Neoplasia
Molecular basis of cancer

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References:

- **Robbins & Cotran Pathologic Basis of Disease- 9th edition**
- **IMAGES- Above mentioned book & internet**

Molecular Basis of Cancer

- Evidence for the **genetic origin** of cancer have been building up for over the decades
- Genetic damage may be
  - **Acquired** (environmental agents) or may be
  - **Inherited**

Molecular Basis of Cancer

- **Non- lethal** genetic damage underlies carcinogenesis
- A tumour is formed by the **clonal expansion** of a single genetically damaged precursor cell **(monoclonal)**

Types of cellular genes involved in Molecular Carcinogenesis

- ***Growth promoting proto- oncogenes***
- ***Growth inhibiting tumour suppressor genes***
- ***Genes regulating apoptosis***
- ***DNA repair genes***

These are the principal targets of cancer causing mutations

Molecular Basis of Cancer
Regulatory genes

PROTO- ONCOGENES

- **Normal cellular genes**
- Whose products promote cell proliferation

ONCOGENES

- Genes that promote autonomous cell growth in cancer cells
- **Mutated** or overexpressed versions of **proto-oncogenes** that function autonomously

ONCOPROTEIN

- A protein products of oncogenes that drives increased cell proliferation

Molecular Basis of Cancer

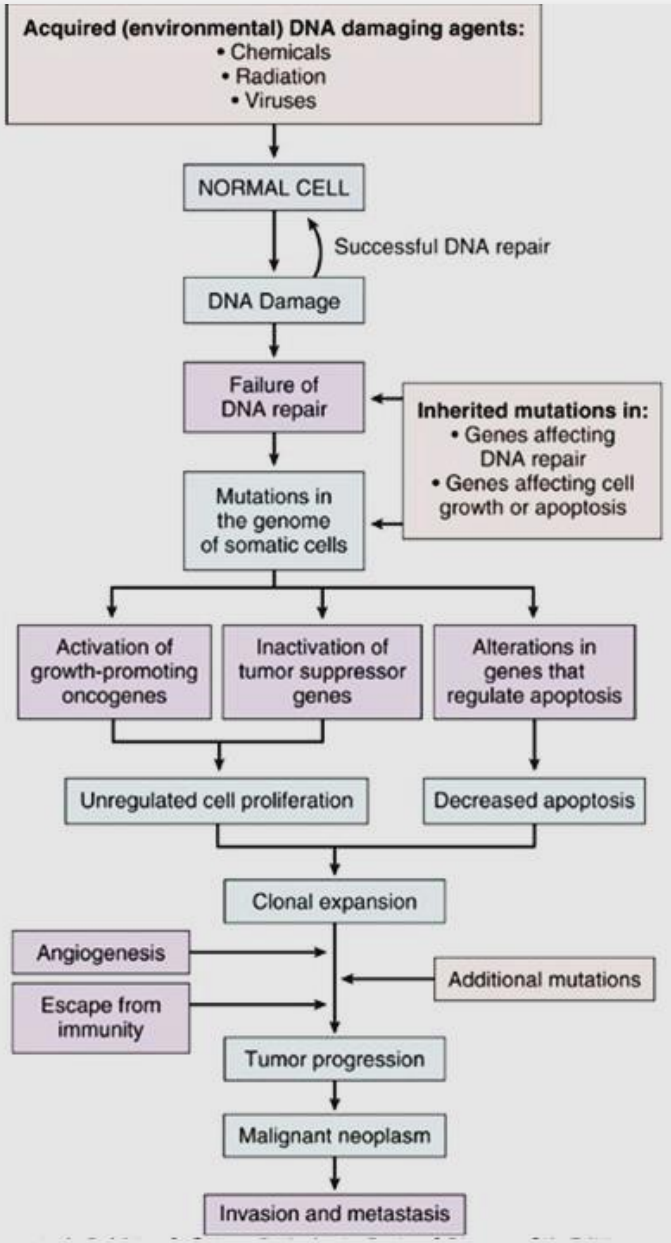
Non lethal genetic damage

Clonal expansion of genetically damaged cells

Involved genes

- **Proto-oncogenes,**
- **Tumor suppressor genes,**
- **Genes regulating apoptosis,**
- **DNA repair genes**

Carcinogenesis is a multi-step process

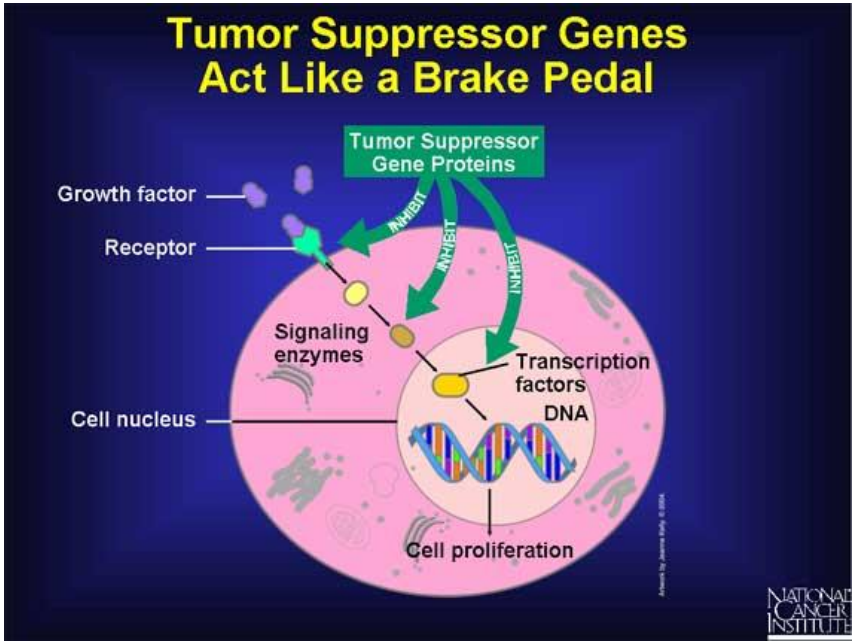


Selected Oncogenes, Mode of Activation and Associated Human Tumours

Category	Proto-Oncogene	Mode of Activation	Associated Human Tumour
GROWTH FACTORS			
PDGF beta	PDGFB	Overexpression	Astrocytoma
FGF	HST1, FGF3	Overexpression, Amplification	Osteosarcoma, stomach ca, bladder ca, breast ca, melanoma
TGFα	TGFA	Overexpression	Astrocytoma
HGF	HGF	Overexpression	HCC, thyroid ca
GROWTH FACTOR RECEPTORS			
EGF receptor family	ERBB1 ERBB2	Mutation Amplification	Adenocarcinoma lung Breast carcinoma
PDGF receptor	PDGFRB	Overexpression	Gliomas, leukaemias

Tumour suppressor gene

- Tumour suppressor genes **apply brakes** to cell proliferation
- They act as **check points** that prevent uncontrolled growth
- **Negatively** regulate cellular proliferation
- Abnormalities in these genes lead to failure of growth inhibition



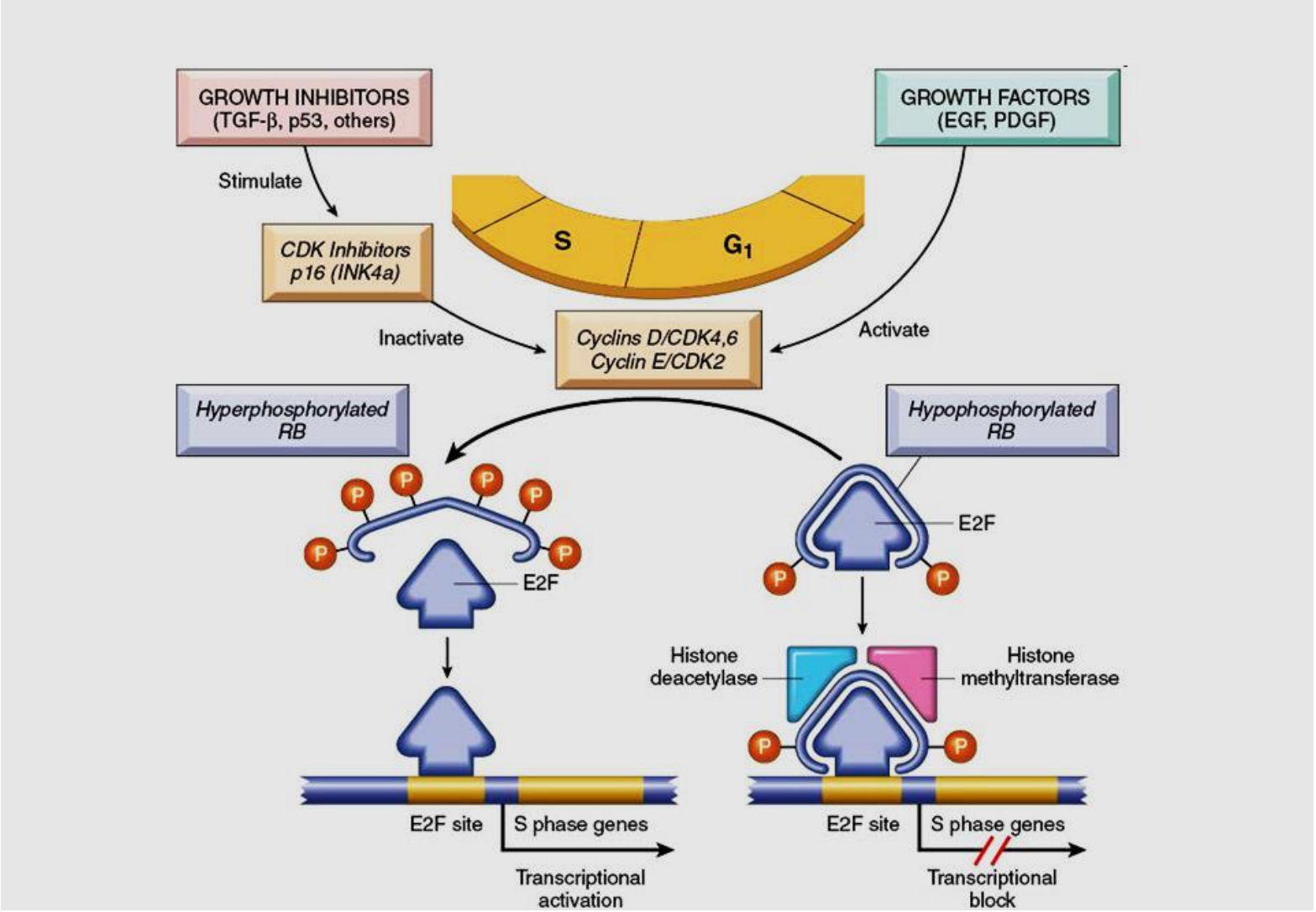
Selected Tumour Suppressor Genes and associated Familial Syndromes

Gene	Familial syndromes	Sporadic cancers
APC	Familial colonic polyps and carcinoma	Carcinoma stomach, colon, pancreas
E-Cadherin	Familial gastric carcinoma	Gastric carcinoma, lobular breast carcinoma
CDKN2A	Familial melanoma	Pancreatic, breast, oesophageal carcinoma, melanoma
RB	Familial retinoblastoma syndrome (retinoblastoma, osteosarcoma, other sarcoma)	Retinoblastoma, osteosarcoma
NF1	Neurofibromatosis type 1 (neurofibroma, and MPNST)	Neuroblastoma
NF2	Neurofibromatosis type 2 (acoustic schwannoma and meningioma)	Schwannoma and meningioma
WT1	Familial Wilms tumour	Wilms tumour and certain leukaemia
PTEN	Cowden syndrome (benign skin, GI, and CNS growth, breast, endometrial and thyroid carcinoma)	Diverse cancers
VHL	Von Hippel Lindau syndrome(cerebellar hemangioblastoma, retinal angioma, RCC)	RCC
TP53	Li- Fraumeni syndrome	Most human cancers
BRCA1,BRCA2	Familial breast and ovarian carcinoma; carcinoma of male breast; CLL	Rare
STK11	Peutz-Jegher syndrome(GI polyps, GI cancers, pancreatic carcinoma, other carcinomas)	Diverse carcinomas

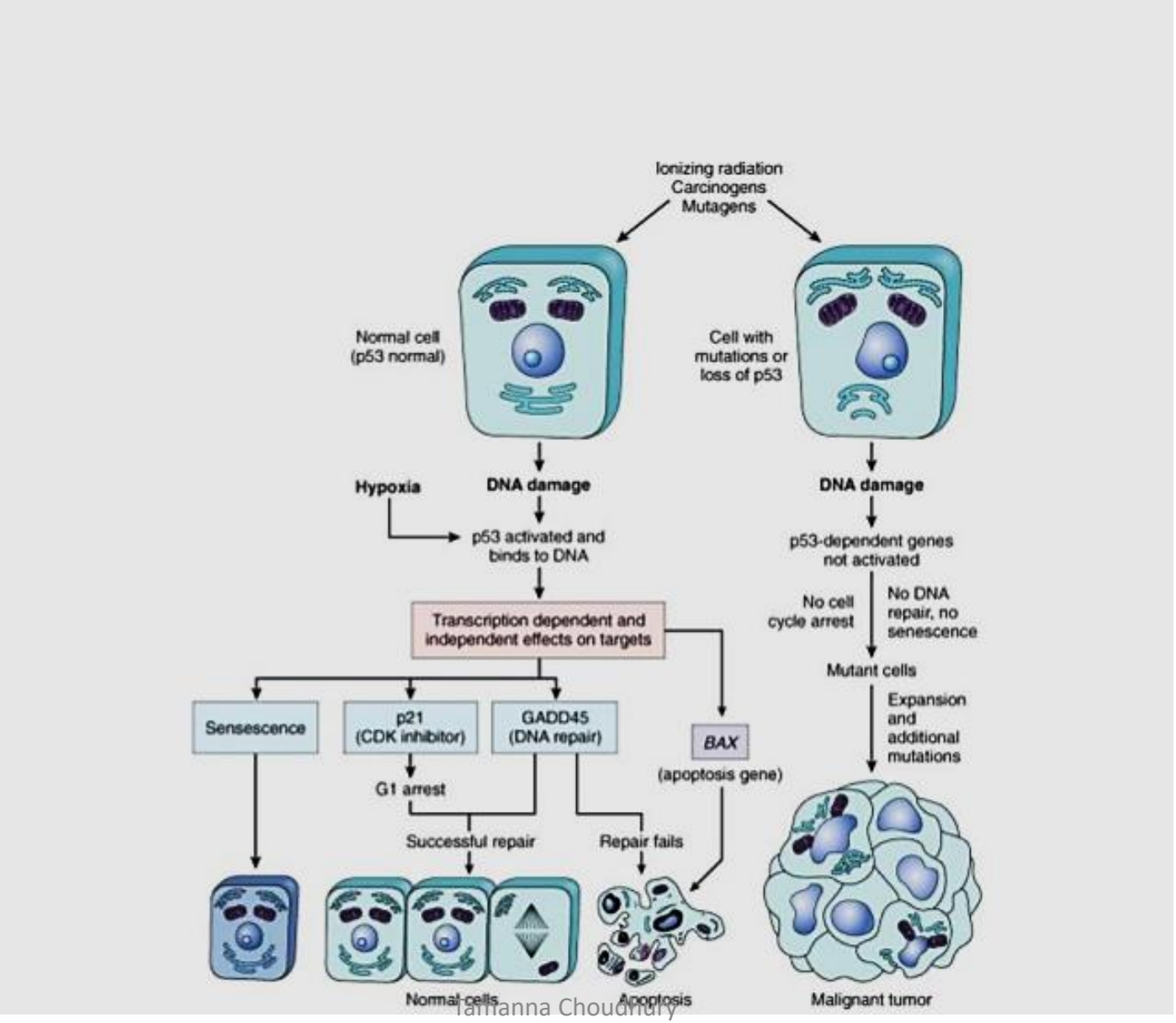
Tumour suppressor genes

- RB – governor of the cell cycle
- P53- guardian of the genome

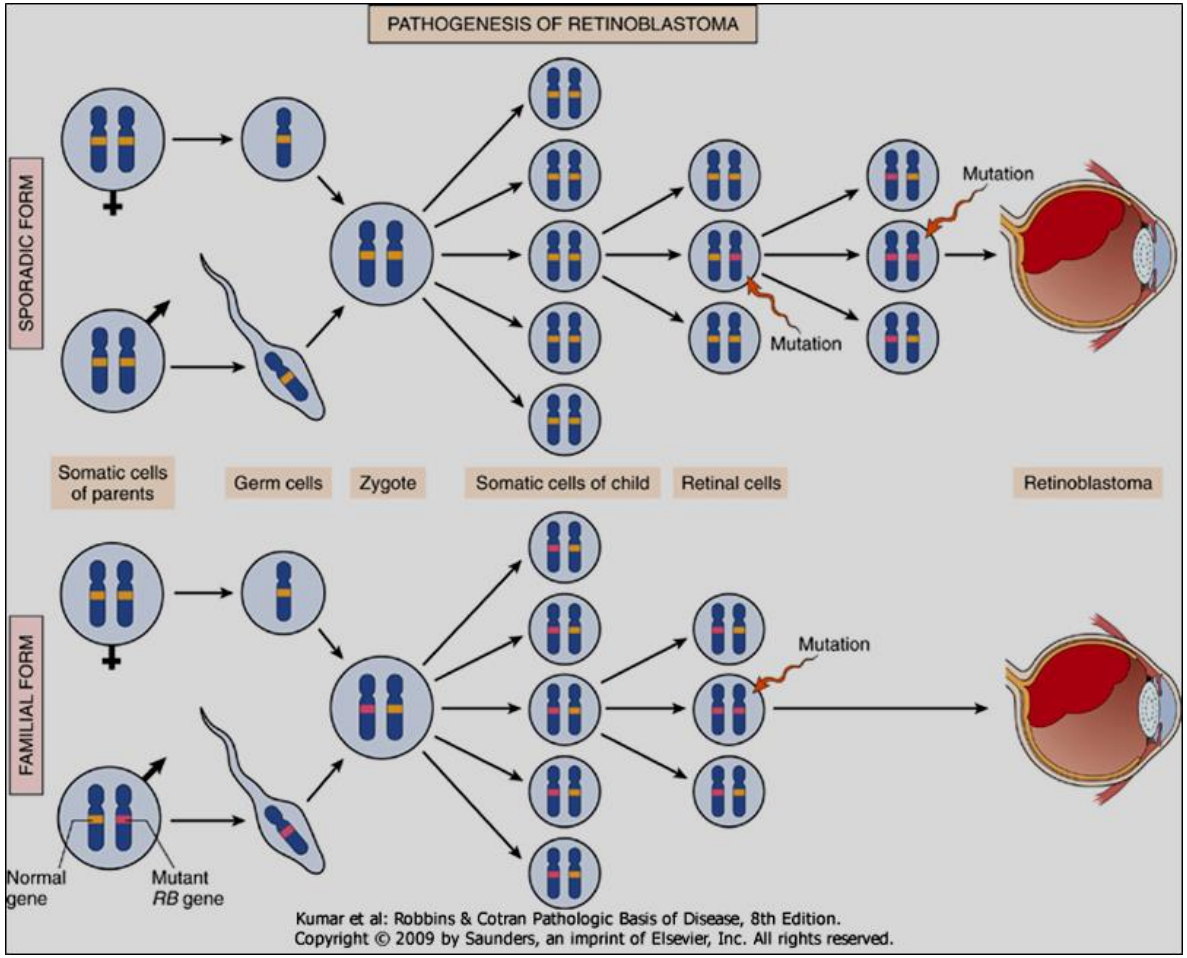
The role of RB gene in regulating the cell cycle



The role of p53 in maintaining genomic integrity

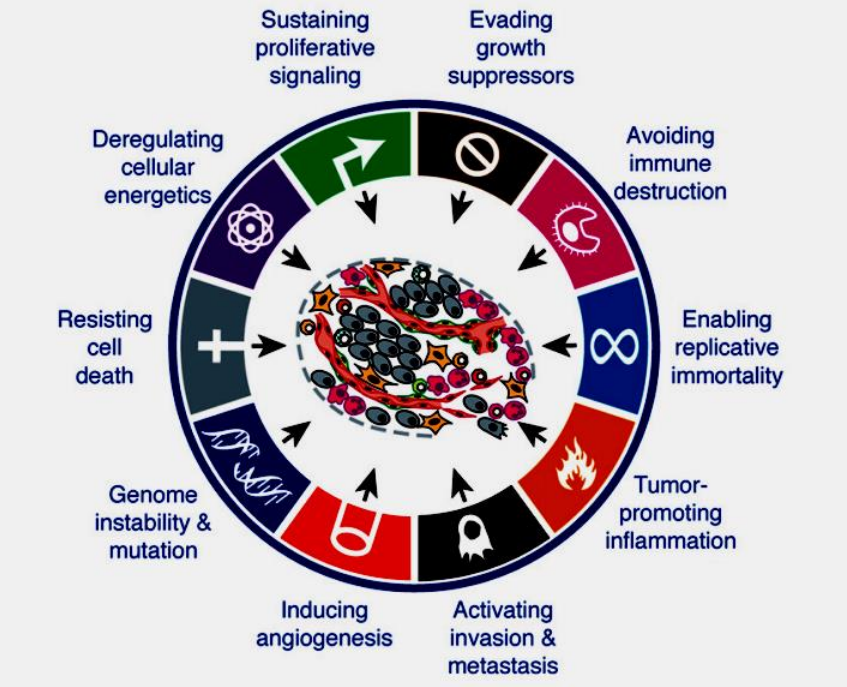


Two hit hypothesis
Pathogenesis of Retinoblastoma

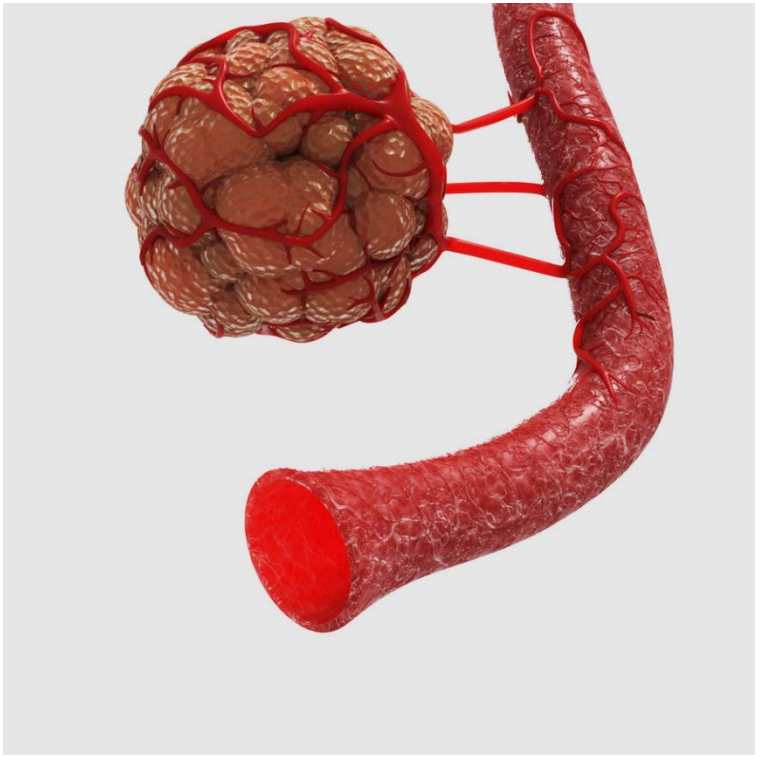


HALLMARKS of CANCER
Attributes of malignancy

1. Self sufficiency in growth signals
2. Insensitivity to growth inhibitory signals
3. Altered cellular metabolism
4. Evasion of apoptosis
5. Limitless replicative potential (immortality)
6. Sustained angiogenesis
7. Ability to invade and metastasize
8. Ability to evade the host immune response



Tumour Angiogenesis



Tumour Angiogenesis

- Host blood vessel growth
- Vascularization of tumours is essential for their growth
- Controlled by the balance between angiogenic and antiangiogenic factors produced by tumour and stromal cells

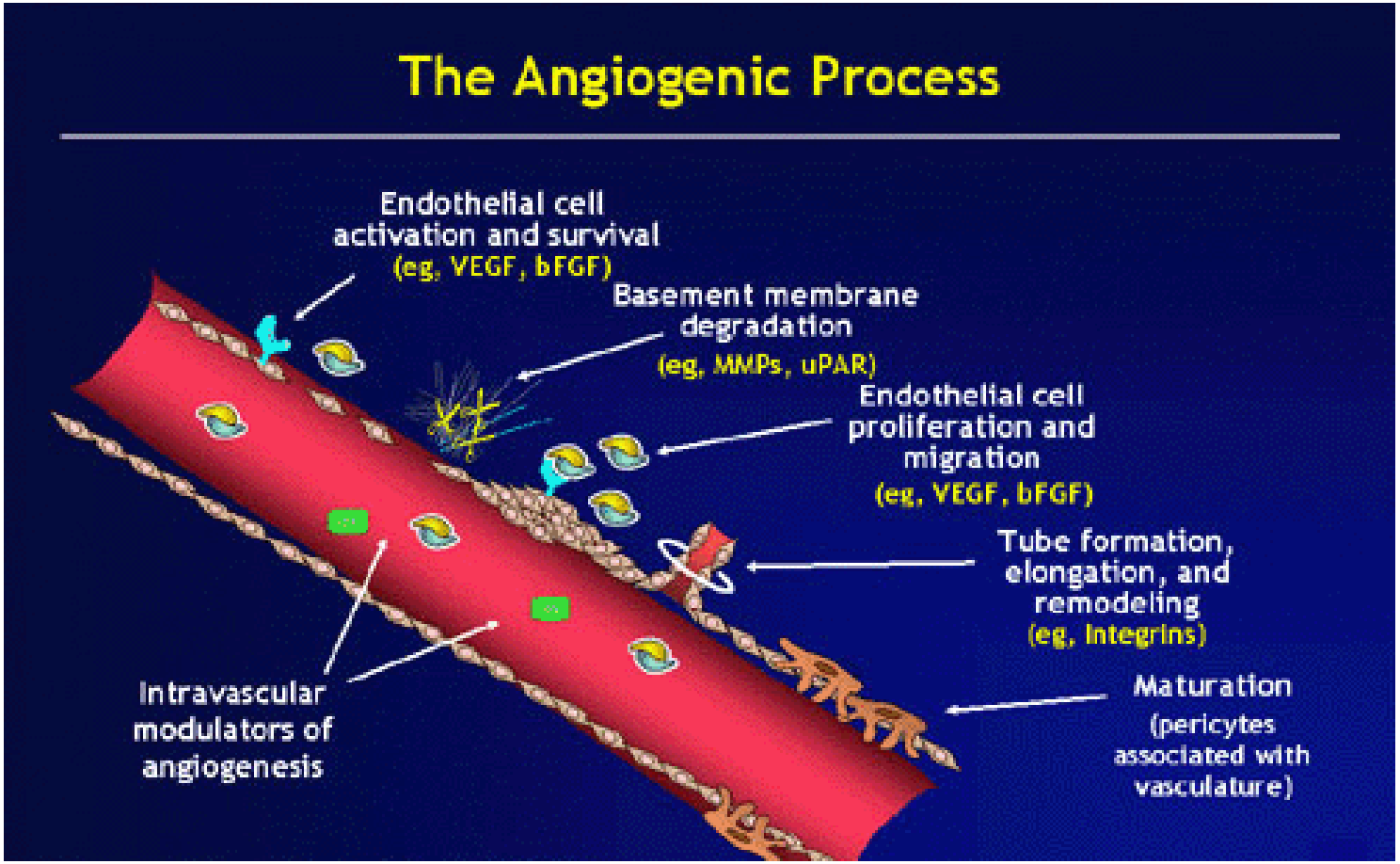
Tumour Angiogenesis

- Even if a tumour possesses all the genetic aberrations that are required for malignant transformation it **cannot enlarge beyond 1 to 2 mm in diameter**
- Unless it has the capacity to induce **angiogenesis**

Tumour Angiogenesis

- Most tumours do not initially induce angiogenesis
- Thus remain small or in situ
- The subsequent ***angiogenic switch*** involves either **production of angiogenic factors** or **loss of inhibitors**

Tumour Angiogenesis



Tumour Angiogenesis

Stimulates angiogenesis

Inhibits angiogenesis

VEGF
Basic Fibroblastic Growth Factor

Thrombospondin

Tumour Angiogenesis

- Neovascularization has a dual effect on tumour growth
- Perfusion supplies needed **nutrients and oxygen**
- The newly formed endothelial cells stimulate **growth of adjacent tumour cells** by secreting growth factors

Today's lecture topic included

- Molecular basis of cancer
- Proto oncogenes
- Oncogenes
- Tumour suppressor genes
- P53 gene
- Rb gene
- Hallmarks of cancer
- Tumour angiogenesis


THANK YOU