Imperial College London

When good cells go bad: Cancer

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Learning objectives:

By the end of today's lecture, you should be able to answer the following :

Discuss the origins of cancer

Understand the difference between genetic and epigenetic mutations

List and discuss the hallmarks of cancer

Discuss the differences between oncogenes and tumour suppressor genes

Describe glioma classification

List the frequently altered pathways in Glioblastoma

What is cancer ?

Umbrella term covering a plethora of conditions characterized by unscheduled and uncontrolled cellular proliferation.

Cancer Groups

Carcinoma - cancer that begins in the skin or in tissues that line or cover internal organs.

Sarcoma - cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue.

Leukaemia - cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the blood.

Lymphoma and myeloma - cancers that begin in the cells of the immune system.

Central nervous system cancers - cancers that begin in the tissues of the brain and spinal cord.

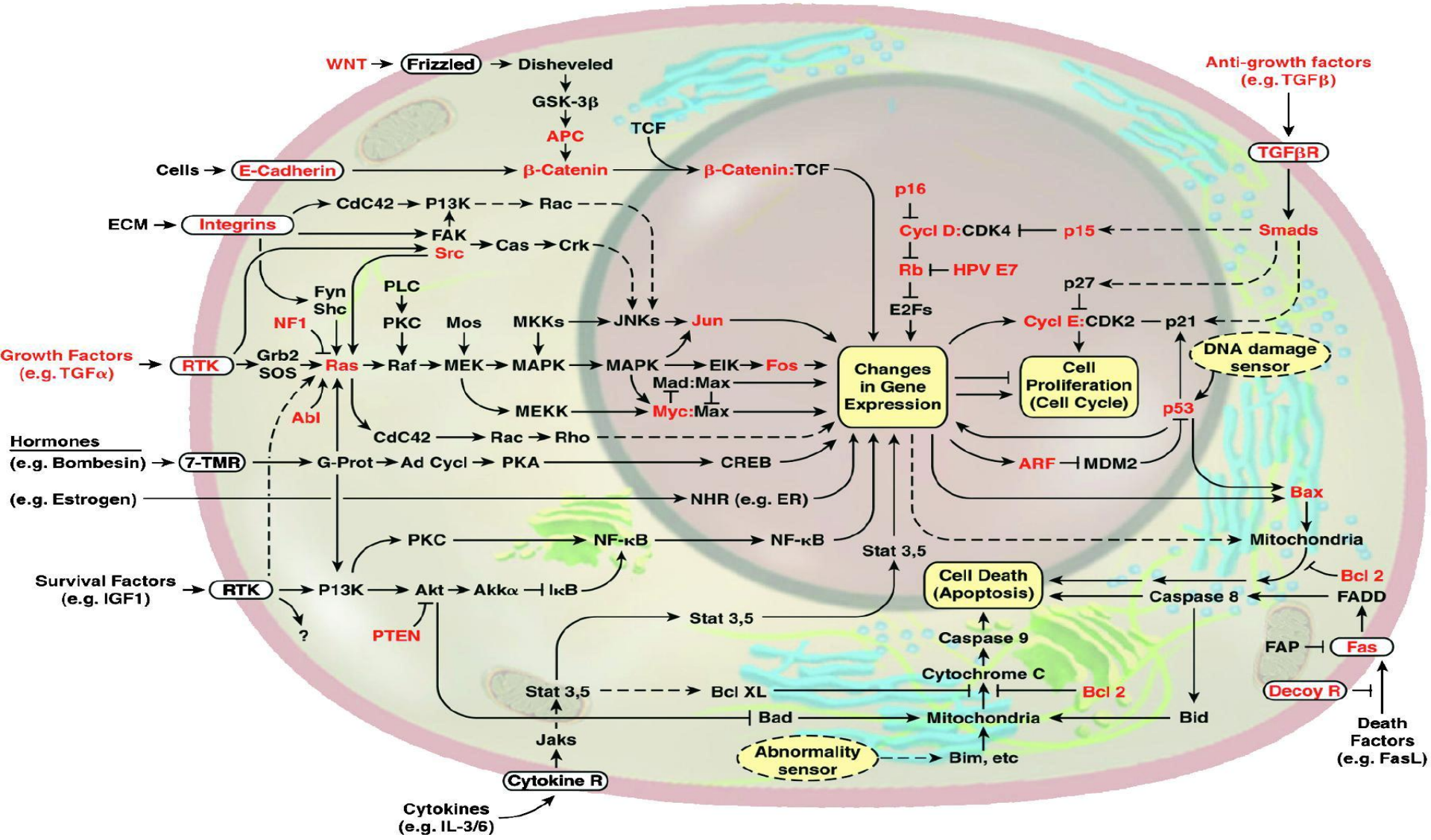
Origins of Cancer

Accumulation of mutations in genes

- genetic
- epigenetic

Derailing a wide spectrum of regulatory and downstream effector pathways.

The Emergent Integrated Circuit of the Cell



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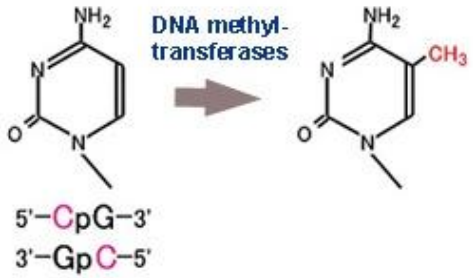
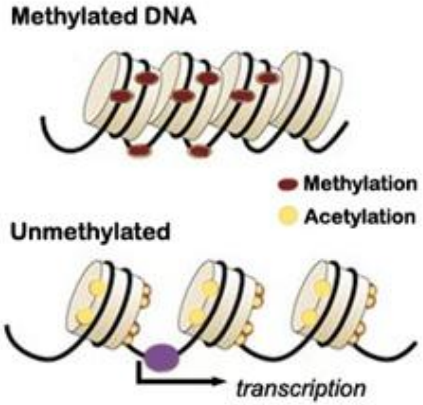
Origins of Cancer

- Genetic – changes DNA sequence
- Epigenetic
  - heritable changes in gene expression that occur without a change in DNA sequence
  - epigenetic mechanisms provide an "extra" layer of transcriptional control that regulates how genes are expressed
  - critical components in the normal development and growth of cells
  - epigenomic profiles can be used as cancer cell markers and markers of tumour prognosis.

Epigenetic modification - Methylation





• Methylation causes “closed” chromatin conformation and prevents transcription complexes binding.

• Demethylation relaxes chromatin structure.

• Aberrant cytosine methylation observed in many cancers

• Methylation profiling can identify distinct subtypes of cancers

• Useful in predicting the clinical properties of cancers in individual patients including sensitivity to anticancer agents.

• Methylation patterns may shed light on the pathways involved in pathogenesis

Origins of Cancer

Depending on how they affect each process, these genes can be grouped into two general categories:

1) Tumour Suppressor Genes (TSG)

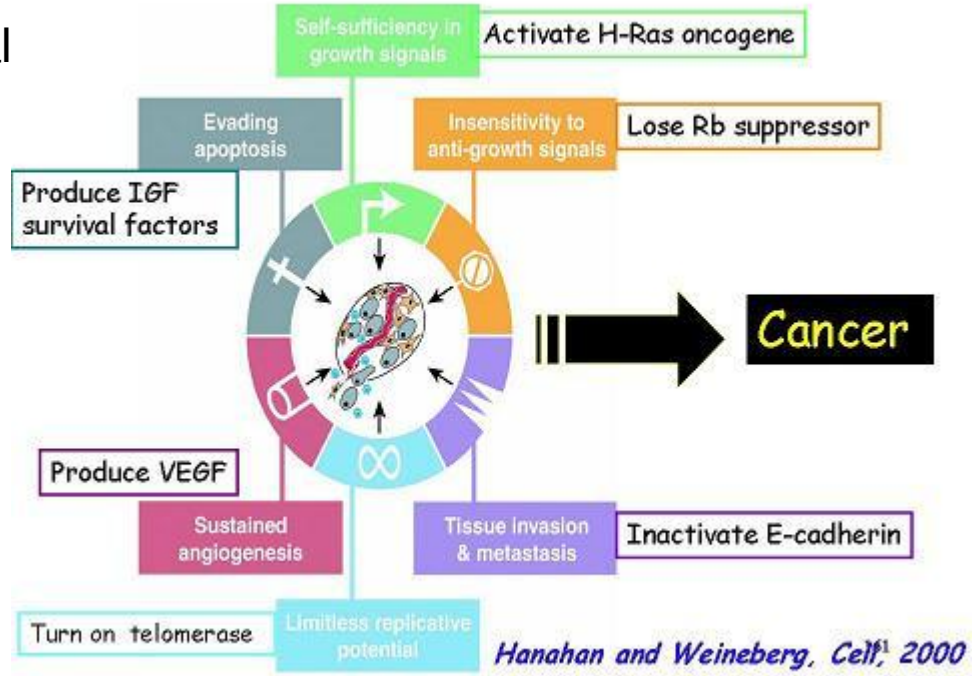
- Normal genes that slow down cell division, repair DNA mistakes and promote apoptosis
- Cause cancer when they are inactivate
- Abnormalities can be inherited as well as acquired

2) Oncogenes

- Result from the activation of proto-oncogenes
- Most develop from mutations in normal genes (proto-oncogenes)
- Acquired mutations

Hallmarks of Cancer

1. Self sufficiency in growth signals
2. Insensitivity to growth inhibitory signal
3. Evasion of apoptosis
4. Limitless replicative potential
5. Sustained angiogenesis
6. Tissue invasion and metastasis



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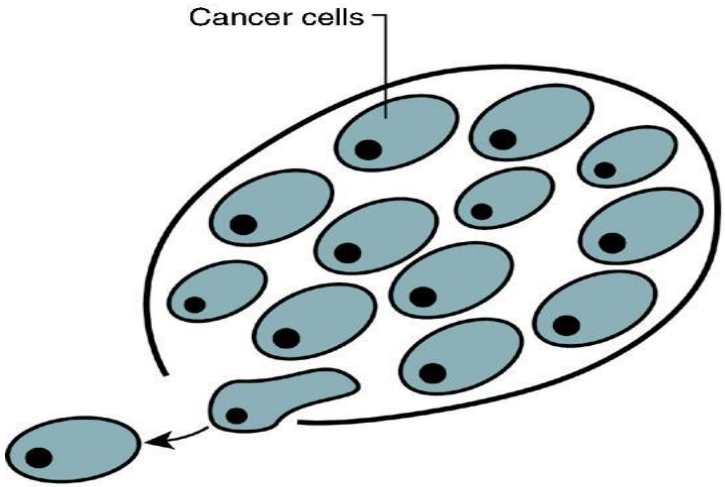
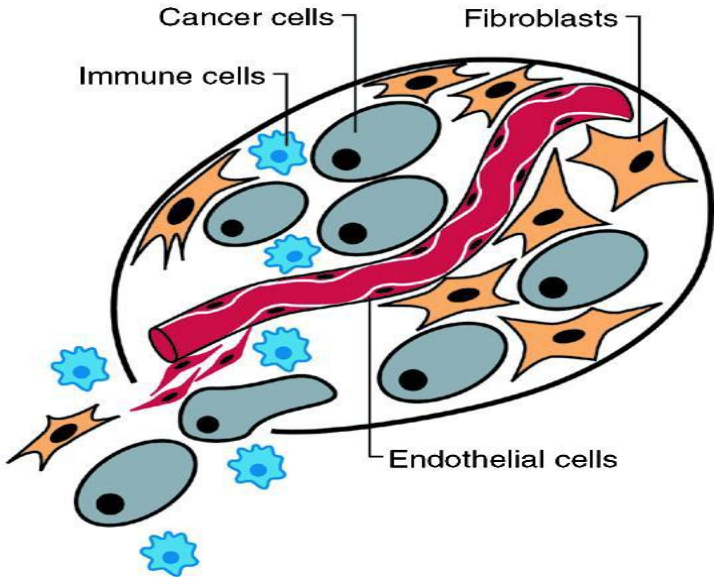
Tumours are Complex Tissues

The Reductionist View



A Heterotypic Cell Biology



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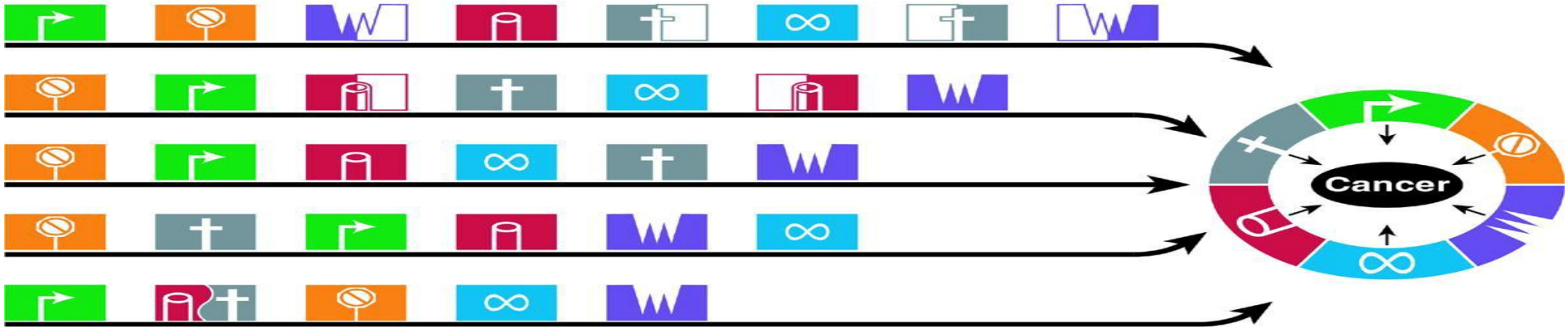
Parallel Pathways of Tumorigenesis

A

Component	Acquired Capability	Example of Mechanism
	Self-sufficiency in growth signals	Activate H-Ras oncogene
	Insensitivity to anti-growth signals	Lose retinoblastoma suppressor
	Evading apoptosis	Produce IGF survival factors
	Limitless replicative potential	Turn on telomerase
	Sustained angiogenesis	Produce VEGF inducer
	Tissue invasion & metastasis	Inactivate E-cadherin

B



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Hallmark 1:

self sufficiency in growth signals

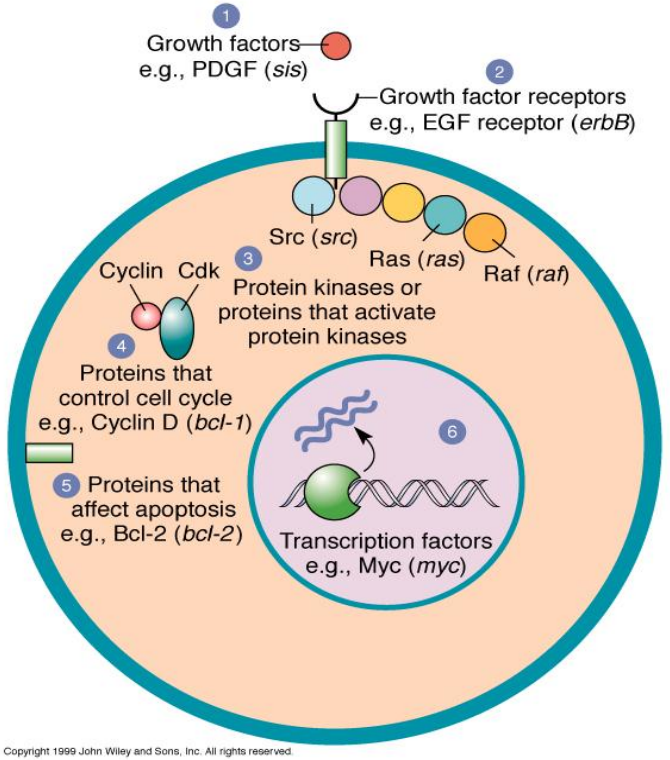
Normal cells

quiescent state ⟶ active proliferative state

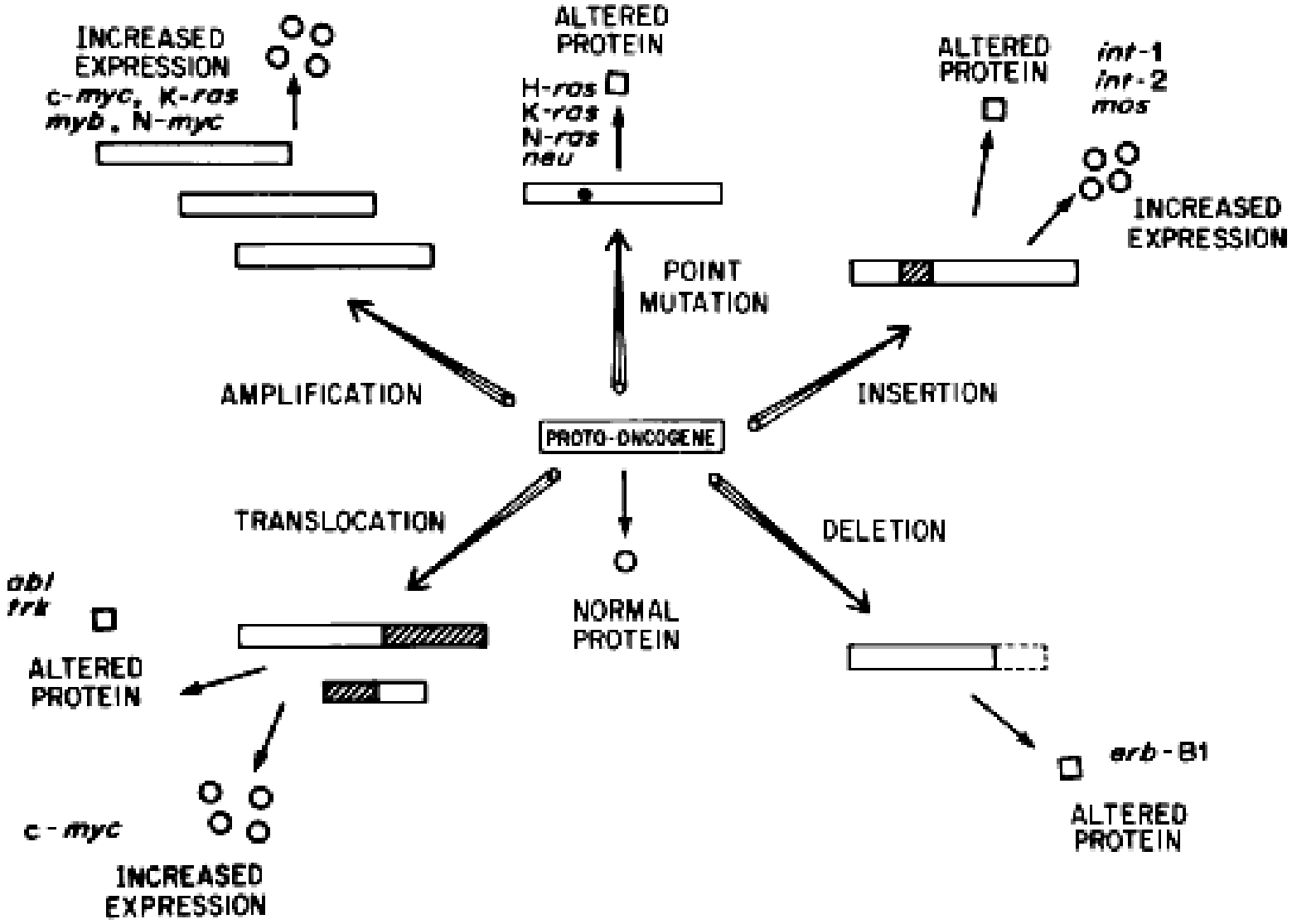
Growth signals

Many oncogenes mimic normal growth signals

Types of proteins encodes by oncogenes



Mechanisms of oncogene activation



Hallmark 2:

insensitivity to negative signals

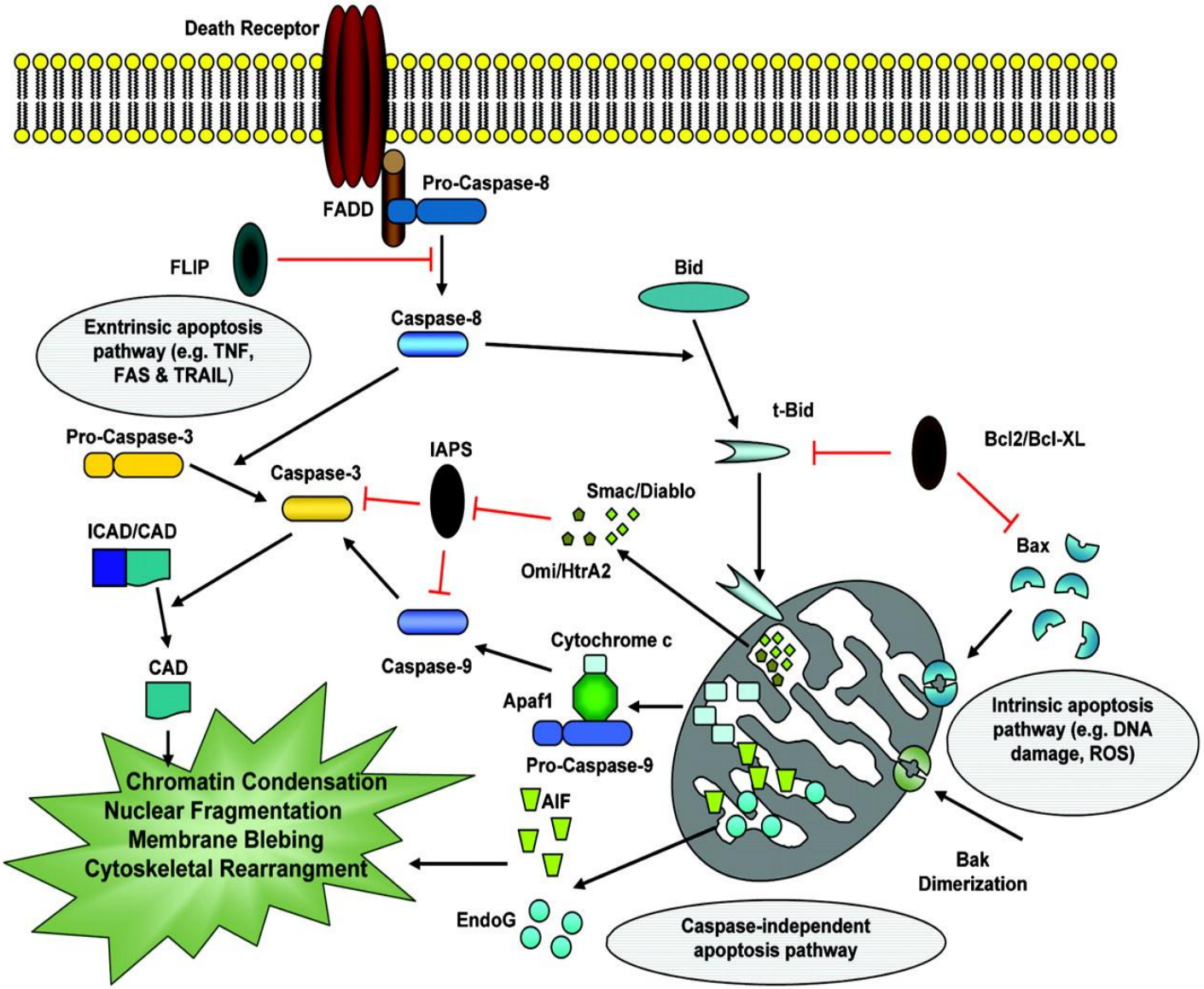
- Inactivating mutations in TSG
  - Point mutations
  - Chromosome deletions
  - LOH
  - Altered methylation of promoters –epigenetics

TSG

- Classic RB gene
  - Germline mutations in RB and one acquired somatic mutation
    - Leads to retinoblastoma
  - 80% of small cell lung cancers have an RB mutation
- P53
  - 50-75% of all cancers have a p53 mutation
    - Loss of both or dominant negative

Hallmark 3:

Evasion of apoptosis



Ghavami S et al. J Med Genet 2009;46:497-510

Hallmark 4:

Acquisition of limitless proliferative capacity

- Normal cells have a finite replicative potential, 50-80 doublings (Hayflick 1997)

- Due to chromosome shortening

  - Results from loss of telomeric DNA from ends of chromosome during each cycle.

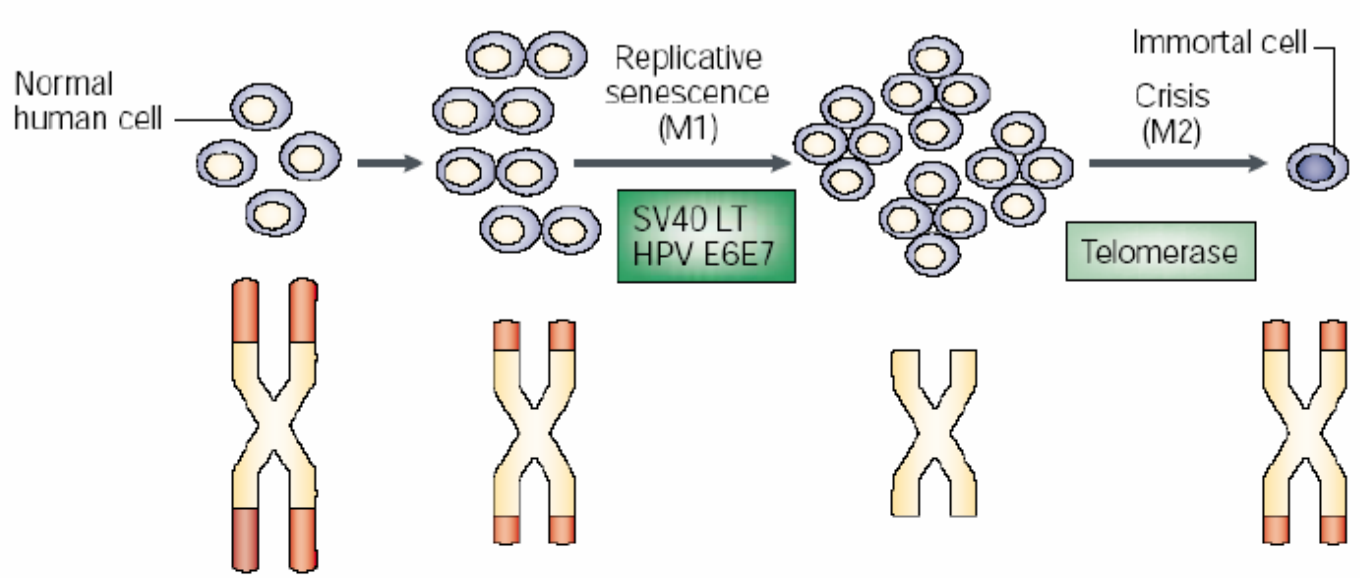
  - Progressive loss through successive cycles of replication leads to inability to protect the ends of chromosomal DNA

    -death of affected cell.

- Telomeres are maintained in most/all malignant cells
  - Upregulation of telomerase

Hallmark 4:

Acquisition of limitless proliferative capacity



Telomerase	OFF	OFF	OFF	OFF	OFF	ON
Immortal	NO	NO	NO	NO	NO	YES
Genome stable	YES	YES	?	?	NO	?

Hallmark 5:

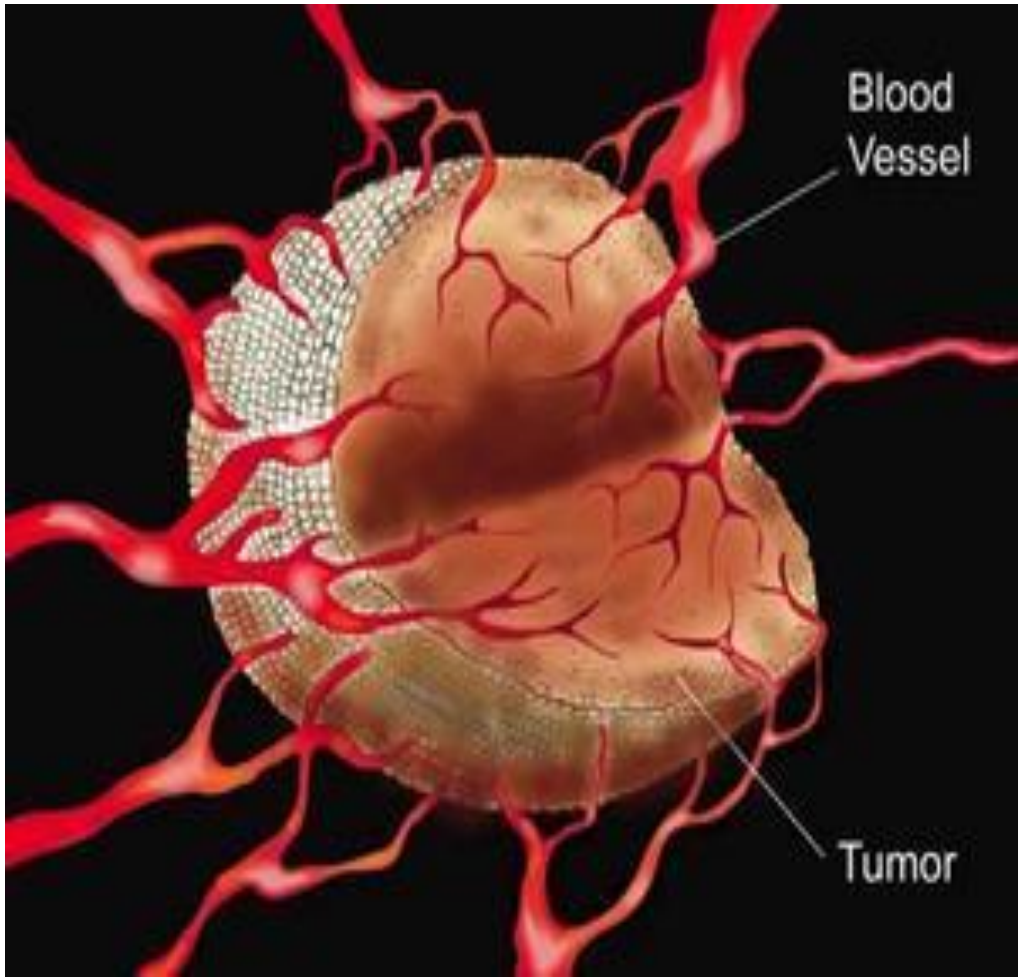
Sustained Angiogenesis

Normal cells:

- angiogenesis is transitory and carefully regulated

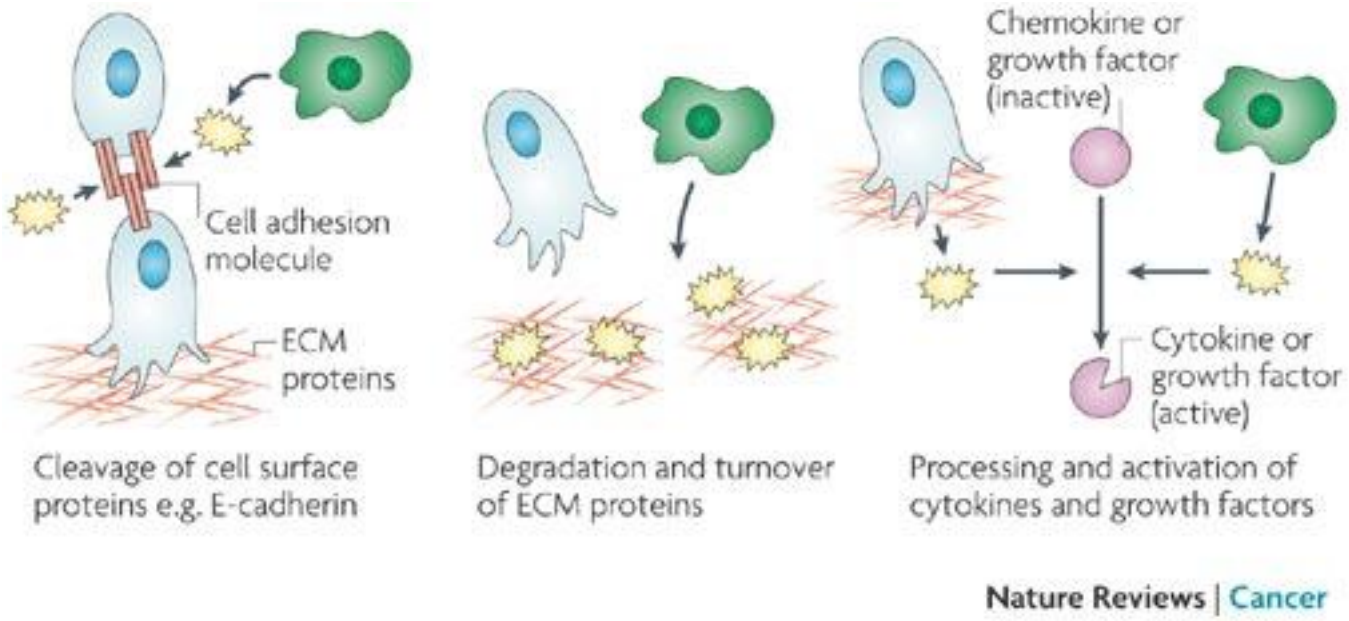
Tumours

- shift this balance by increased gene transcription of VEGF and FGF1&2
- signals endothelial cell proliferation and growth of blood vessels

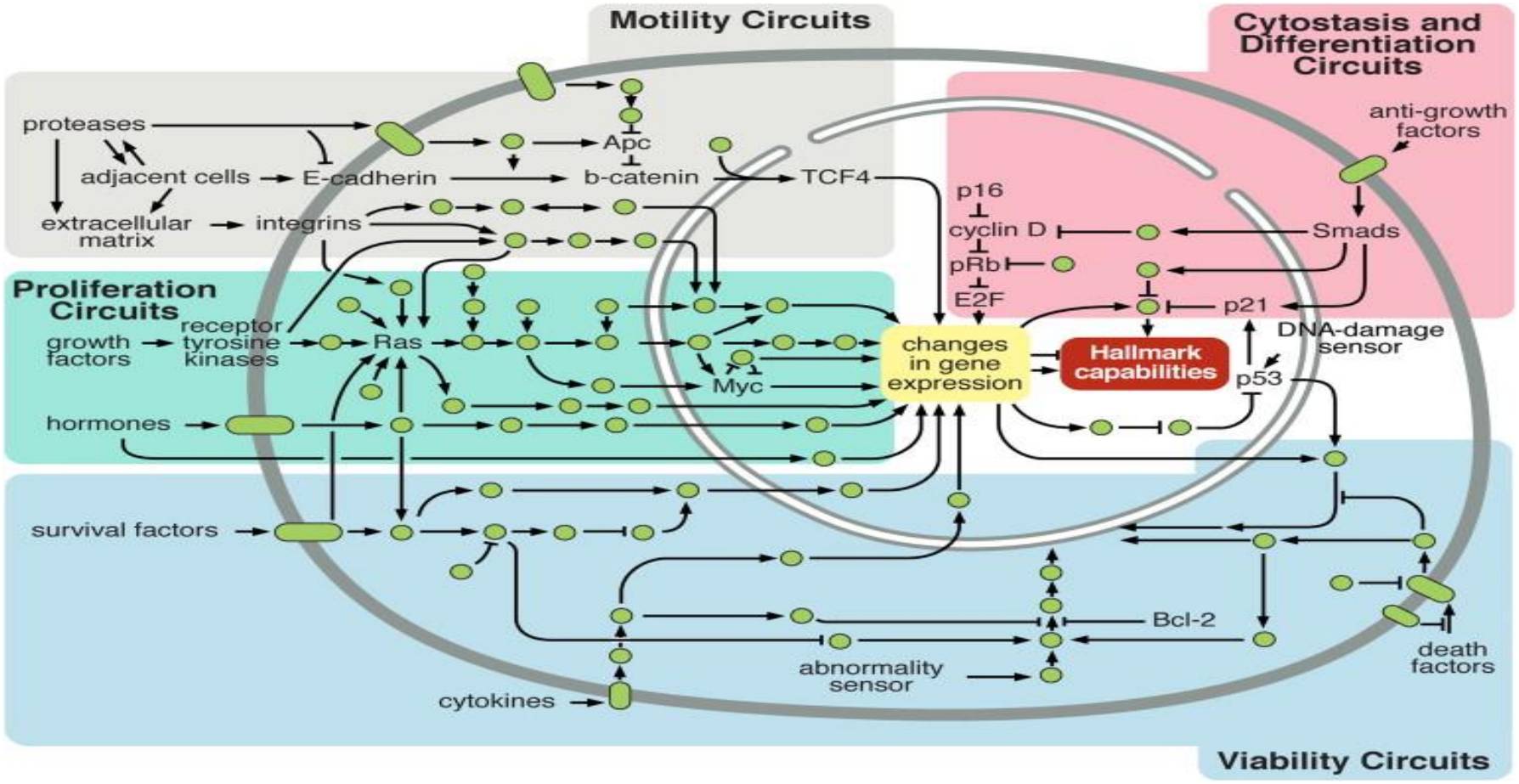


Hallmark 6:

Tissue invasion and metastasis



Intracellular Signaling Networks Regulate the Operations of the Cancer Cell



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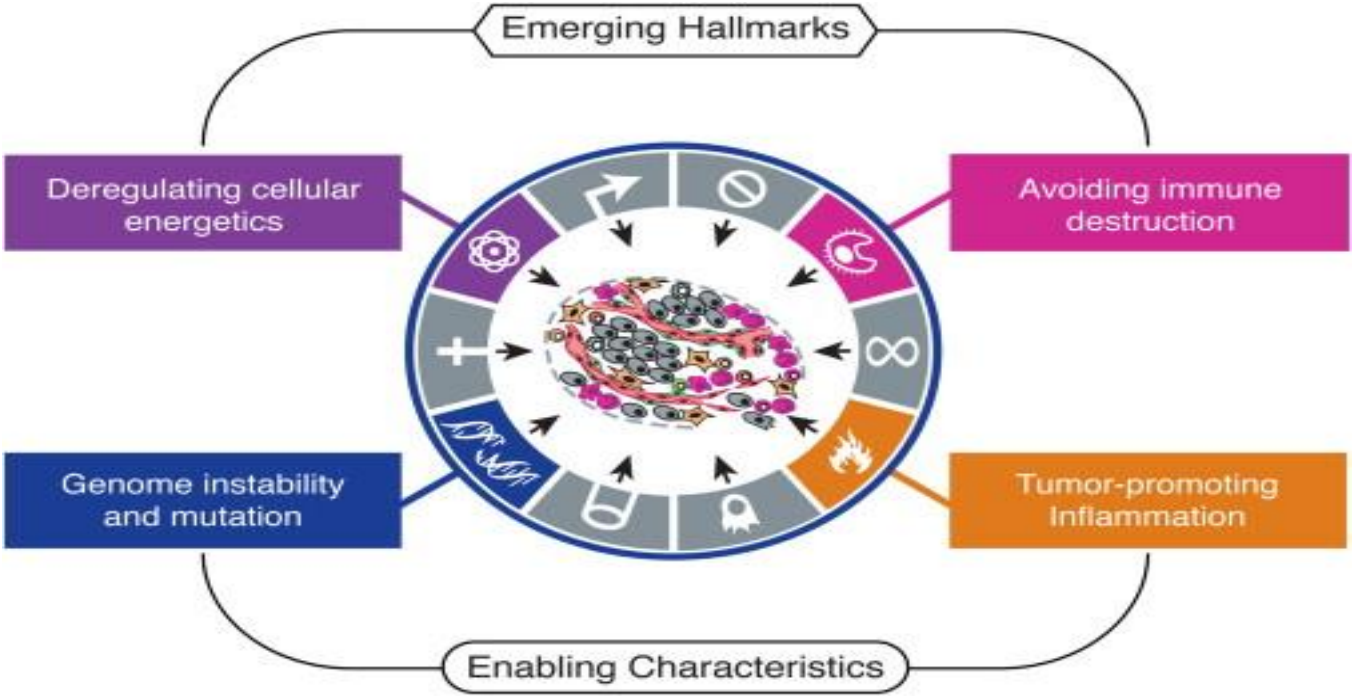
Emerging Hallmarks and Enabling Characteristics



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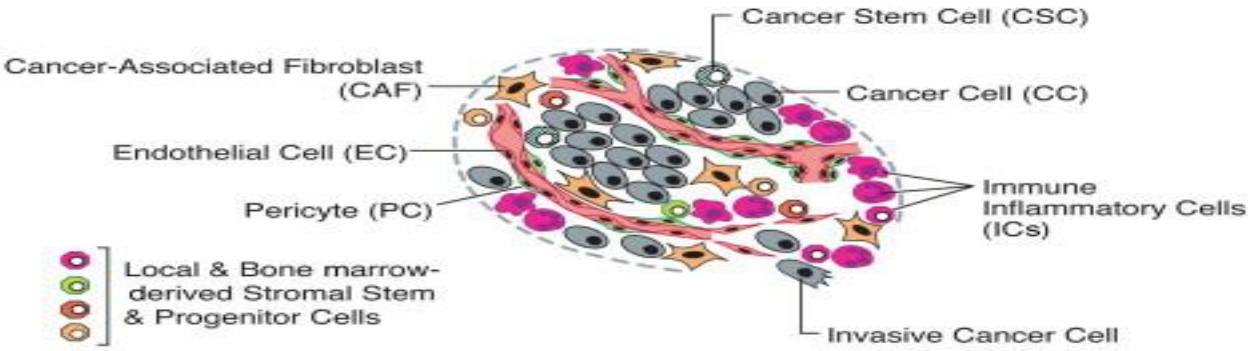
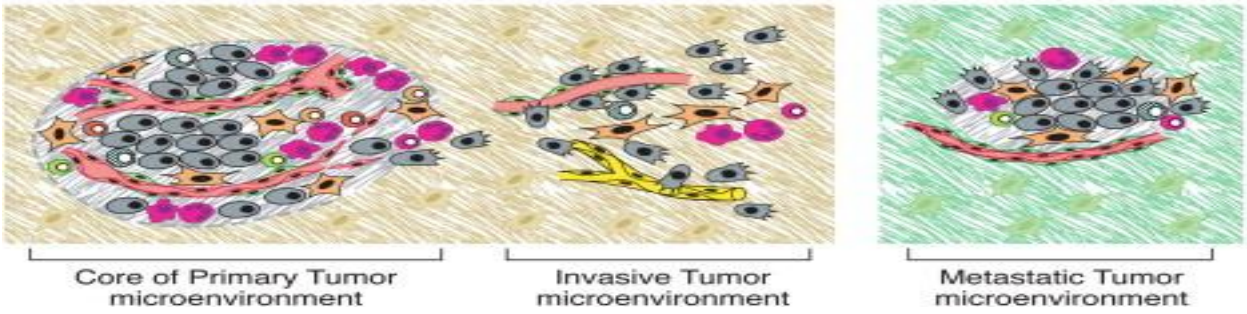
The Cells of the Tumour Microenvironment



The distinctive microenvironments of tumours.



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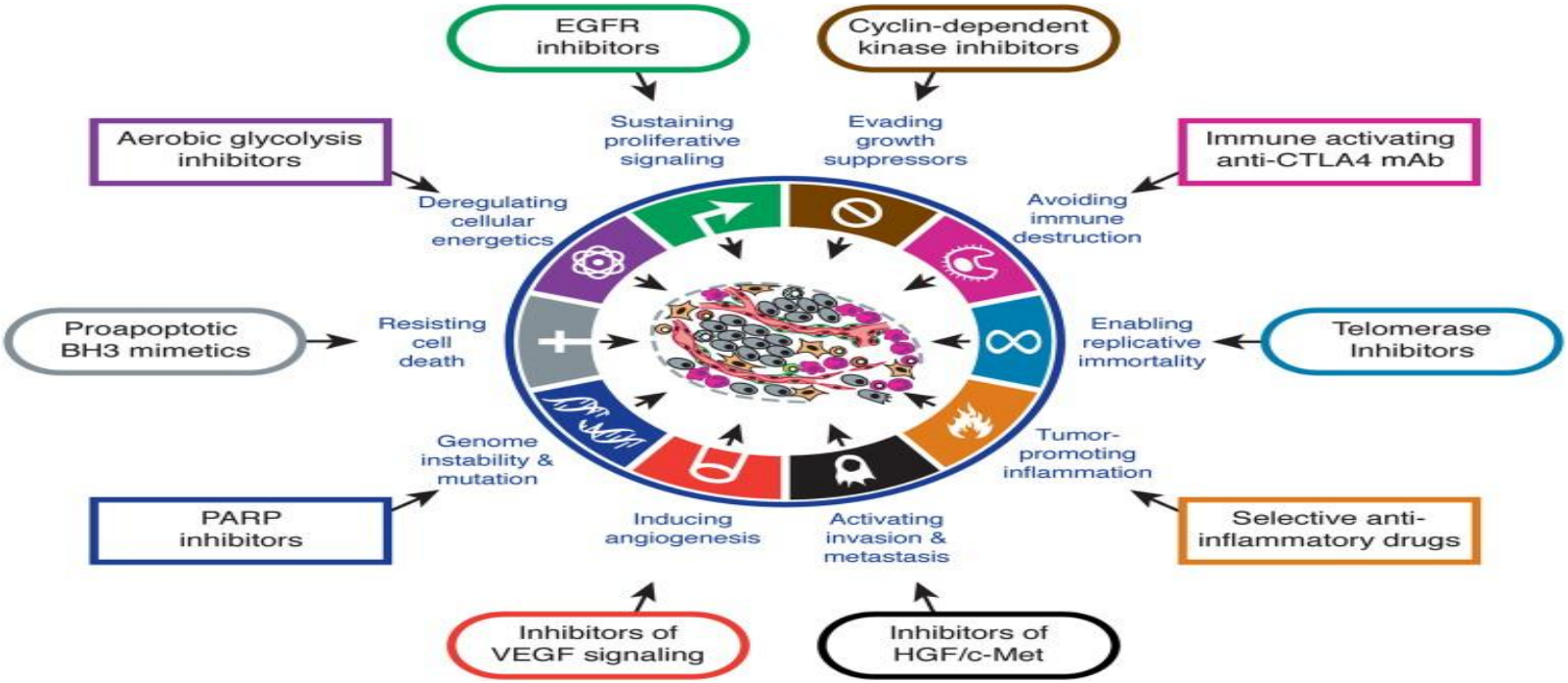
Therapeutic Targeting of the Hallmarks of Cancer



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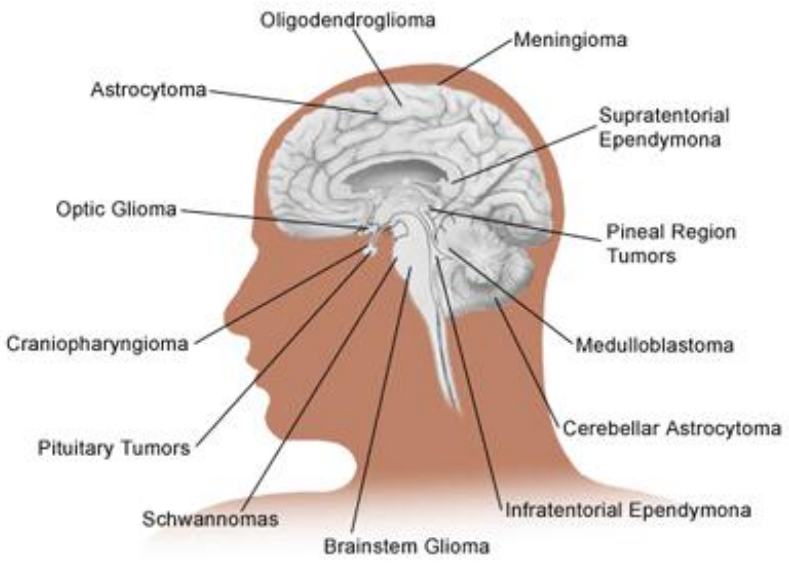
Central Nervous System Tumours

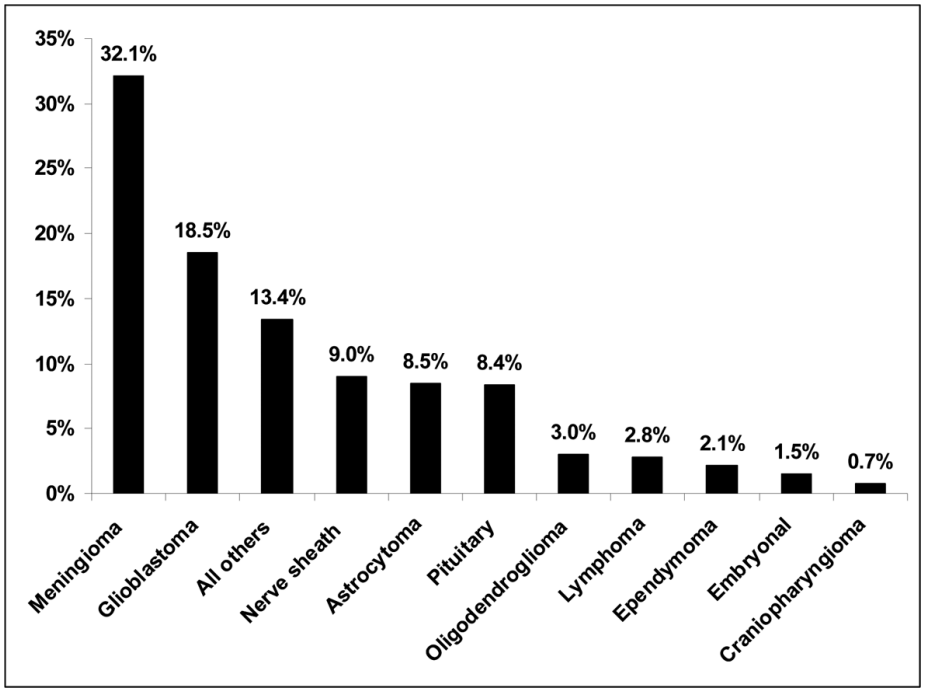
CNS tumours

- Malignant: infiltrating
- Benign: non-infiltrating (capsulated)
- Prognosis related to many factors:

  - age, location, histology
- Adults – 50% malignant (50% Primary, rest metastasis)
- Pediatric (<20) - >75% malignant

Distribution of Primary CNS





Gliomas

- Most common type of primary brain tumour
- Represent a group of low and high grade tumours that originate from glia

  - brain tissue traditionally viewed as providing support to neural cells

- True partners to neurons involved in complex processess

  - signal transduction, neurotransmission

- Neurons excluded form oncogenesis

  - cellular programme involved in neuronal differentiation protects against oncogenic transformation?

Gliomas

Astrocytomas: Astrocytic cells (adults and children)
slow (low grade) fast (high grade),
focal, diffuse

Adults
- Anaplastic – (grade 3)
- Glioblastoma Multiforme (GBM, grade 4)

Ependymomas: Ependymal cells (children and young adults),
high or low grade

Oligodendrogliomas: Oligodendrocytes, mostly in adults
- low grade (grade 2)
- high grade, anaplastic (grade 3)

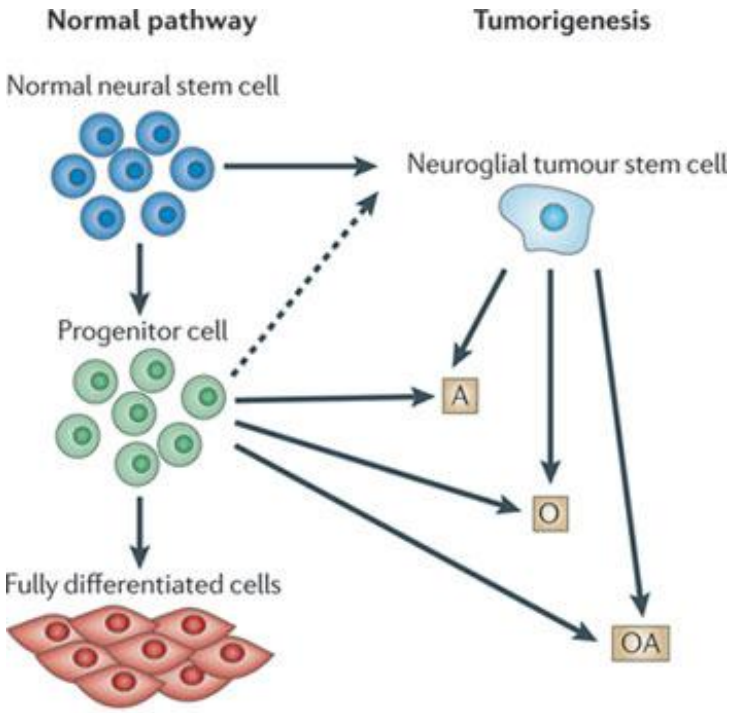
Mixed Gliomas: Mixture of the above

The cell(s) of origin for the formation of gliomas is currently unknown.

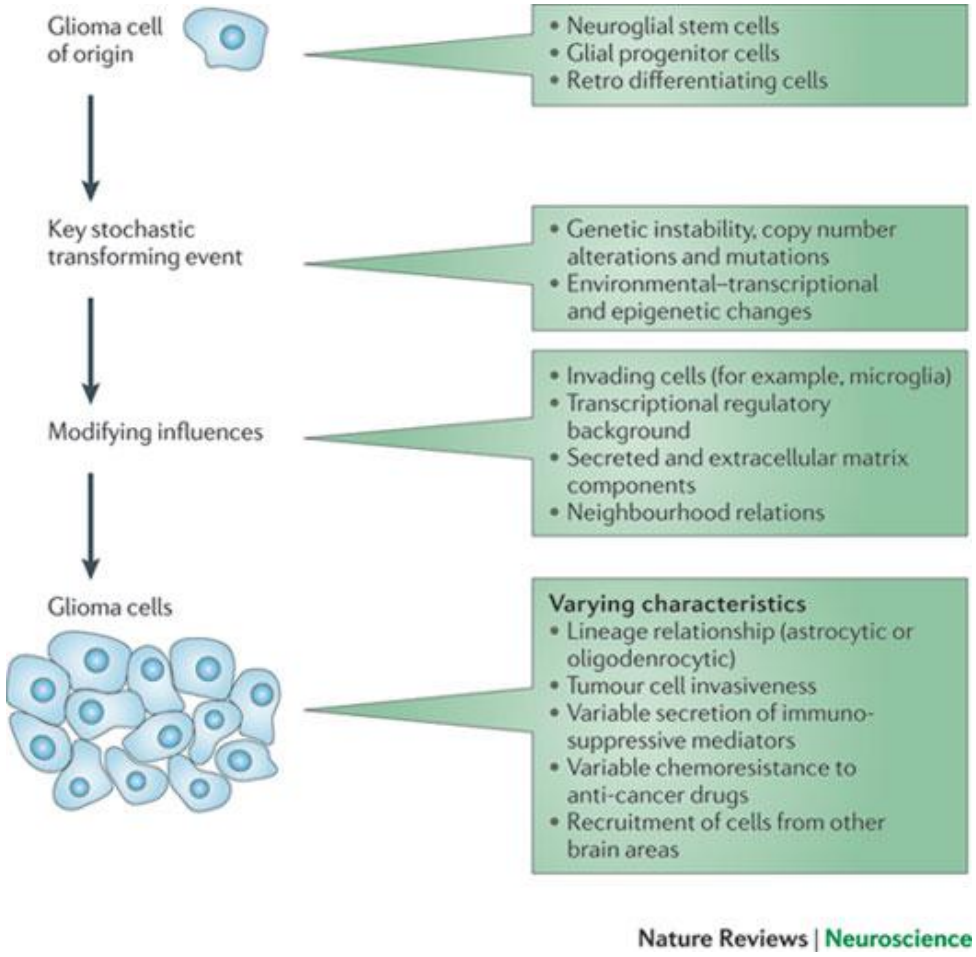
One major theory postulates that:

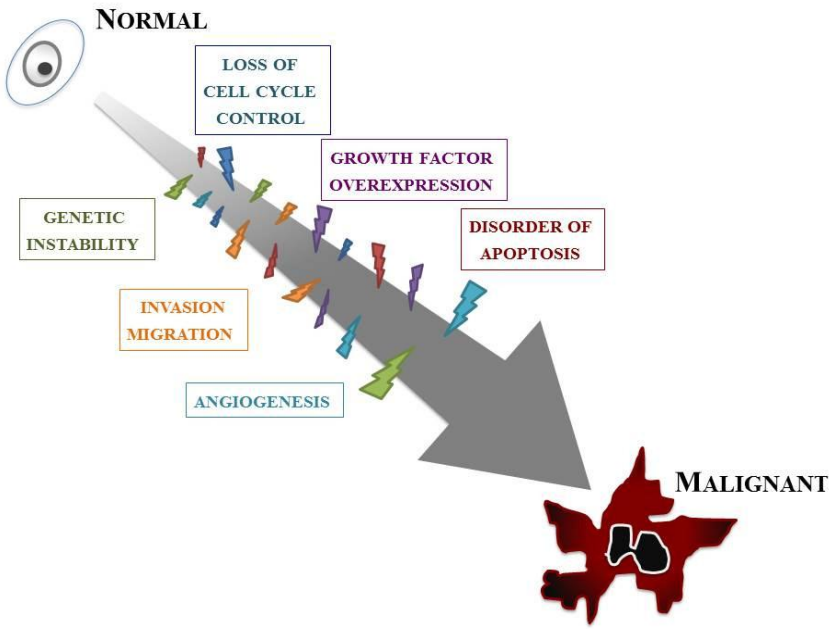
neural stem cells or neural progenitors undergo transformation events when they are in a transit-amplifying phase during development.

Other evidence points to the mutation-induced dedifferentiation of mature brain cells such as astrocytes and oligodendrocytes.

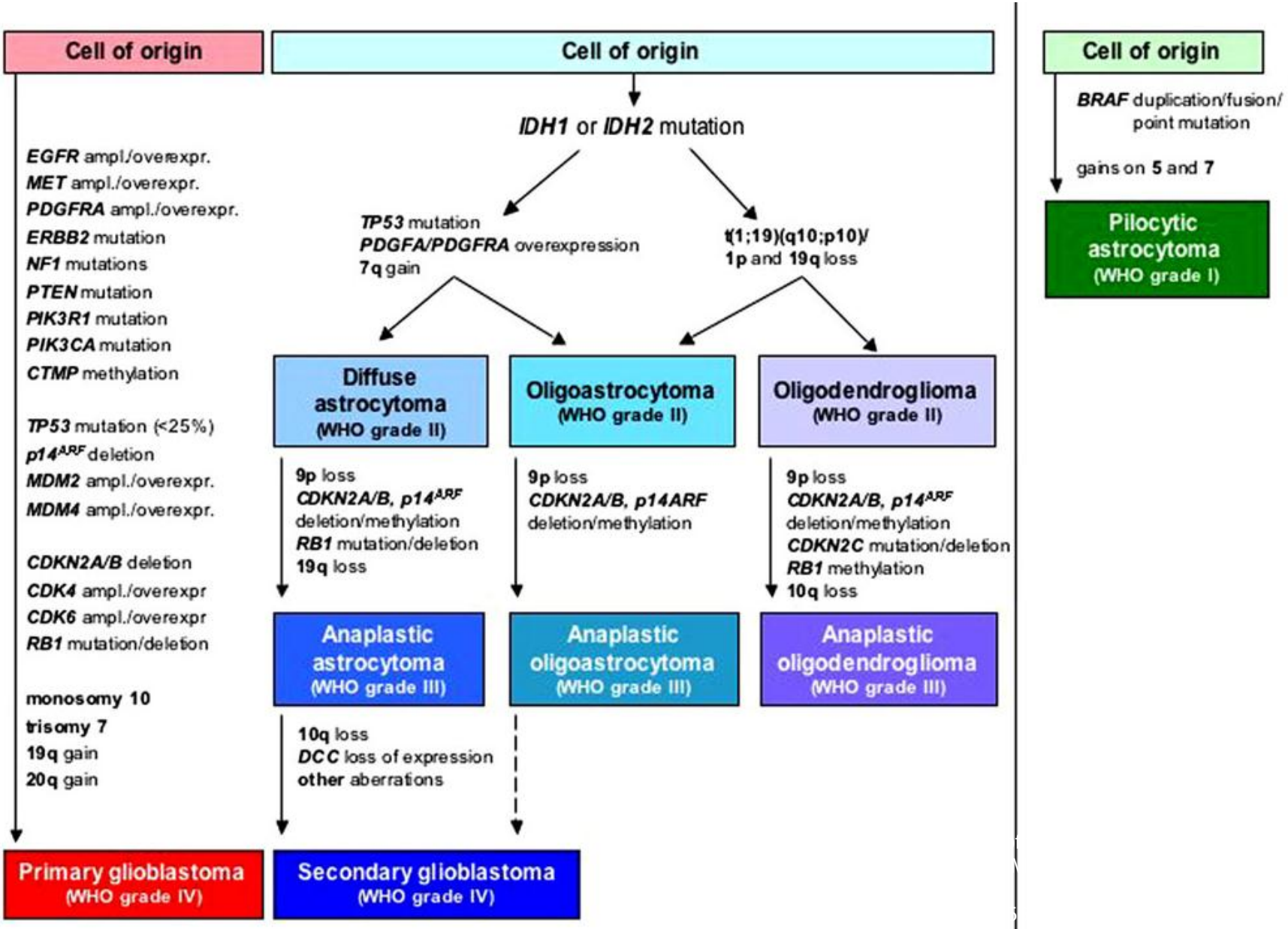


Sequential events that cause glioma diversity and that are relevant to clinical tumour characteristics.





Molecular classification of gliomas

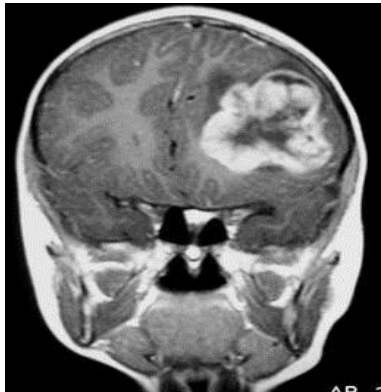


Glioblastoma (GBM): the key facts

- WHO grade IV astrocytoma, most biologically aggressive glioma subtype

- 90% of GBMs arise *de novo* (primary GBM) while 10% arise from a lower-grade tumour

- Outcome of patients with GBM is still poor. (12-18months survival post surgery)

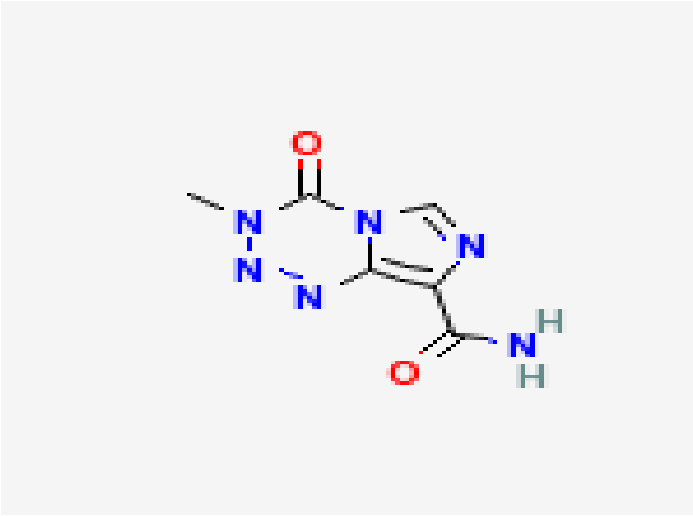


The problem

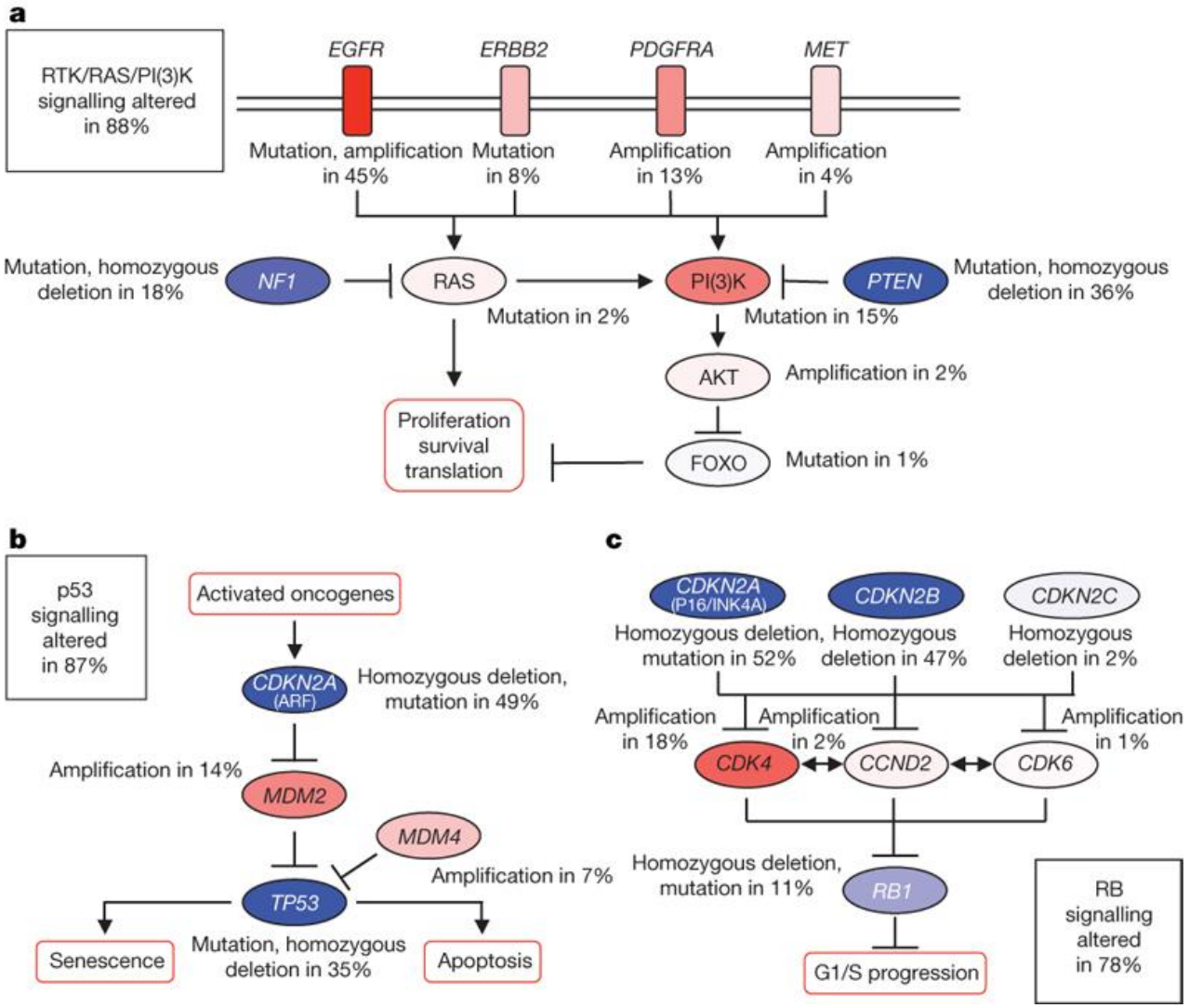
- Highly proliferative, infiltrative cancer.
- Impossible to completely resect
- Most chemotherapeutic agents do not efficiently get into the brain (BBB).
- Less common than most solid tumours and so very limited research.

Current treatment approaches

- Surgery
- Radiotherapy (High dose) over 6 wks +/- TMZ (25% alive over 2 yrs)
- Radiotherapy (Low dose) over 2 weeks (months)
- Gliadel wafers
- Best supportive care



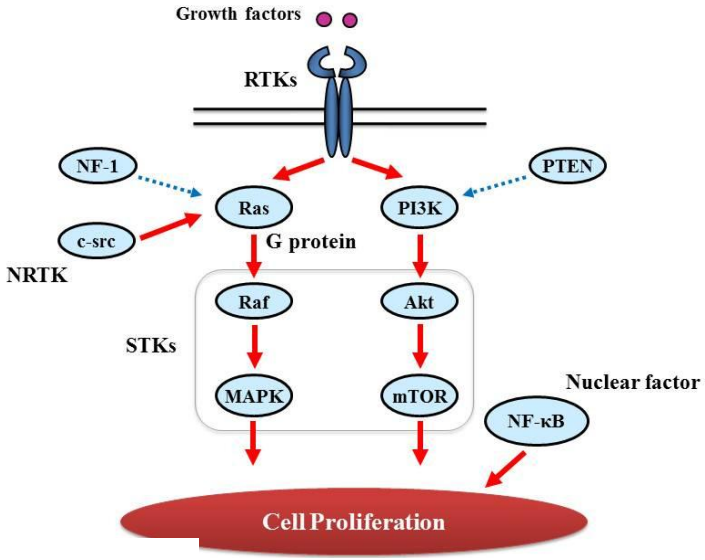
Frequent genetic alterations in three critical signalling pathways



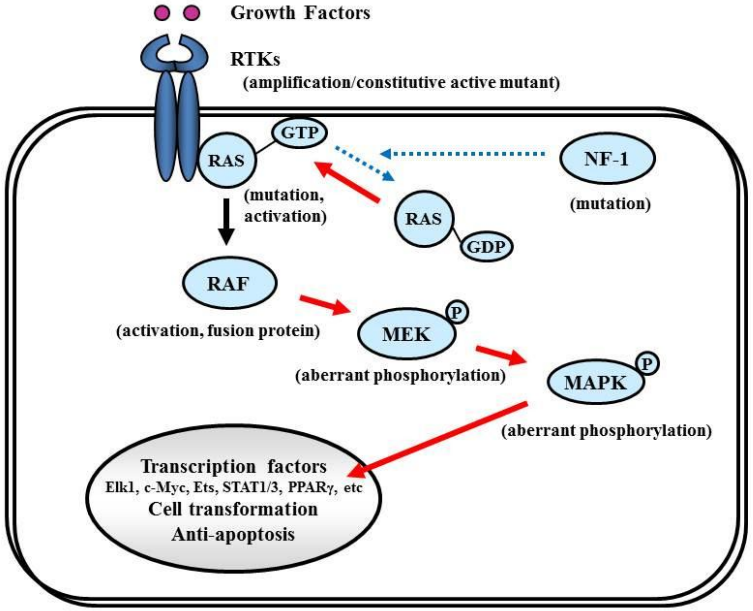
The Cancer Genome Atlas Research Network *Nature* **000**, 1-8 (2008)

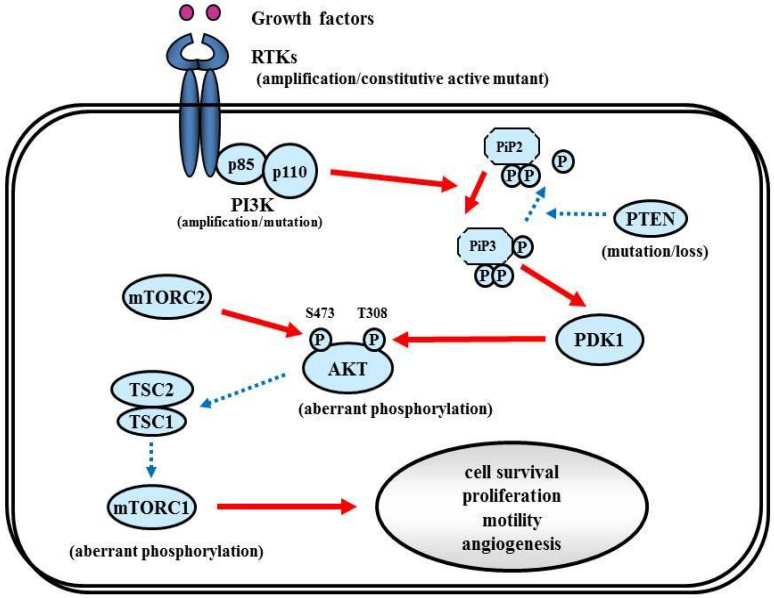
nature

Genetic Alterations in Glioblastoma frequently affect signalling pathways



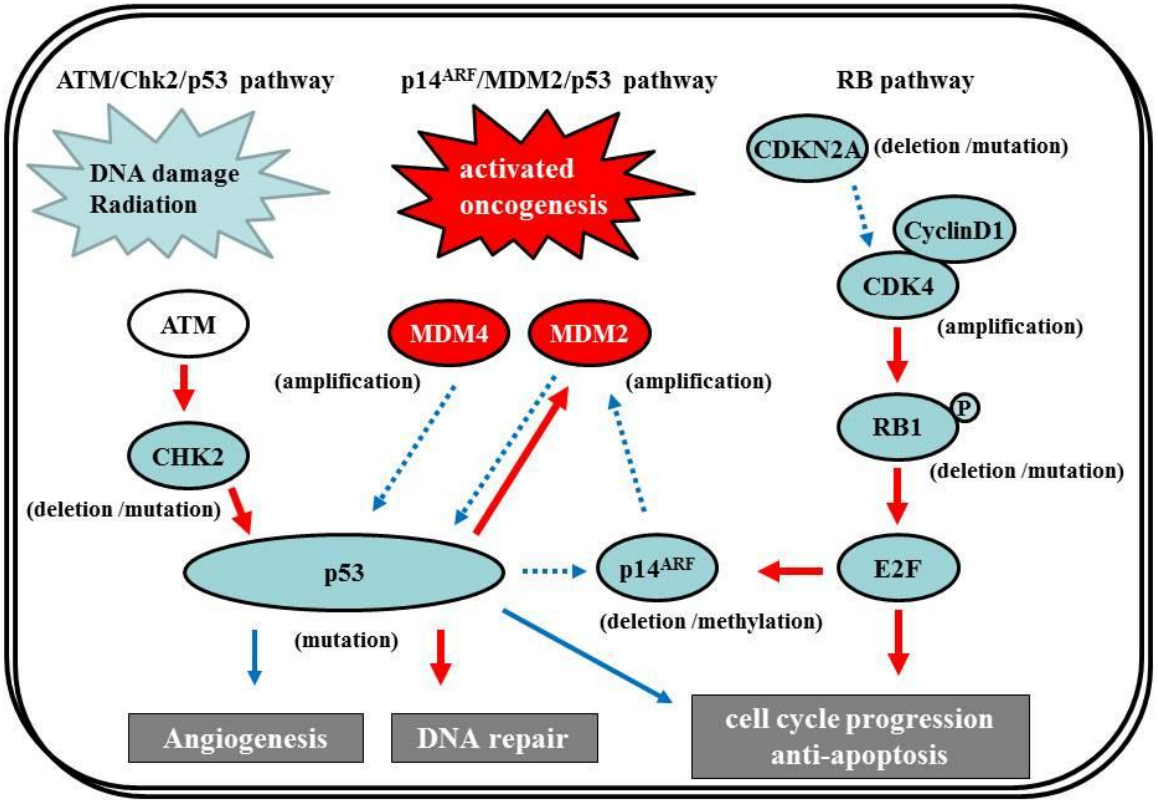
RTK/PI3K/Akt – EGFR, PDGFR
VEGFR





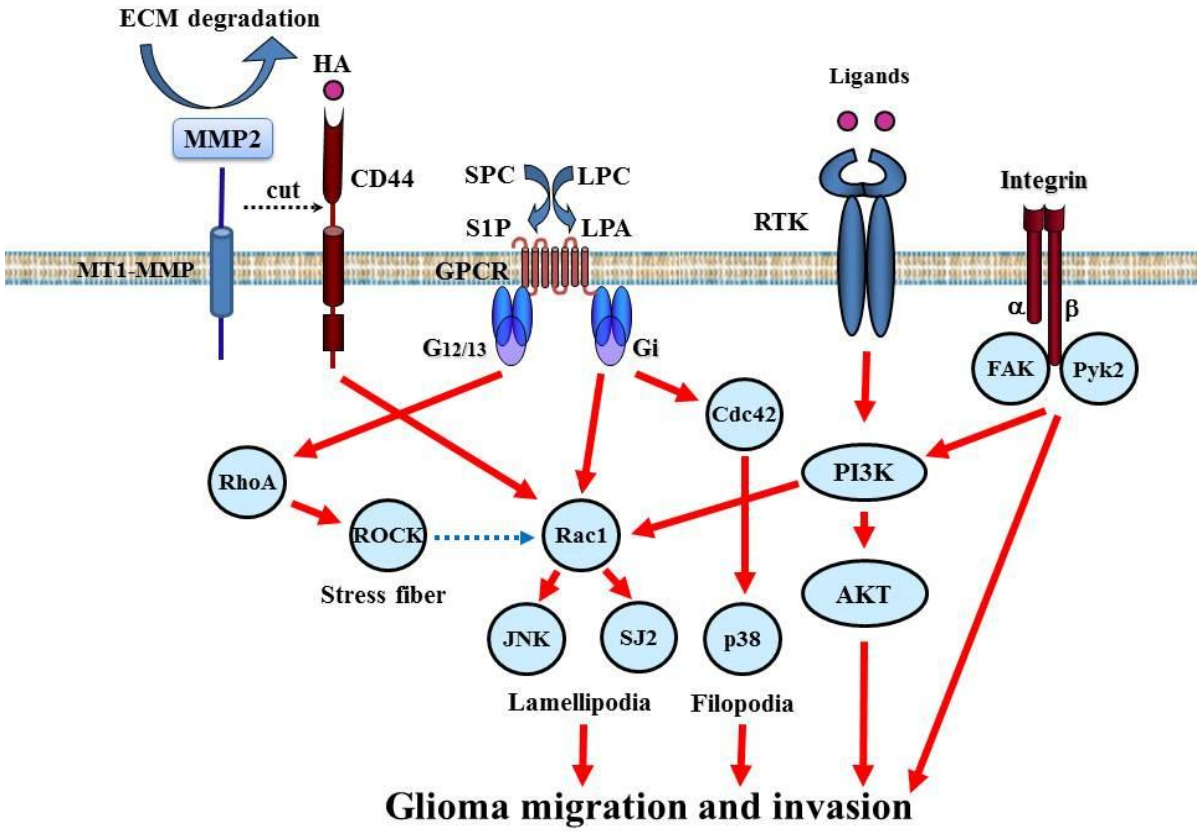
Cancer 2011, 3, 324-327

The p53 pathway and RB tumour suppressor signalling



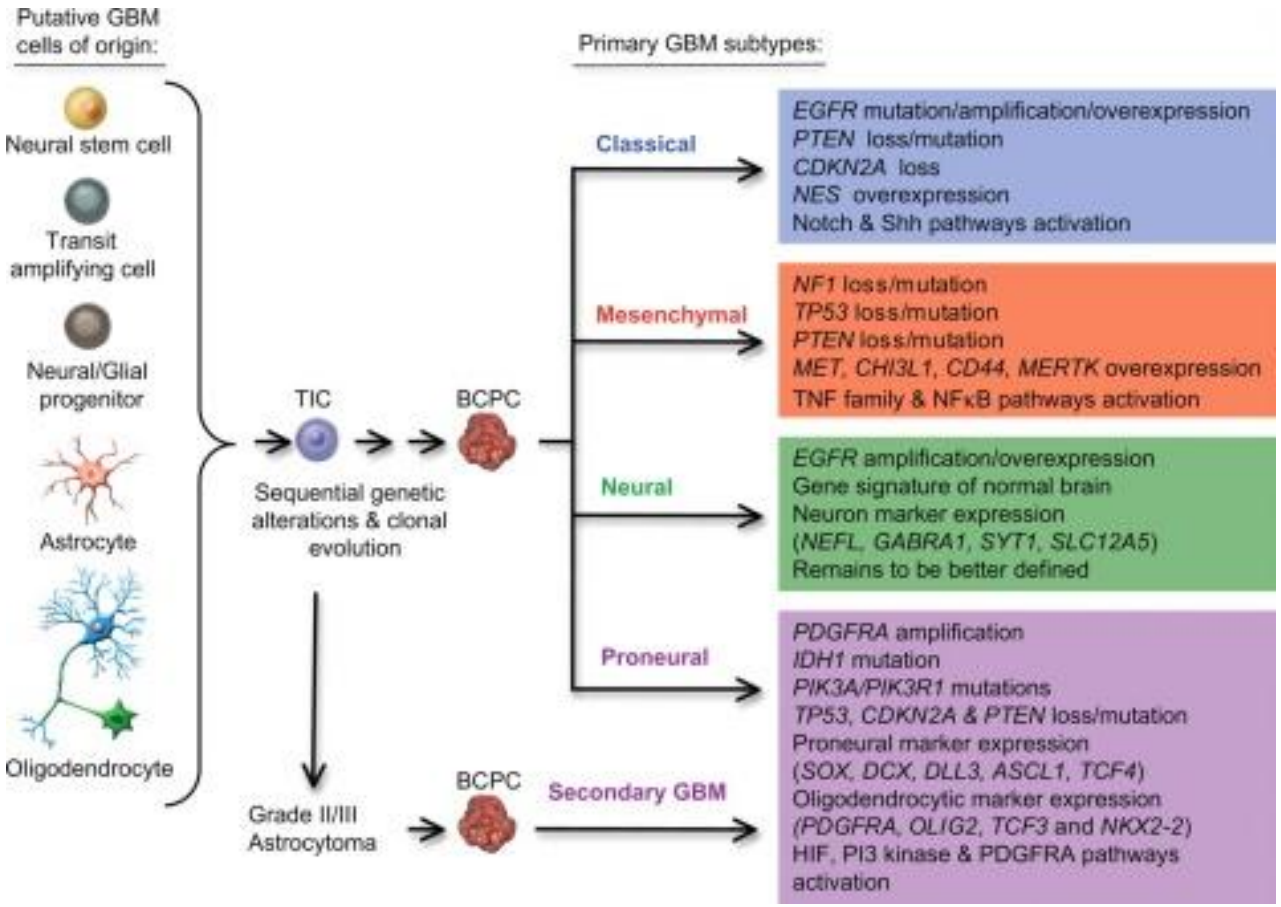
Cancer 2011, 3, 324-327

Novel signalling influences glioma invasion



Cancer 2011, 3, 324-327

New Developments in the Classification of Human Glioblastoma



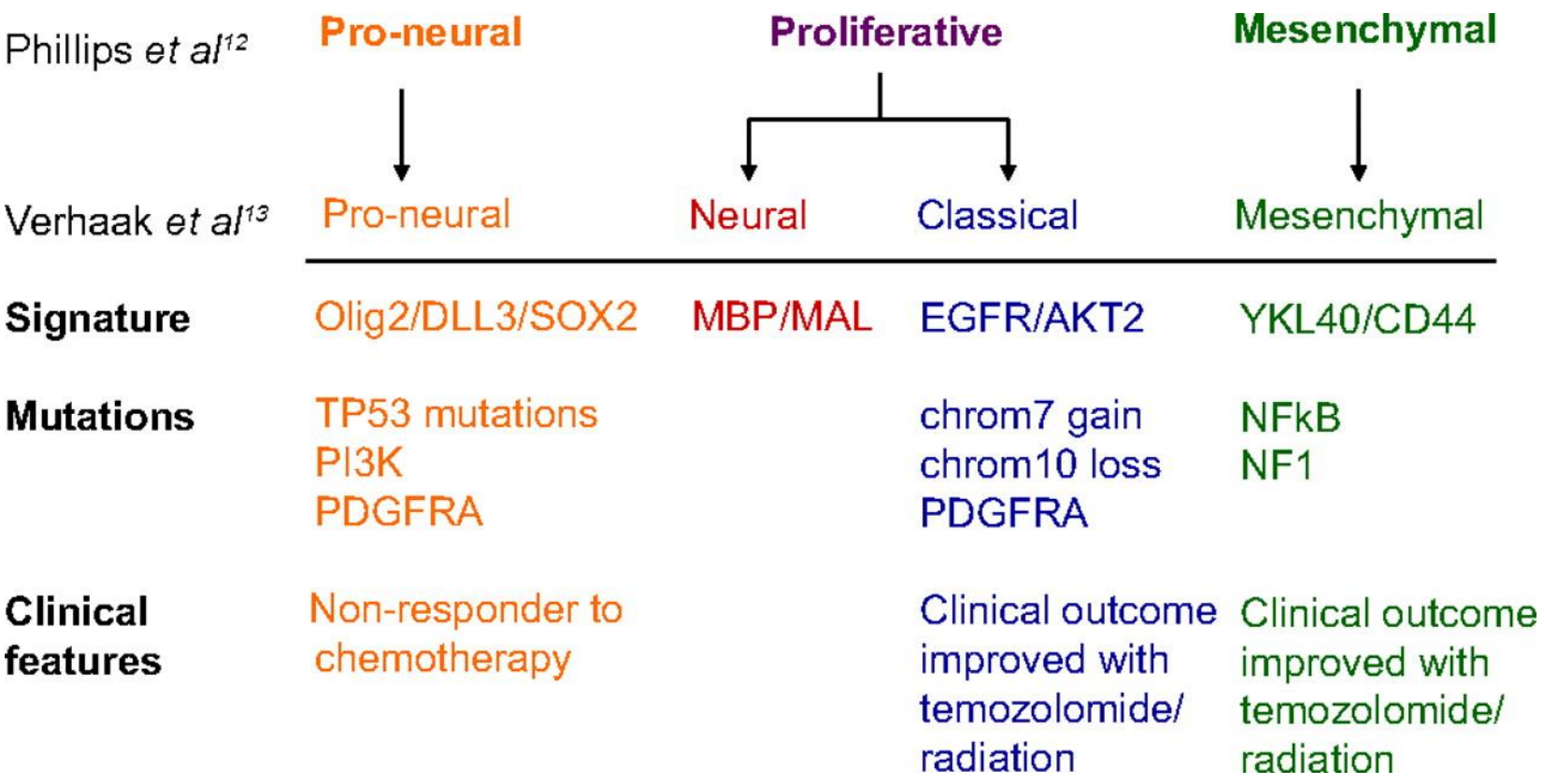
Sequential Genetic Changes Observed in the Pathogenesis of Different Subtypes of Glioblastoma:

Some cells in the normal brain undergo genetic alterations, which leads to a population of tumour–initiating cells (TICs),

These accumulate further genetic and epigenetic changes to become brain cancer propagating cells, BCPC

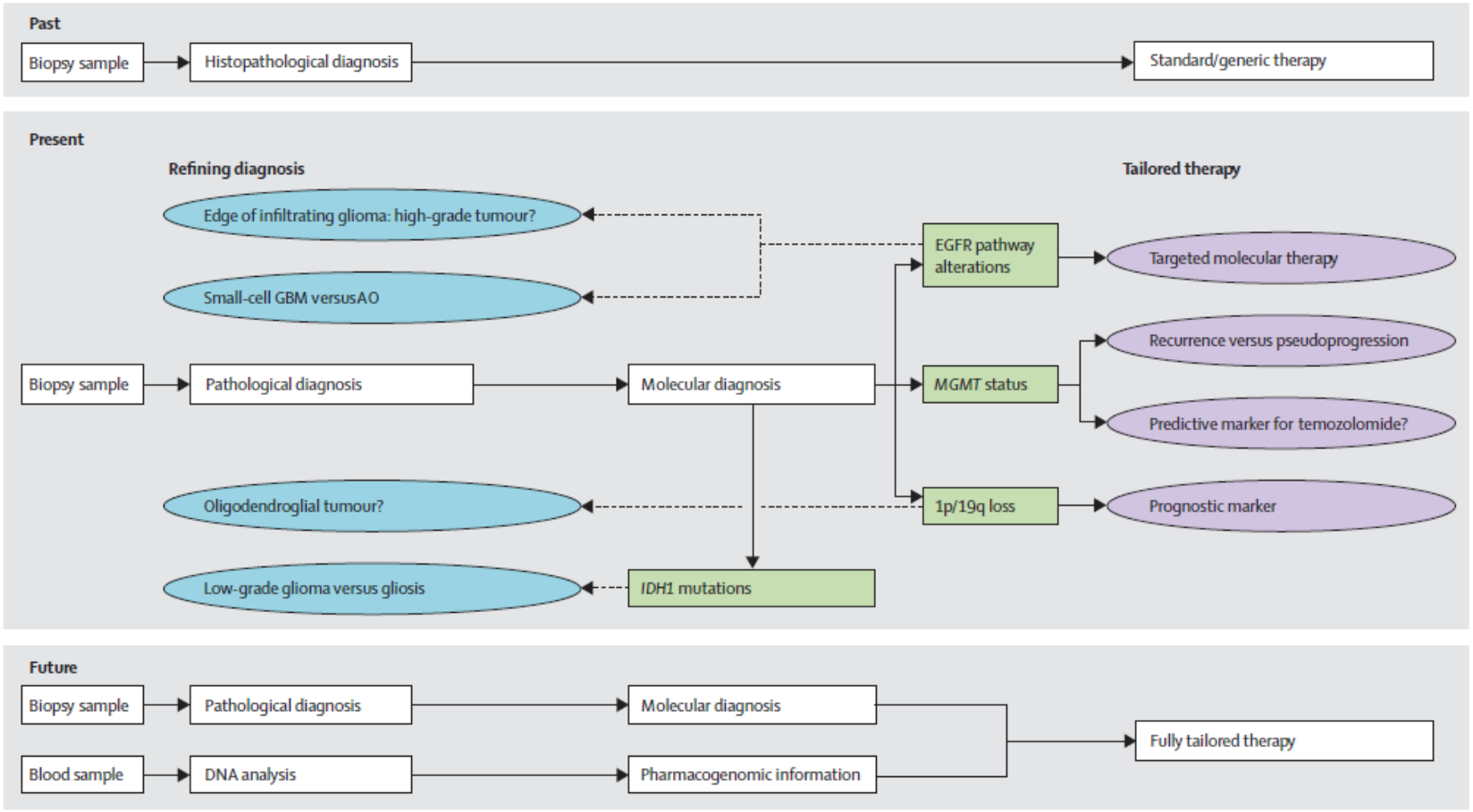
BCPC are responsible for the formation of glioblastoma

Transcriptomal subtypes of glioblastoma.



Bartek J et al. J Neurol Neurosurg Psychiatry 2012;83:753-760

The past, present and future of diagnostic glioma therapy



References

The hallmarks of cancer
Hanahan D, Weinberg RA. Cell. 2000 Jan 7;100(1):57-70. Review

Hallmarks of cancer: the next generation
Hanahan D, Weinberg RA. Cell. 2000 Jan 7;100(1):57-70. Review

Central nervous system
Adamson DC, Rasheed BA et al. Cancer Biomark. 2010;9(1-6):193-210

Glioma development: where did it all go wrong?
Sukhdeo K, Hambardzumyan D, Rich JN. Cell 2011 Jul 22;146(2):187-8

Developmental origins of brain tumours
Liu C, Zong Hui. Curr Opinion in Neurobiology 2012, 22:1-6

The neurobiology of gliomas: from cell biology to the development of therapeutic approaches
Westphal M, Lamszus K. Nature Reviews Neuroscience 12, 495-508 (Sept 2011)