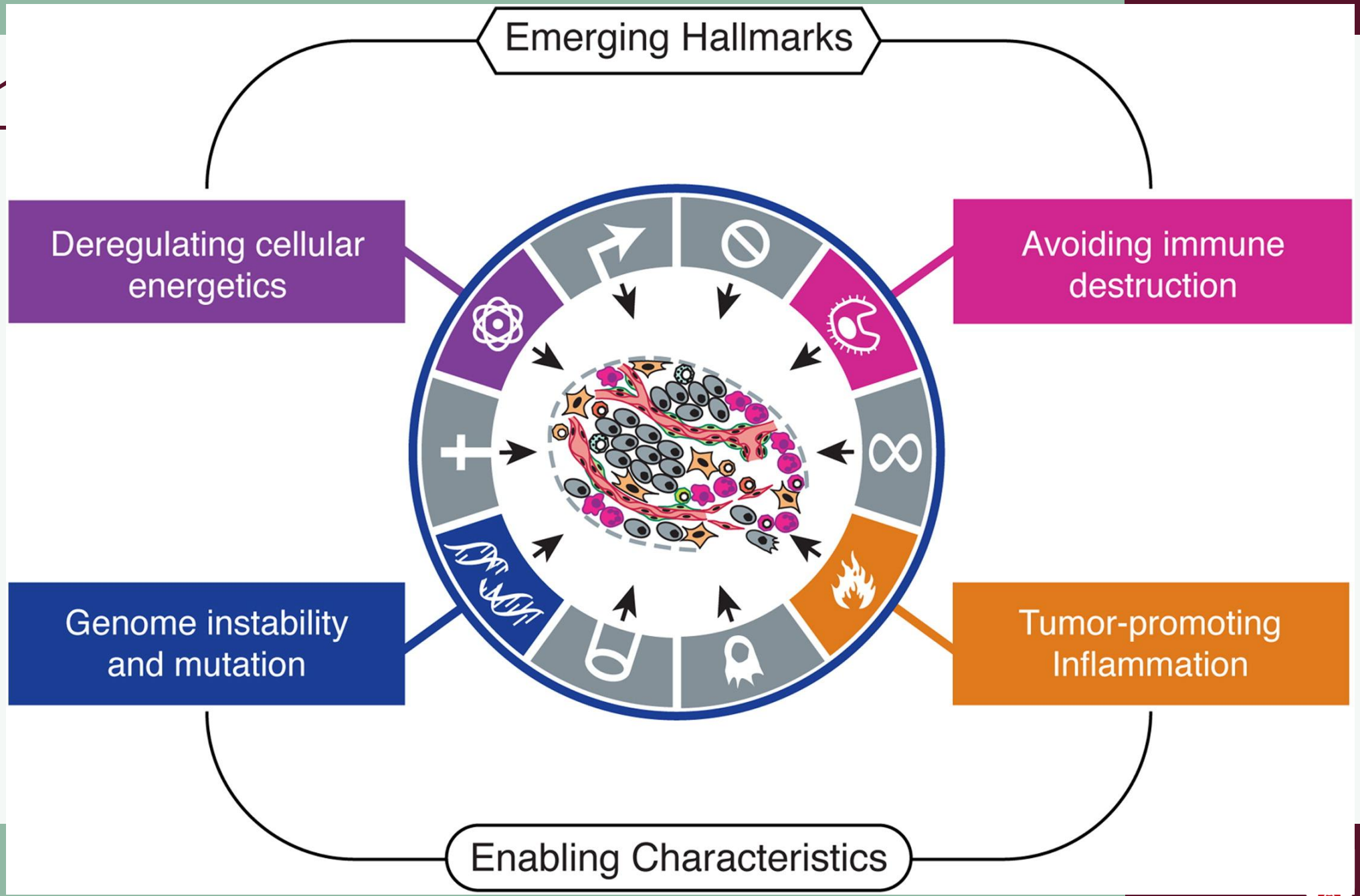
- Apototosis is often attenuated in high-grade malignant and resistant cells
- Loss of TP53
- Increasing expression of antiapoptotic regulators or survival signals
- Downregulating pro-apoptotic factors
- Constitutive activation of ligand induced extrinsic pathway

Neoplastic cells

Dr Katja Vogt

Forms of cell death

	Apoptosis	Autophagy	Necrosis	Necroptosis
Predisposing factor	Gene regulation under physiological conditions	Nutritional deficiencies or hormone induction	Pathological irritation or Drastic injury	Pathological irritation
Cell morphology	Cellular sequestration	Bubble	Cell swelling, irregular changes	Cell swelling, rounding
Cell membrane	Membrane structure integrity	Membrane structure integrity	Rupture of cell membrane	Rupture of cell membrane
Organelle	Completeness	Phagocytosis by autophagosomes and eventual digestion by lysosomes	Swelling, endoplasmic reticulum	Swollen organelles and mitochondrial damage



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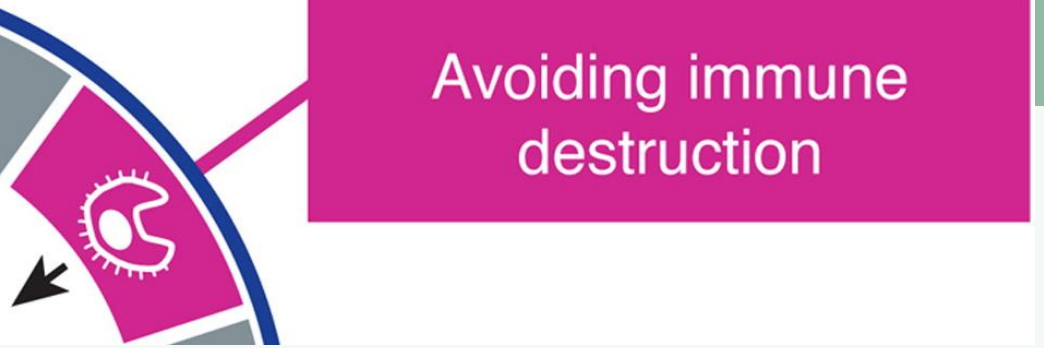

- Striking increases of certain cancers in immunocompromised individuals
- Mainly through CD8+ cytotoxic T lymphocytes, CD4+ Th1 helper T cells and natural killer (NK) cells
- Cancer cells inhibit immune system→ express TGF-b and/or recruit regulatory T cells

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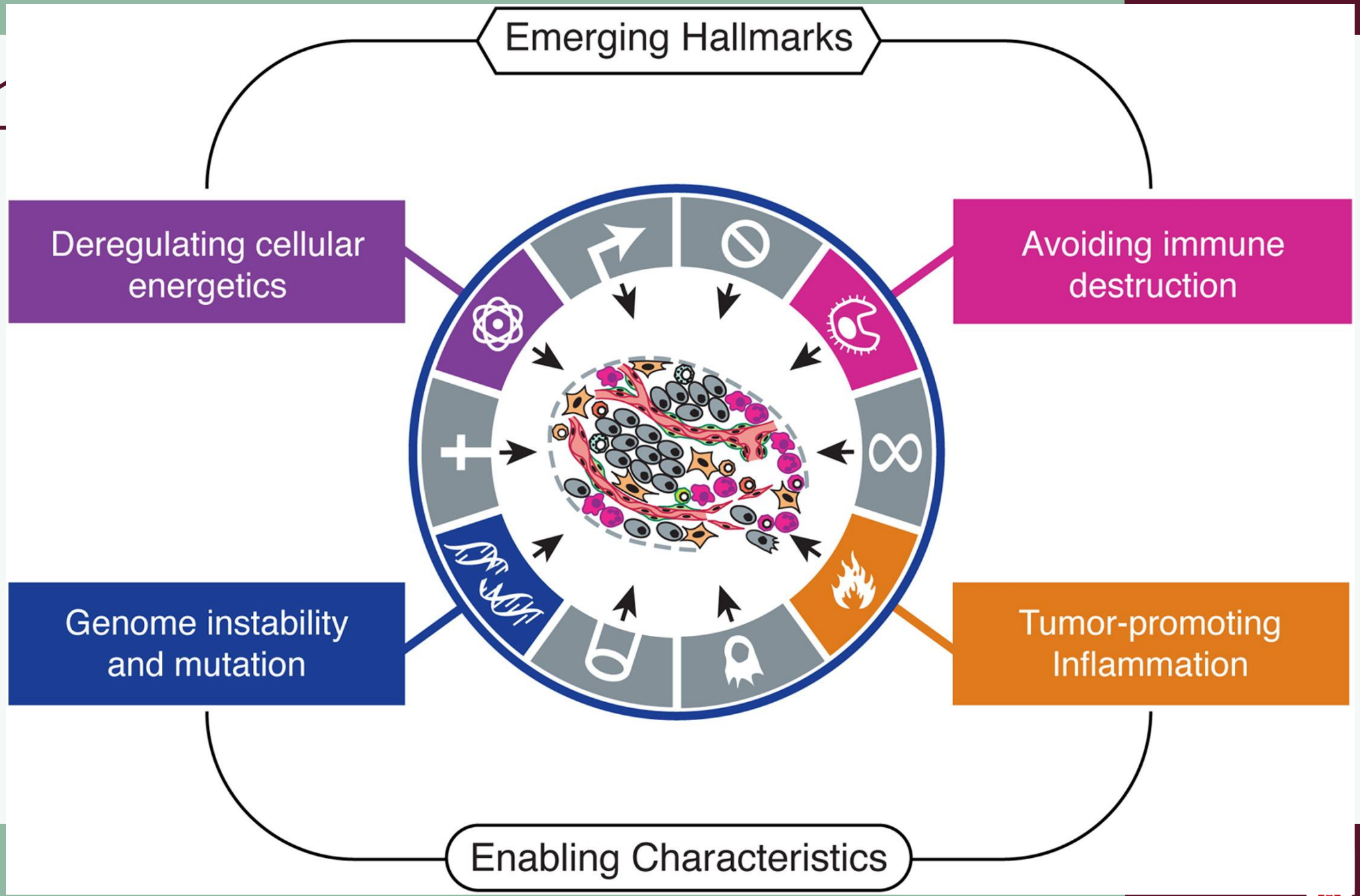

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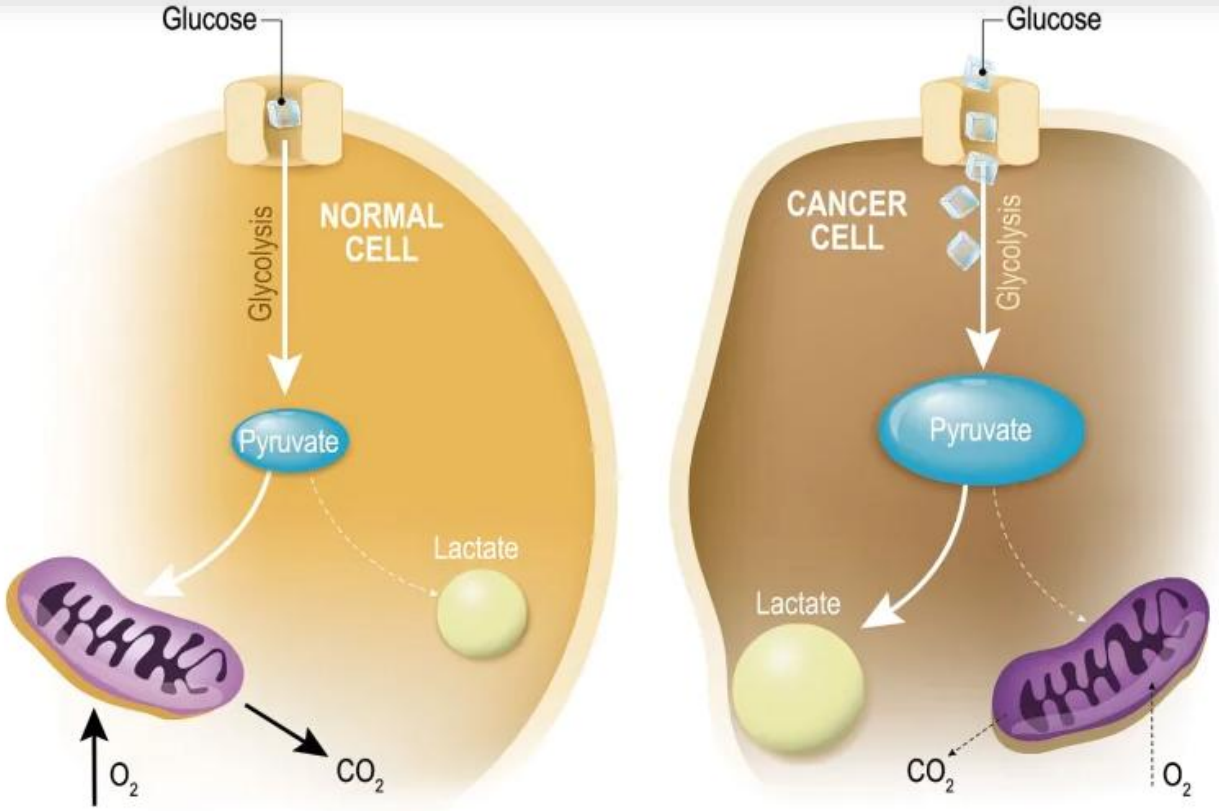
Deregulating cellular energetics

Increased glycolysis allows the diversion of glycolytic intermediates into various biosynthetic pathways

- "Aerobic glycolysis" or **Warburg effect**: in the presence of oxygen cells limit their energy metabolism largely to glycolysis,
- Upregulate glucose transporters, notably GLUT1 but also other proteins and enzymes



Warburg effect

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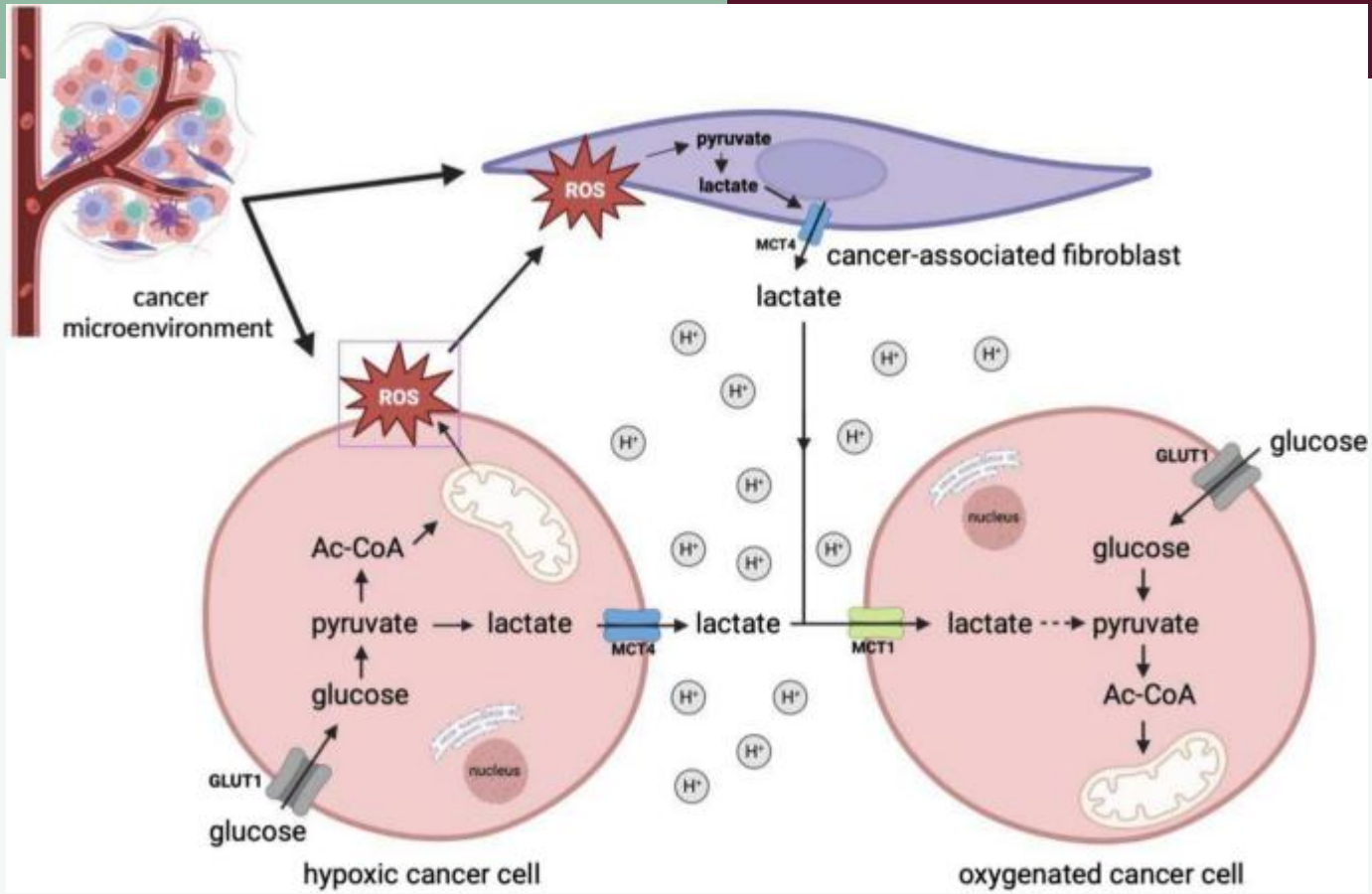
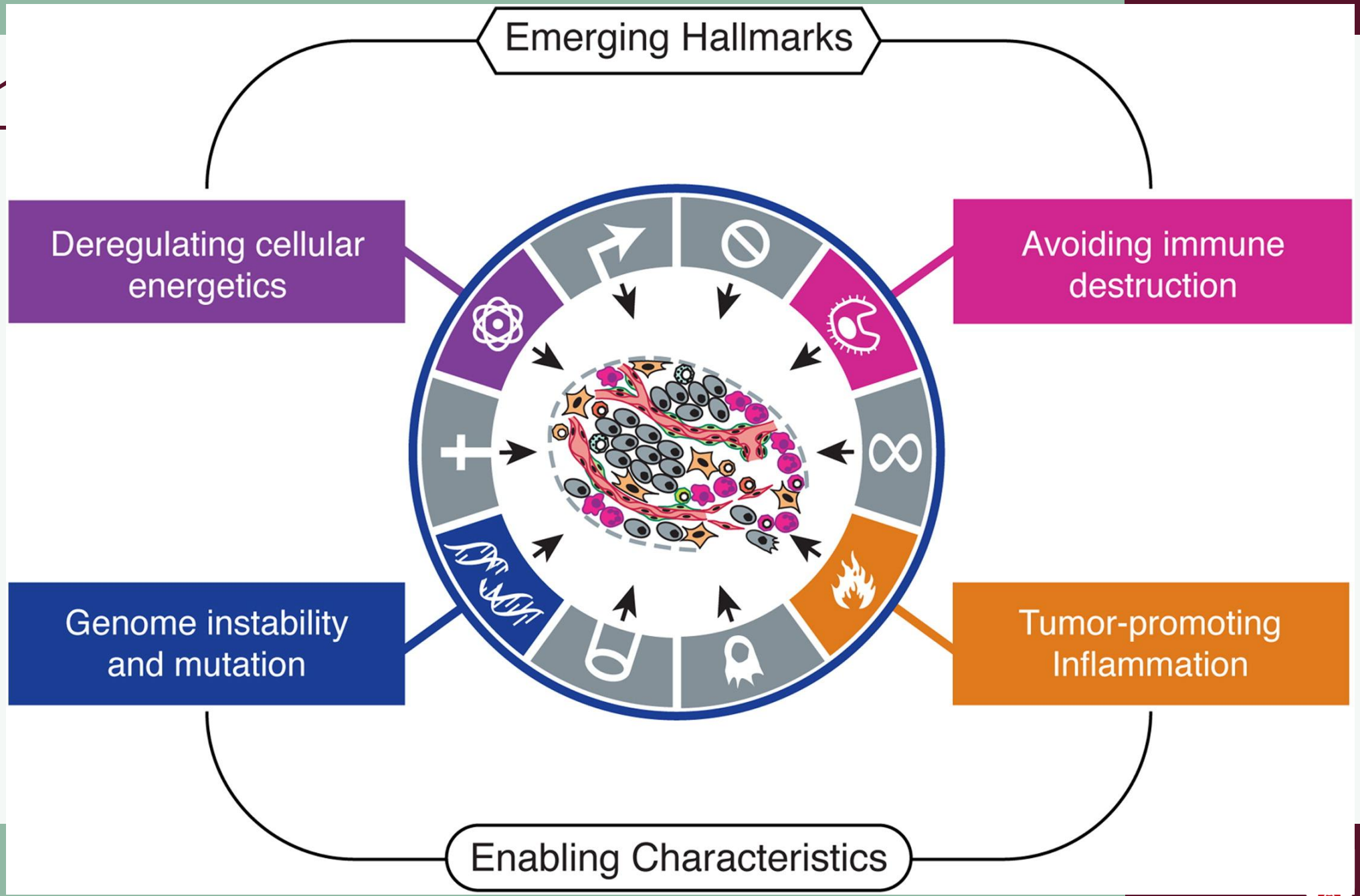
Deregulating cellular energetics

- ‘Model of intratumoural symbiosis: cooperation between lactate-secreting and lactate-utilizing cells to fuel tumour growth (also seen in muscle)
- Oxygenation, ranging from normoxia to hypoxia fluctuates temporally and regionally likely as a result of the instability and chaotic organization of the tumour-associated neovasculature



Associated with activated oncogenes (e.g., *RAS*, *MYC*) and mutant tumour suppressors (e.g., *TP53)*



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- Immune cells are present in every neoplastic lesion
- Tumour-associated inflammatory response assists neoplasias to acquire hallmark capabilities by **supplying bioactive molecules** to the tumour microenvironment:
  - Growth factors that sustain proliferative signalling
  - Survival factors that limit cell death
  - Proangiogenic factors
  - Extracellular matrix-modifying enzymes that facilitate angiogenesis, invasion, and metastasis,
  - Inductive signals that lead to activation of EMT other hallmark-facilitating programs
- Inflammatory cells can **release chemicals**, notably reactive oxygen species, that are **actively mutagenic**
- Evident at the earliest stages

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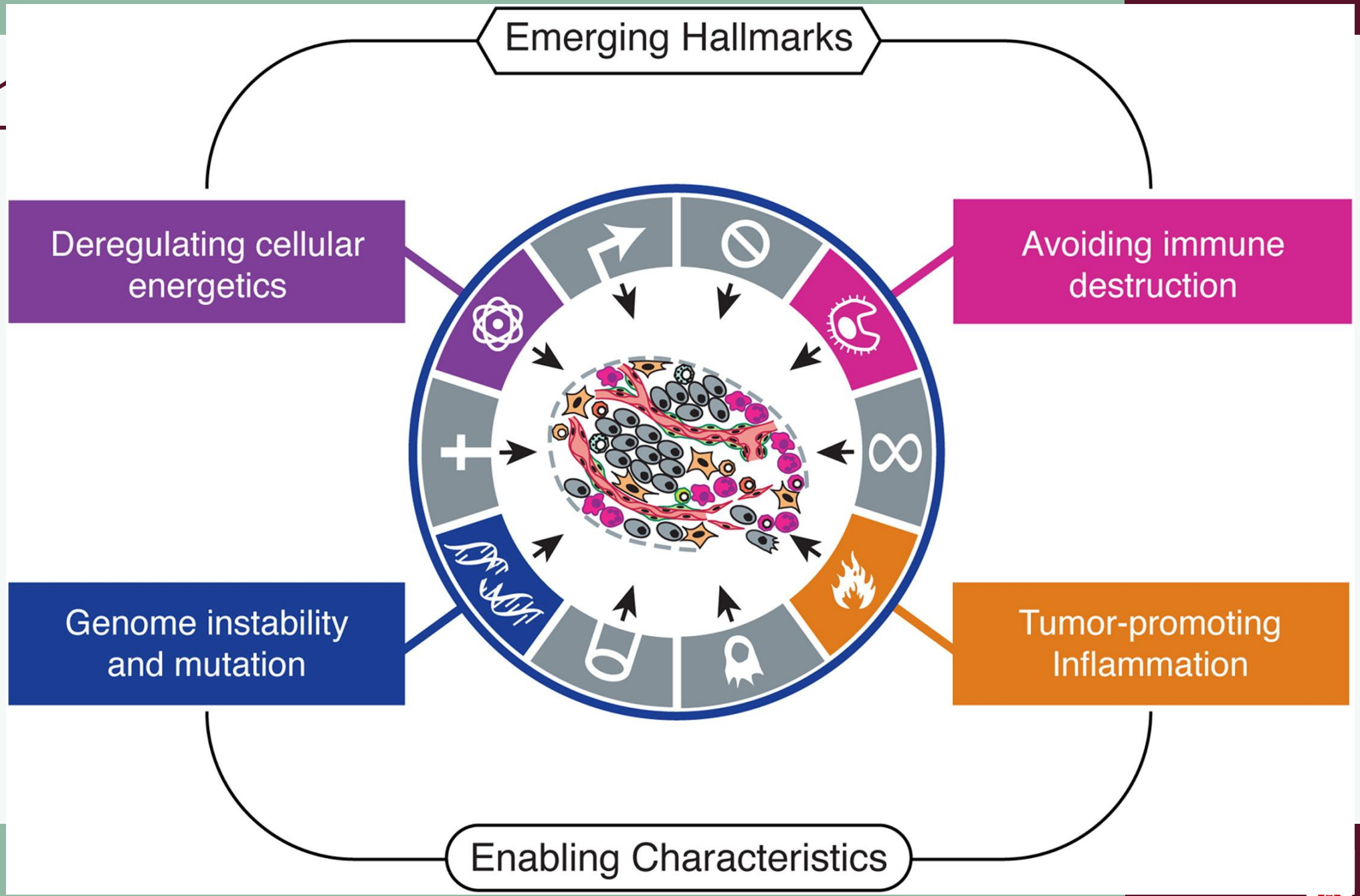

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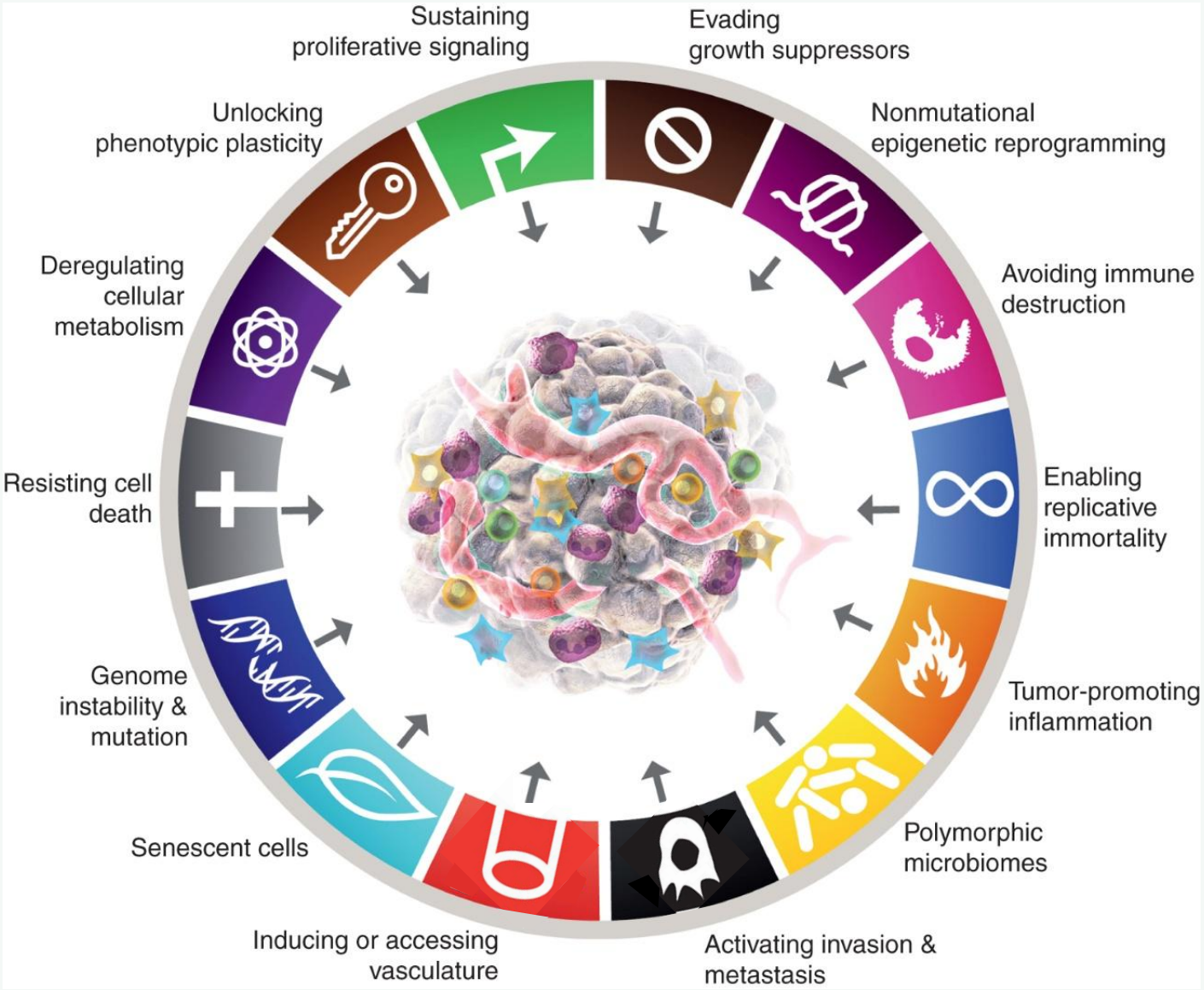
Genome instability and mutation

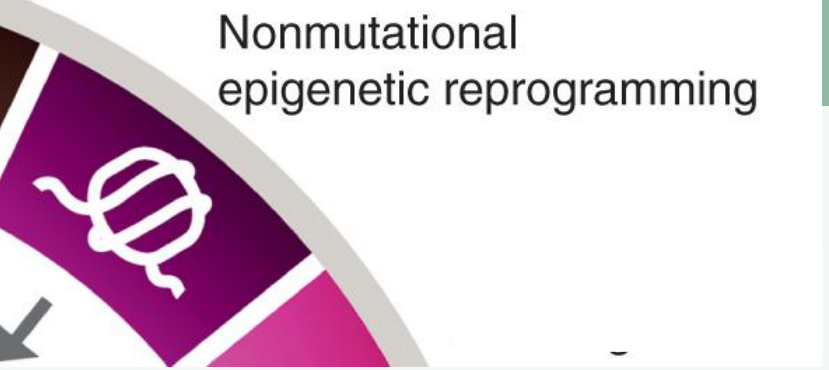
Individual sequence of mutation is very much varied , but instability of the genome is inherent to the majority of human cancer cells.

- Increased mutability accelerates the process of tumour progression
- Due to increased sensitivity to mutagenic agents and/or the breakdown in one or more of the DNA maintenance machinery components

- TP53 central role here, but there are additional “care-taker genes” which:
  - Detect DNA damage and activate the repair machinery
  - Directly repair damaged DNA
  - Inactivate or intercept mutagenic molecules before they have damaged the DNA
- Behave much like tumour suppressor genes, in that their functions can be lost during tumour progression
- Loss of telomers contributes and telomerase is a “care-taker”

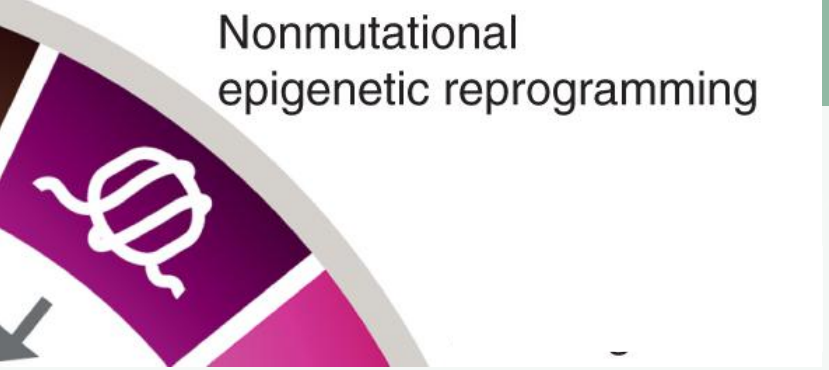


Cancer Discov. 2022;12(1):31-46. doi:10.1158/2159-8290.CD-21-1059

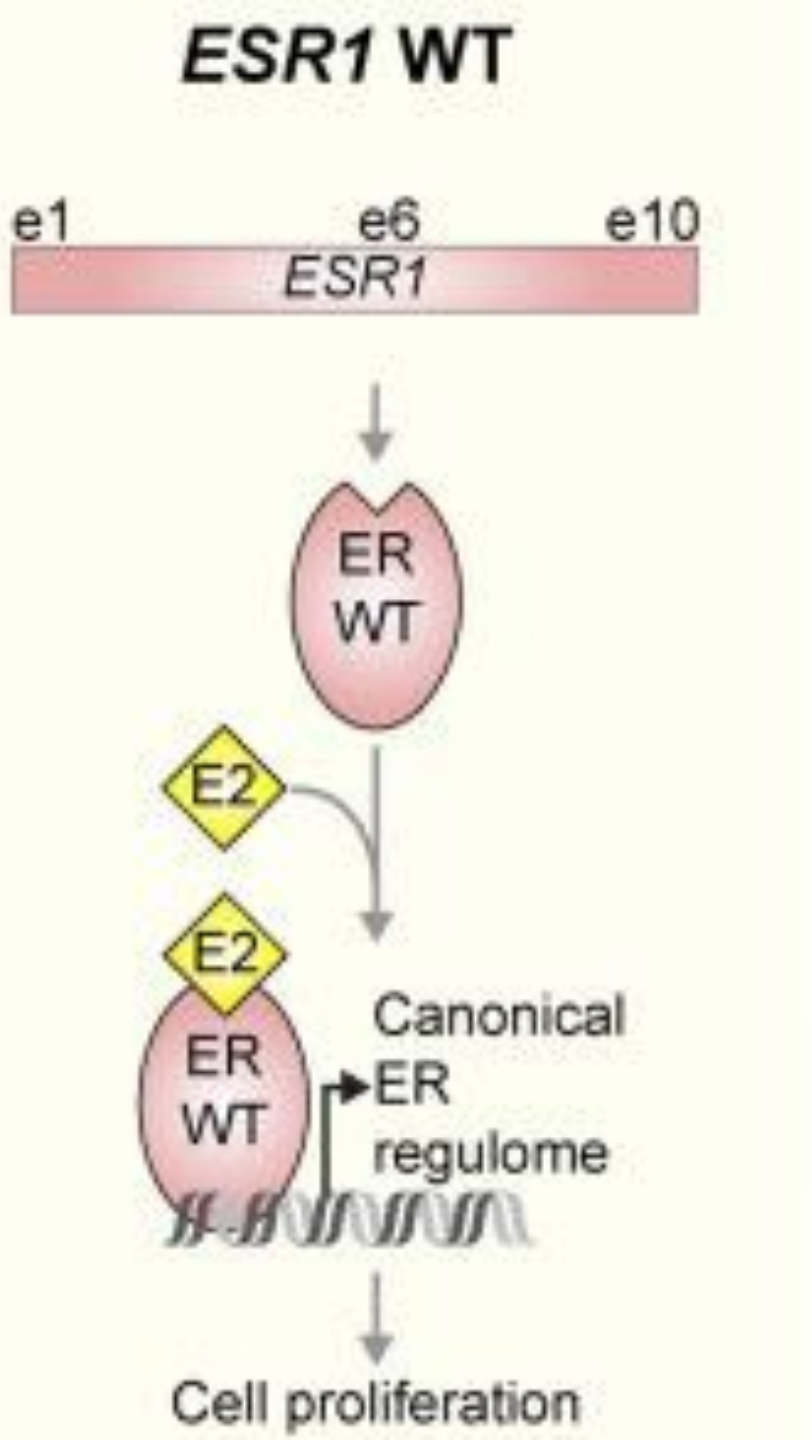


- Cancer-associated fibroblasts, innate immune cells, and endothelial cells and pericytes of the tumour vasculature— are epigenetically reprogrammed upon their recruitment by soluble and physical factors that define the solid tumour micro- environment
- Best evidence on hypoxia driven epigenetics, eg. Causing hyper methylation
- A master regulator of the EMT (*ZEB1)* also induces expression of a histone methyltransferase, that induced a positive feedback loop to maintain EMT

Example : paediatric ependymoma, lacking recurrent mutations in oncogenes and tumour suppressors → the aberrant growth of these cancer cells is demonstrably governed by a gene regulatory program induced by hypoxia.



- Triple negative breast cancer cells exposed to cortisol underwent epigenetic reprogramming:
  - Decreased methylation of the ESR1 promoter, leading to decreased expression of ESR1

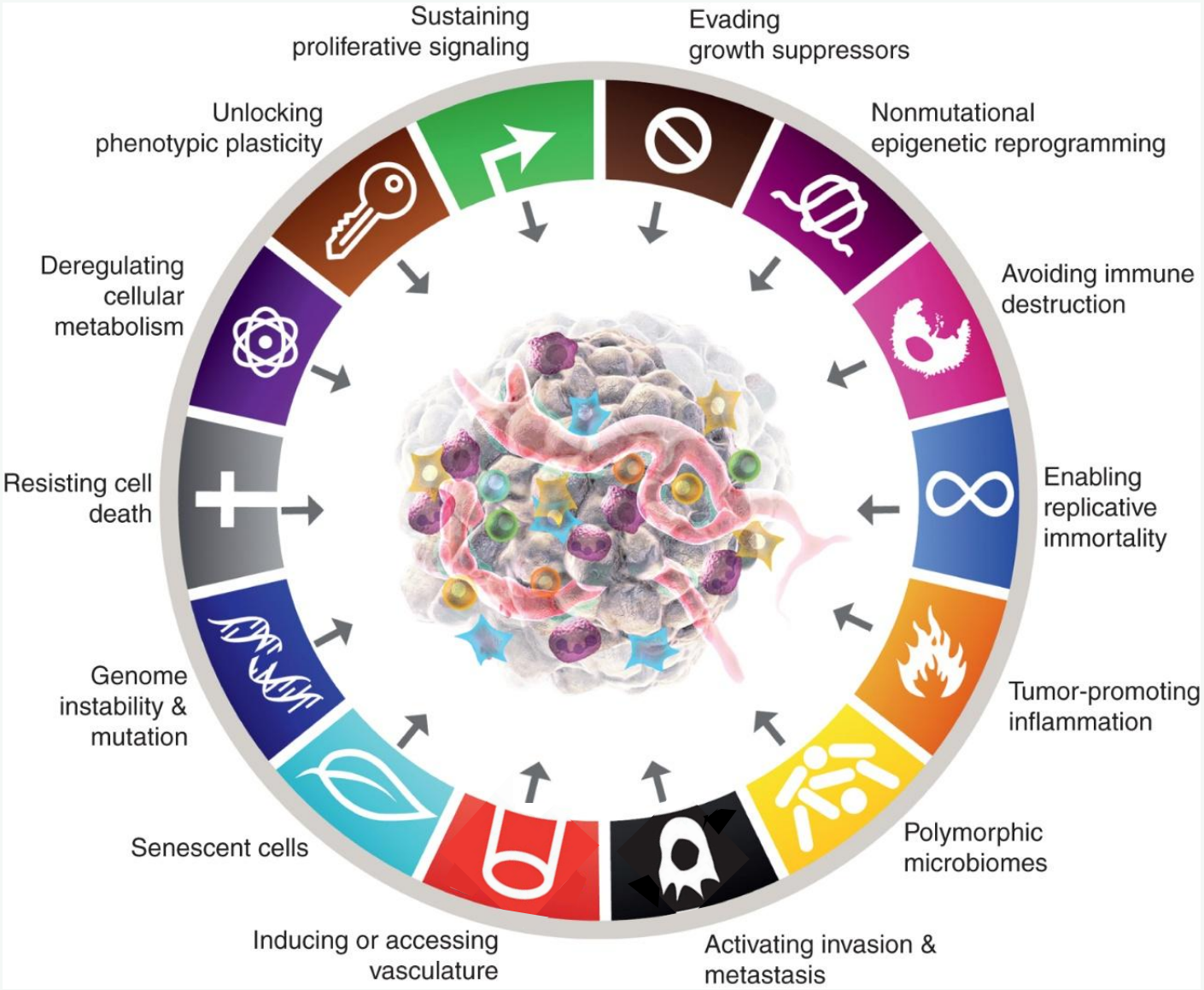


Epigenetics

Epigenetics: phenotypic changes that do not result from changes in the nucleotide sequence of DNA

- Processes include: methylation, acetylation, phosphorylation, ubiquitylation, and sumolyation, but also histone modification, chromatin accessibility, and posttranscriptional modification and translation of RNA

https://www.youtube.com/watch?v=_aAhcNjmvhc



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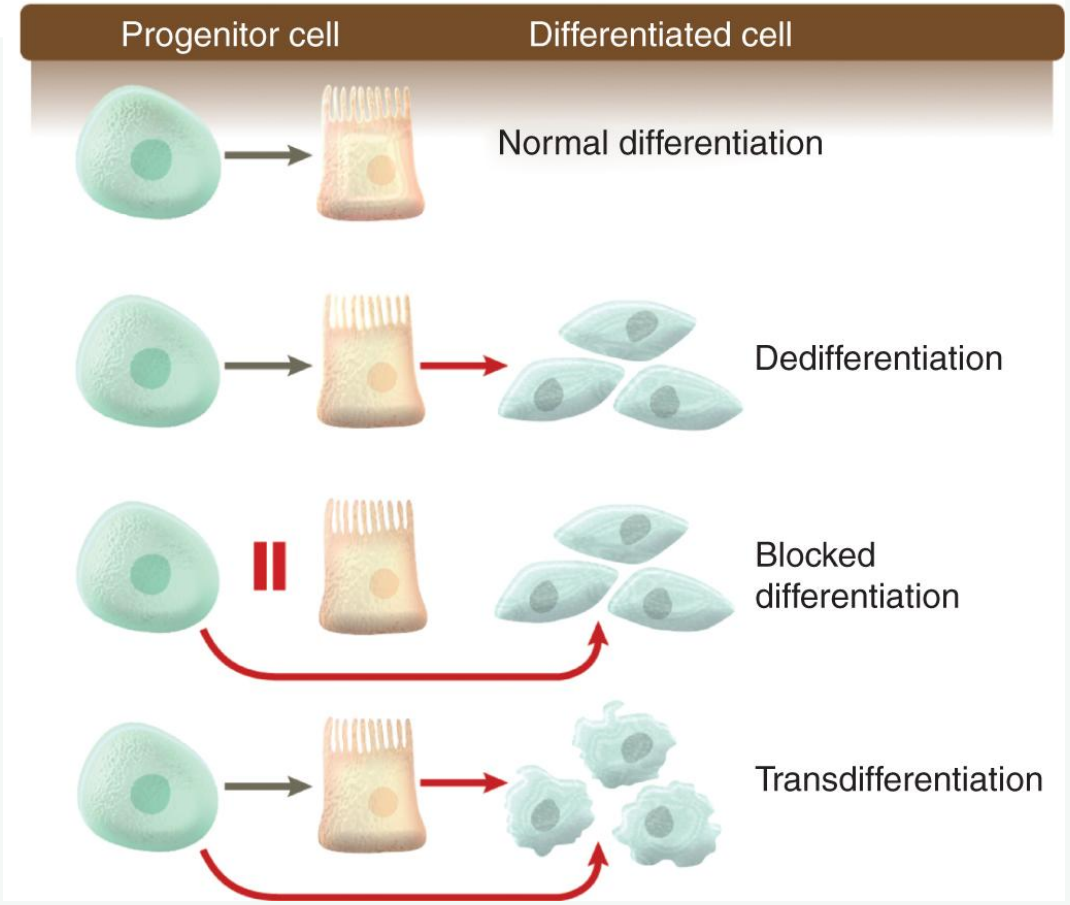
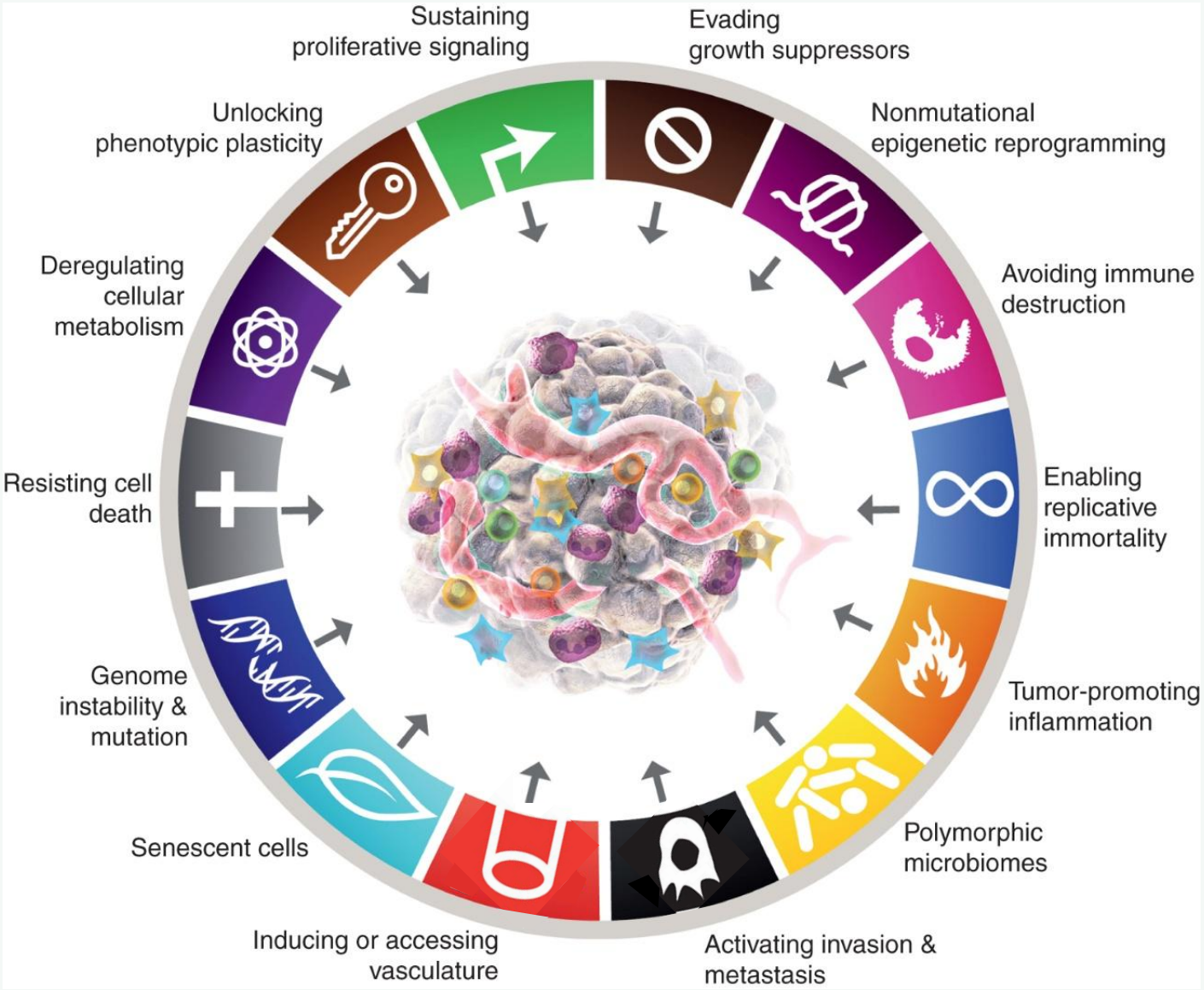
Unlocking cellular plasticity to enable various forms of disrupted differentiation



1. Dedifferentation:
2. Blocked Differentiation
3. Transdifferentiation (Metaplasia)



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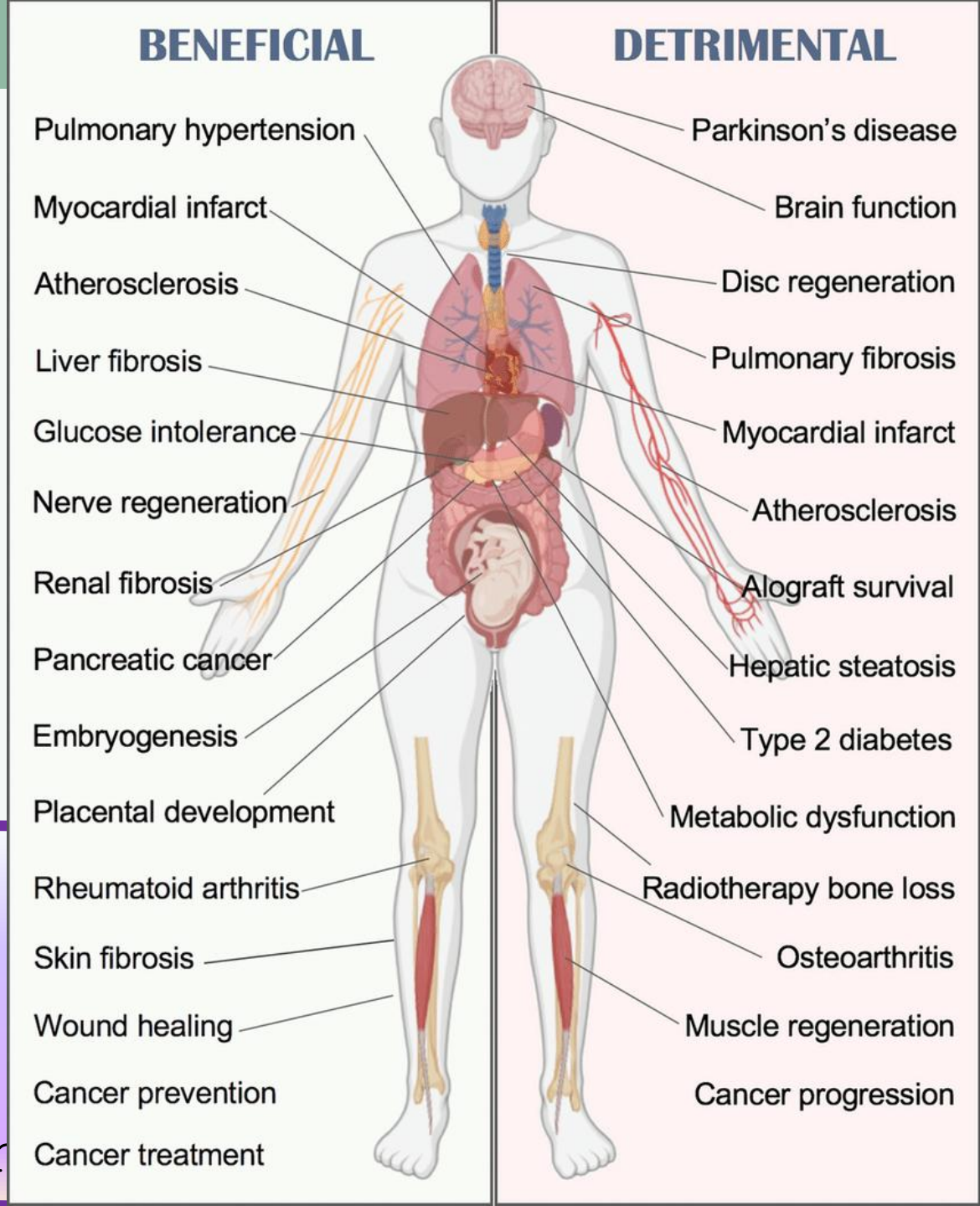
Senescence

- Proliferative arrest
- Typically irreversible
- Complementary mechanism to programmed cell death
- Changes in cell morphology and metabolism and the activation of a senescence-associated secretory phenotype (SASP)
- Triggers are microenvironmental stresses
- Protective mechanism against neoplasia

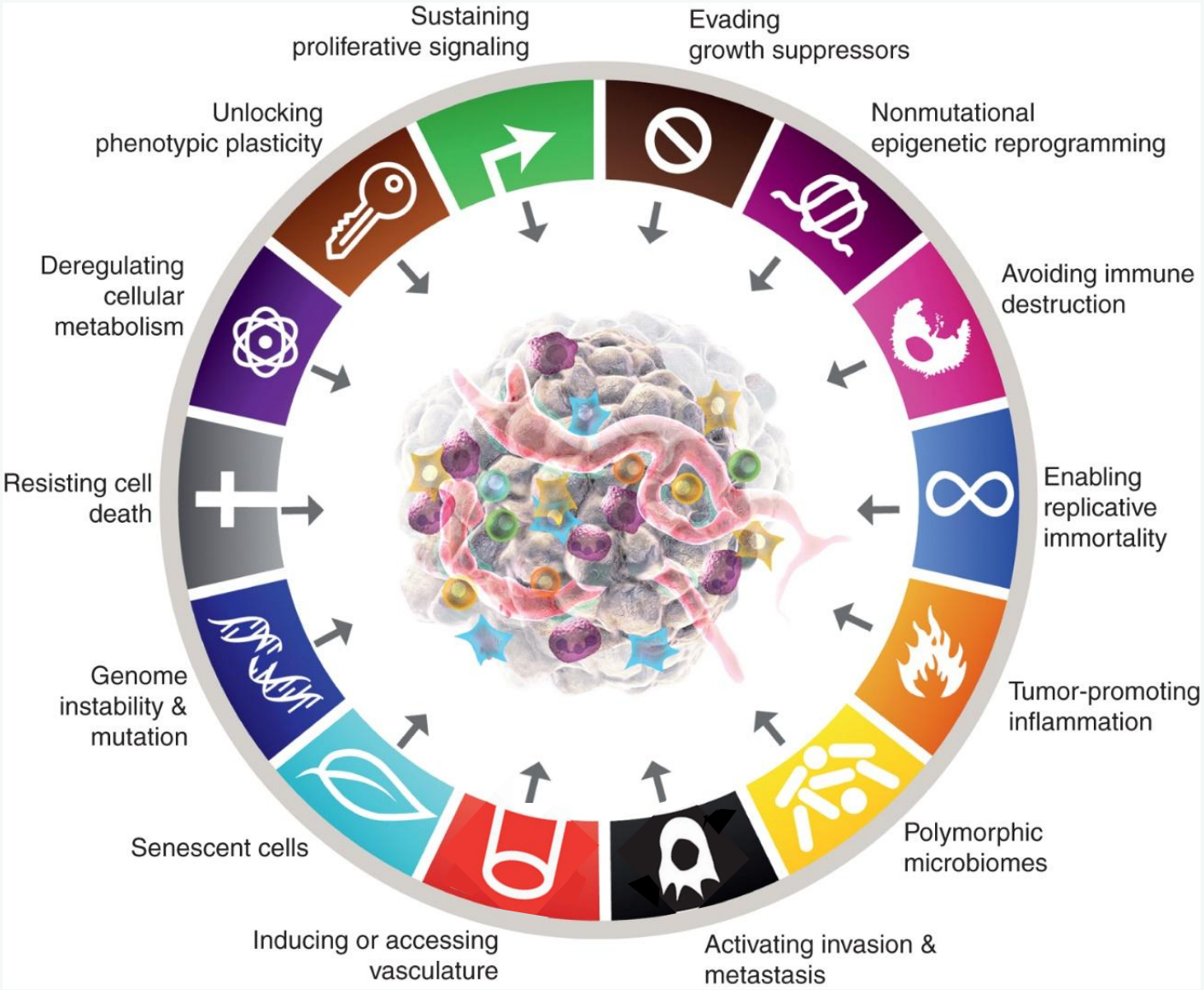
⭐ The process by which cells irreversibly stop dividing and enter a state of permanent growth arrest without undergoing cell death



- SASP signal directly to cancer cells and to other cells in the TME, which also conveys hallmark capabilities
- Senescent cells involve transitory, reversible senescent cells
- Contribute to proliferative signalling, avoiding apoptosis, inducing angiogenesis, stimulating invasion and metastasis, and suppressing tumour immunity

Causes of senescence in cancer:

- Oncogene-induced due to hyperactivated signalling
- Therapy-induced consequent to cellular and genomic damage
- Senescent cells variously stimulate tumour development and malignant progression cancer- associated and fibroblasts in tumours, but also normal fibroblast undergo senescence, which themselves then are tumour-promoting
- Therapy-induced senescent tumour endothelial cells can enhance proliferation, invasion, and metastasis



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- Microbiomes between individuals in a population can have a profound impact on cancer phenotypes
- Role of intratumoral microbiota established

The microbiome is tumour-promoting

- Mutagenesis of the (colonic) epithelium
- Produce ligand mimetics that stimulate epithelial proliferation
- Butyrate-producing bacteria:
  - Induction of senescent epithelial and fibroblastic cells.
  - Pleiotropic and paradoxical effects on differentiated cells versus undifferentiated (stem) cells leading to disruption of the intestinal barrier is disrupted (dysbiosis)
- Affecting cellular energetics and metabolism, histone modification, cell-cycle progression, and (tumour-promoting) innate immune inflammation and immunosuppressive of adaptive immune responses.
- Activate damage sensors on epithelial or resident immune cells

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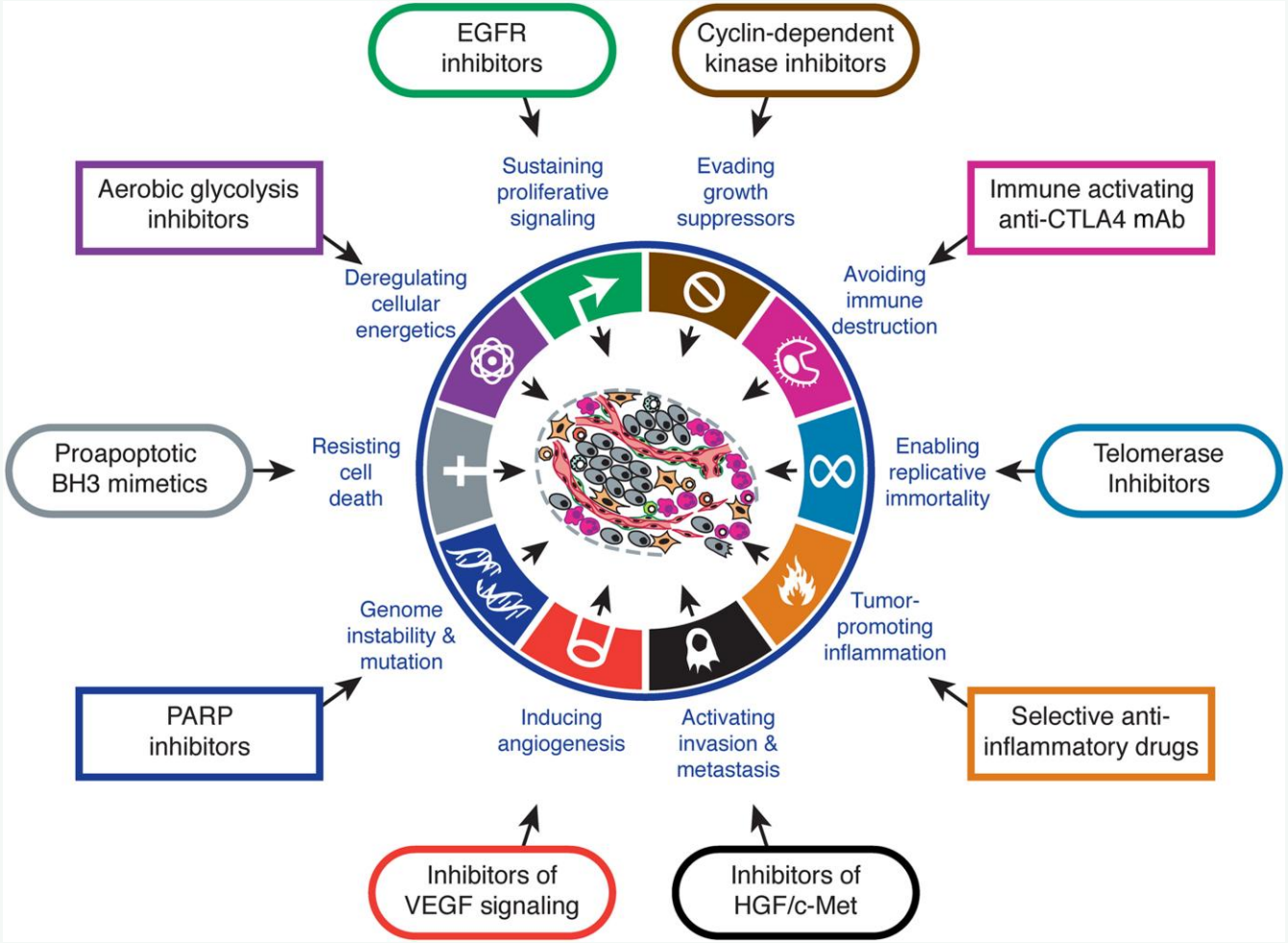

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