Mechanisms of carcinogenesis

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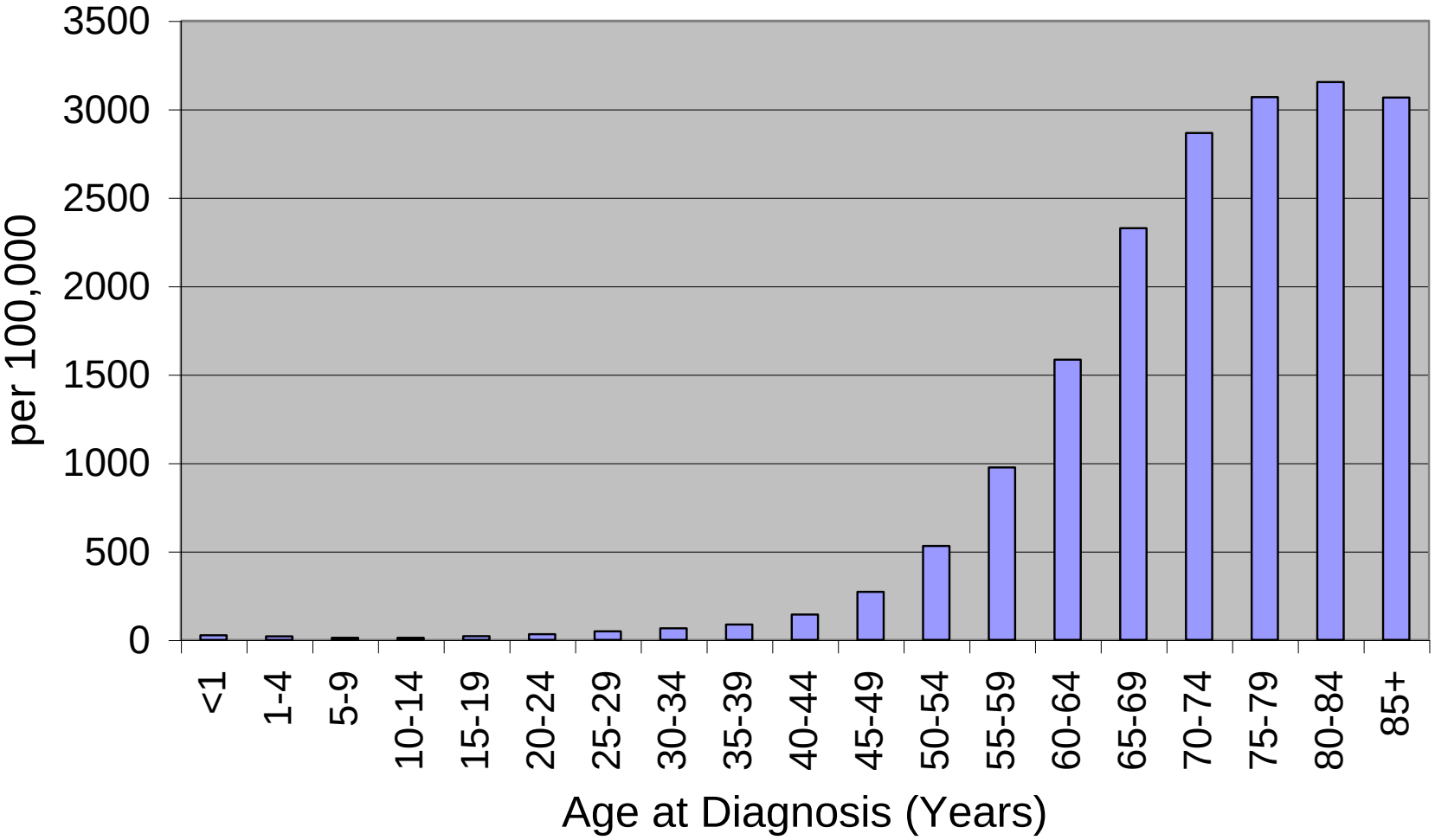
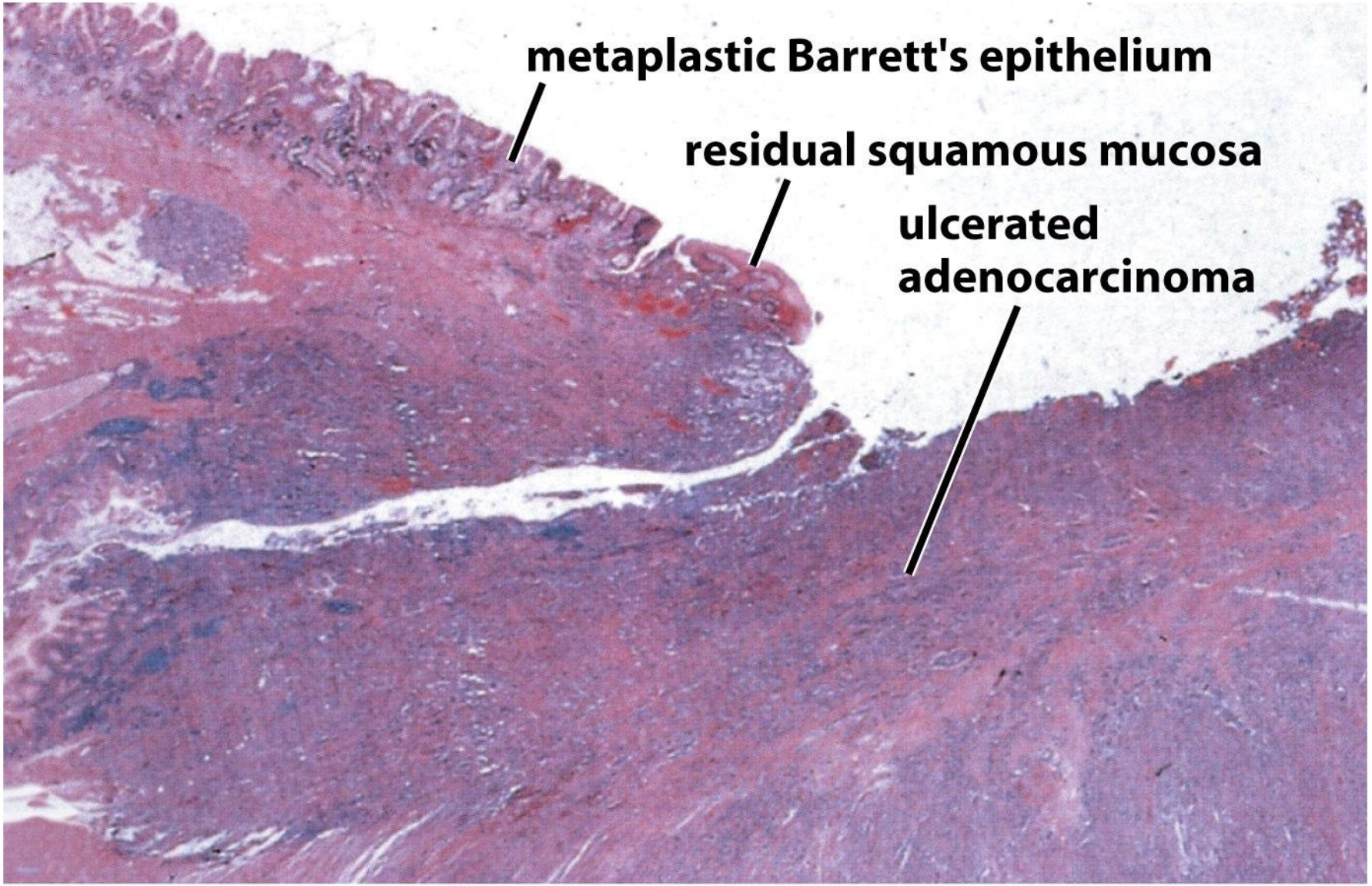
1. Cancer: basic facts

1. Cancer is a disease of old age



data from National Cancer Institute
http://www.cdc.gov/cancer/npcr/uscs/report/

2. Cancer seems to develop progressively

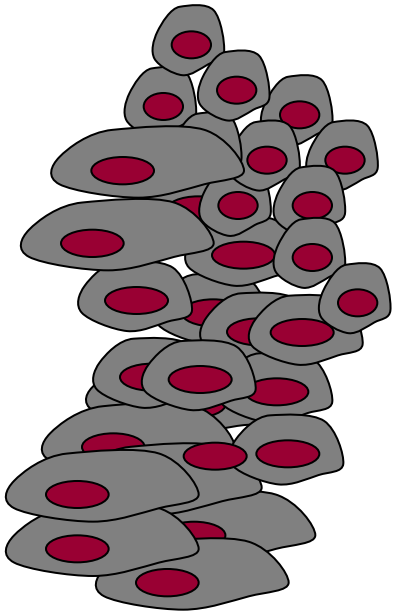


2. Cancer seems to develop progressively

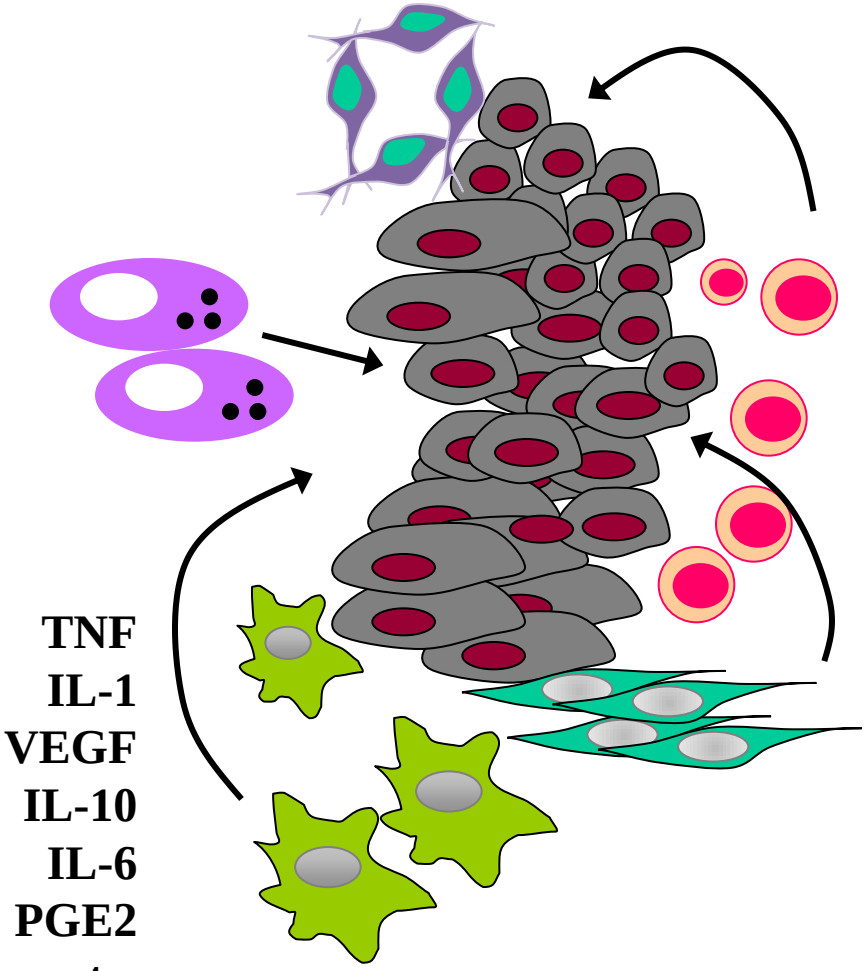
1. **Normal cells**
2. **Hyperplasia:** Excessive numbers of otherwise normal cells
3. **Dysplasia:** Cytologically abnormal cells (e.g. variability in nuclear size and shape; increased number of nucleoli; increased mitotic activity)
4. **Carcinoma in situ:** invasion to underlying tissue, e.g. connective tissue
5. **Metastatic melanoma**: invasion and colonization at distant sites.

3. A Tumor is not just a mass of malignant cells

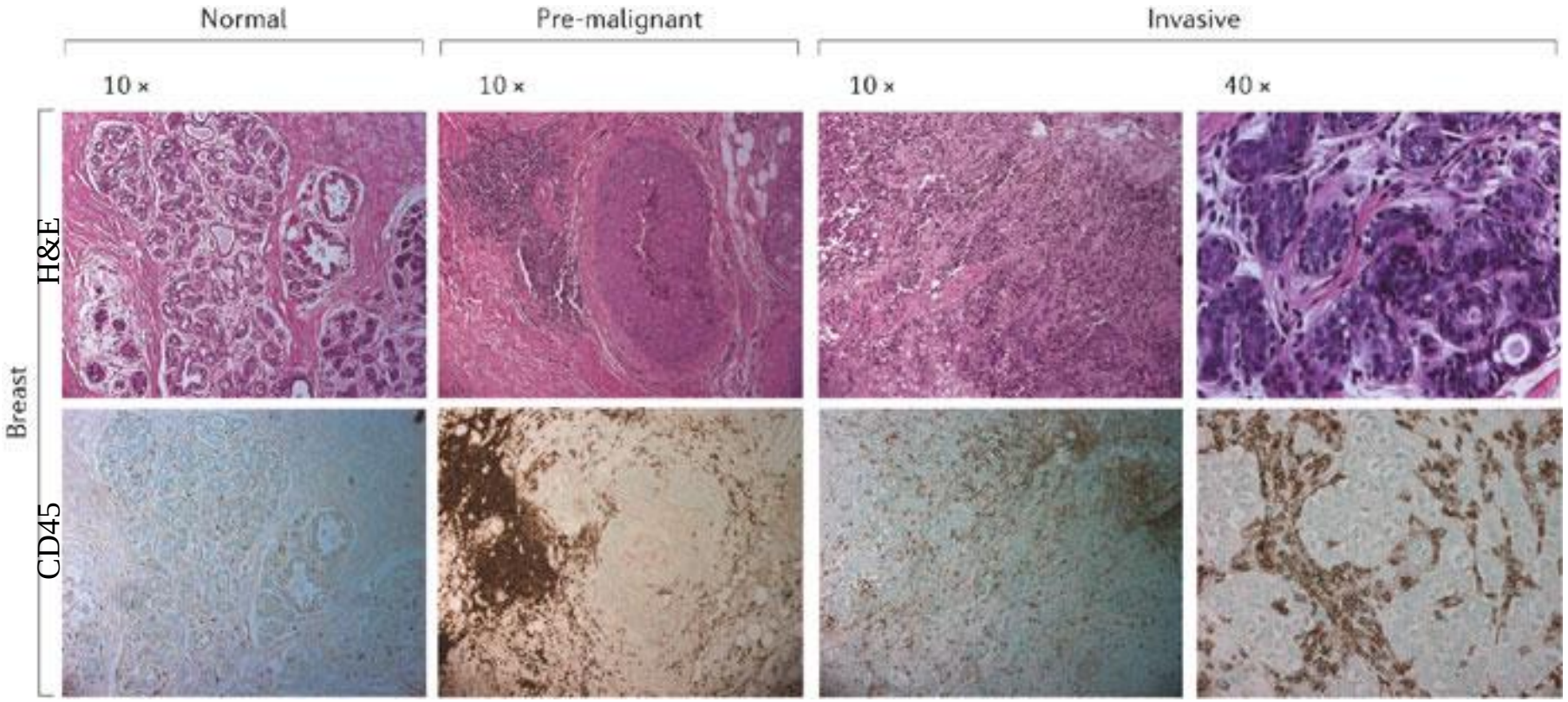
Tumor: the historic perspective



Tumor: current view



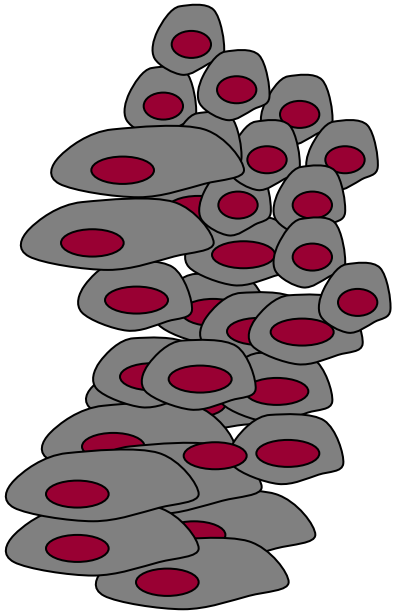
3. A Tumor is not just a mass of malignant cells



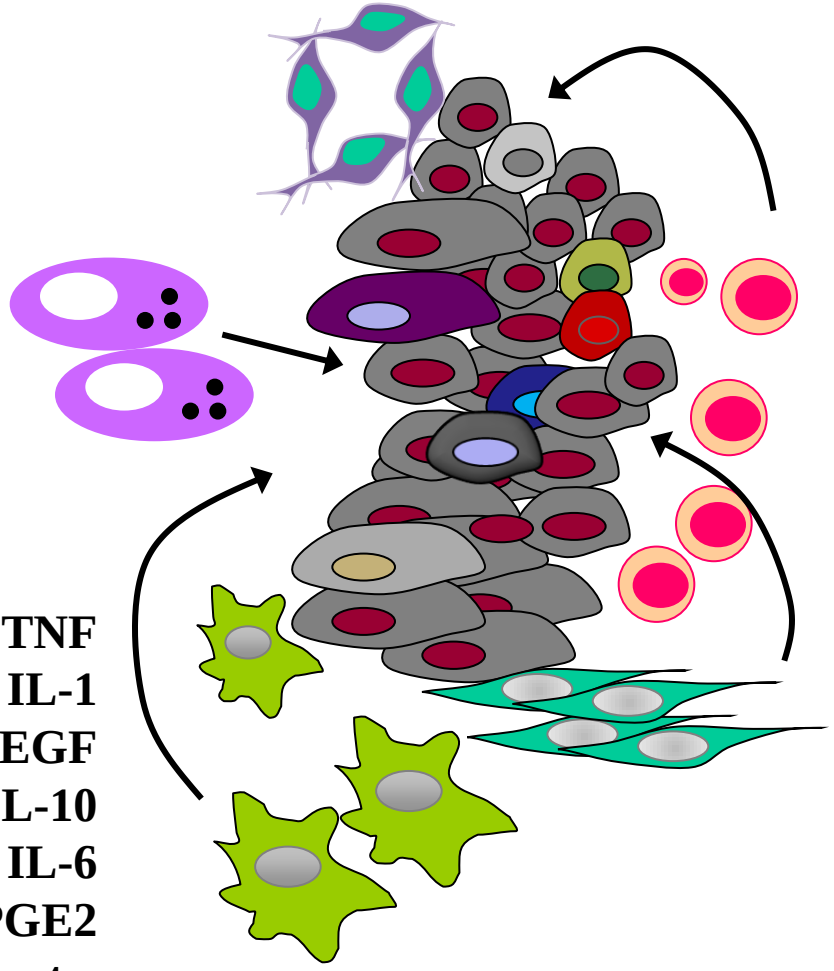
De Visser et al. Nat.Rev.Cancer 2006

4. Genetic heterogeneity of cancer cells

Tumor: the historic perspective

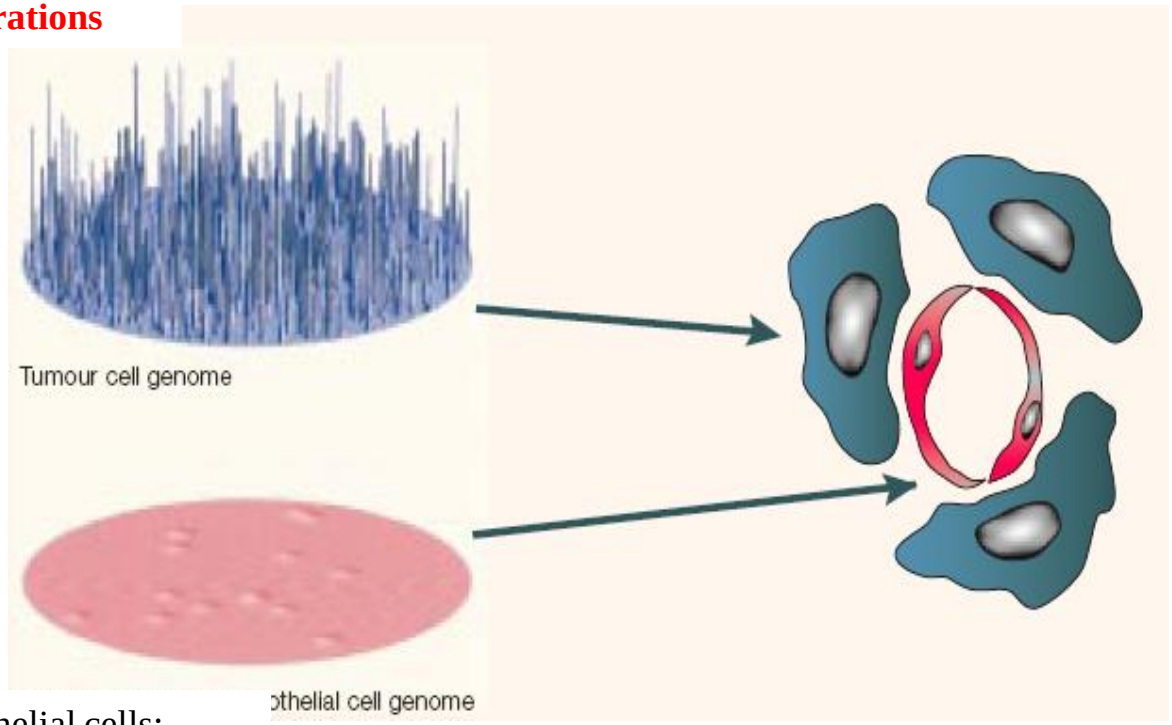


Tumor: current view



4. Genetic heterogeneity of cancer cells

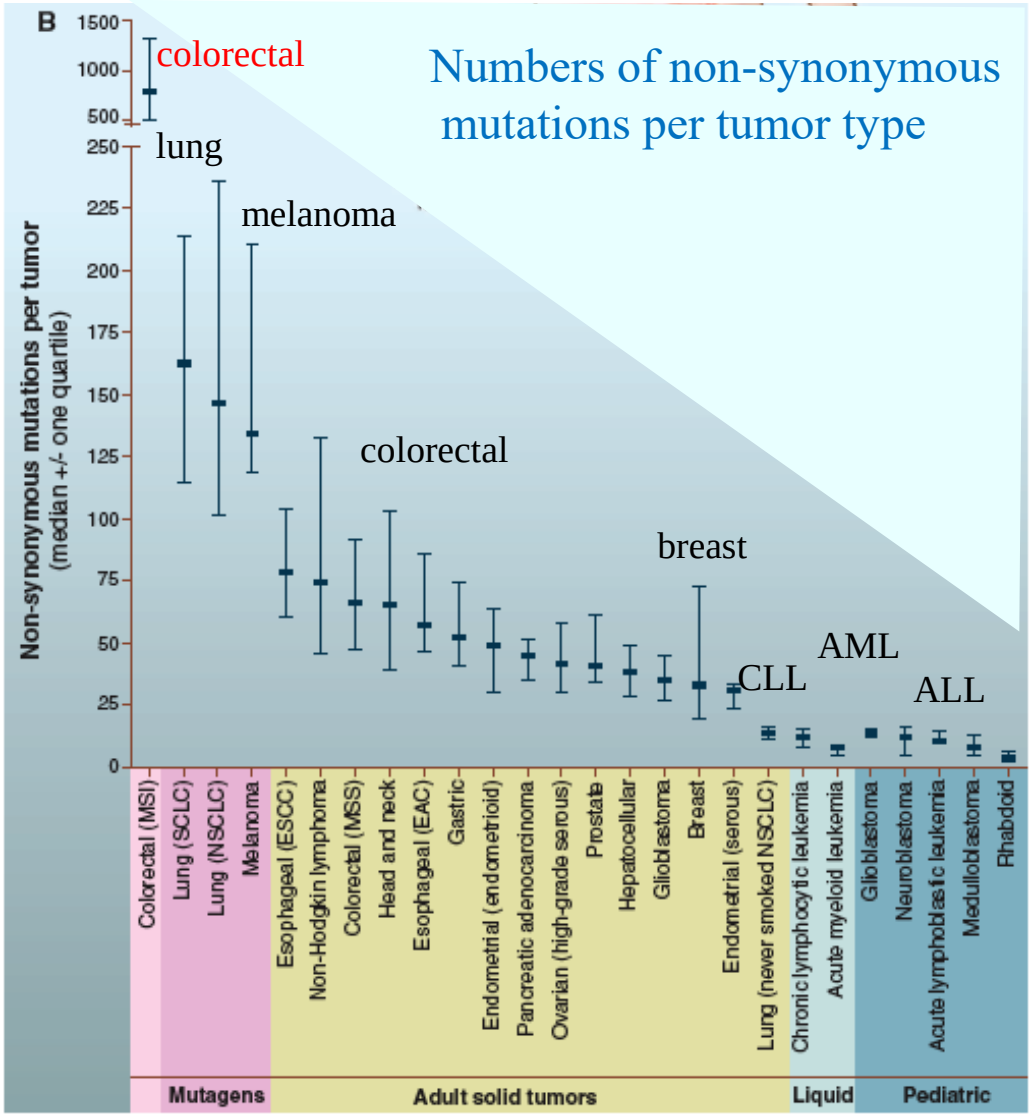
Colorectal tumor cells:
• heterogenous
• ~ **11,000 genomic alterations**



Tumor-associated endothelial cells:
• homogenous
• ~ 79 differences in gene expression

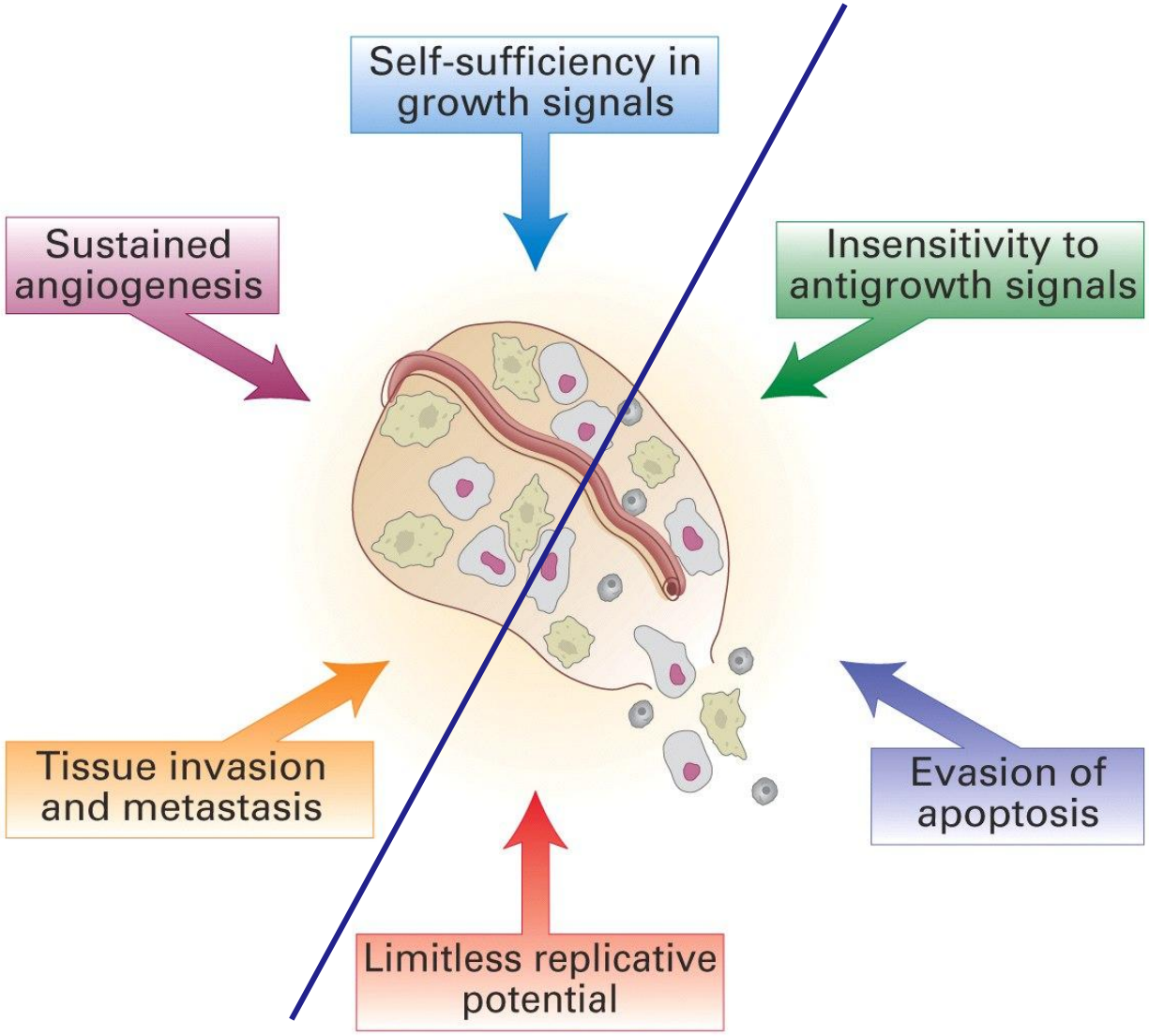
Folkman et al., Nature Rev. Cancer, 1: 76-78, 2000
Stoler et al., PNAS, 96: 15121- 15127,1999

4. Genetic heterogeneity of cancer cells



B Vogelstein et al. Science 2013;339:1546-1558

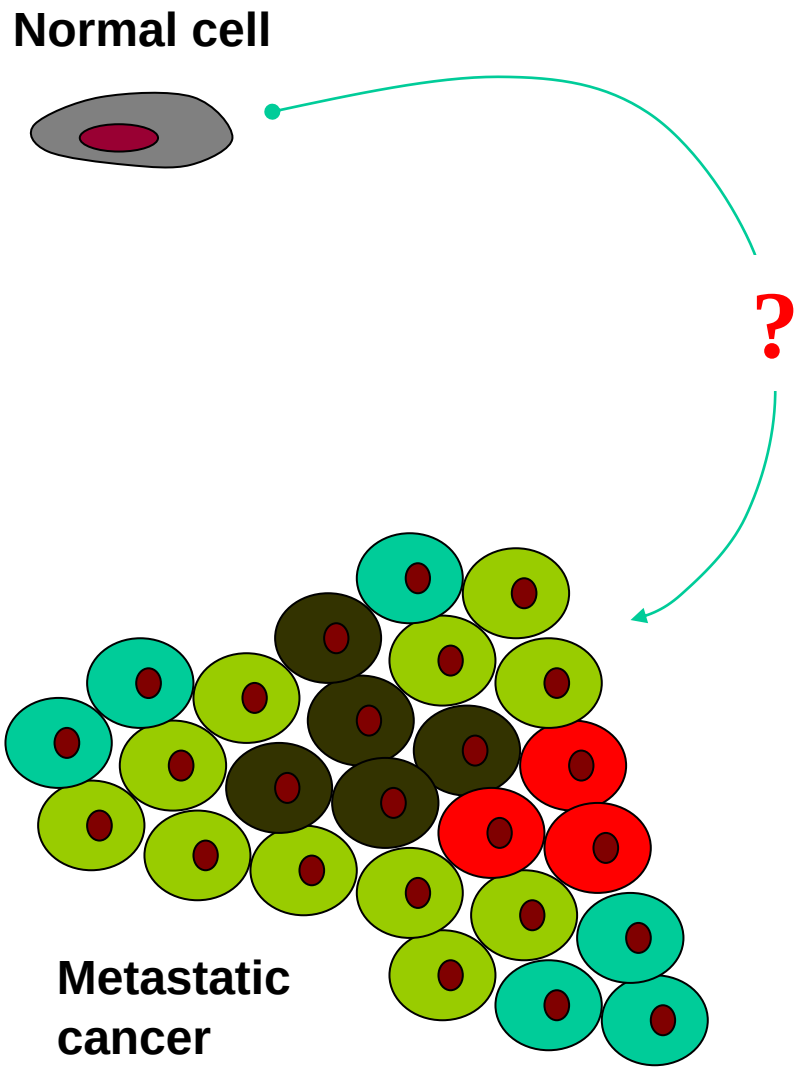
5. Common characteristics (hallmarks)



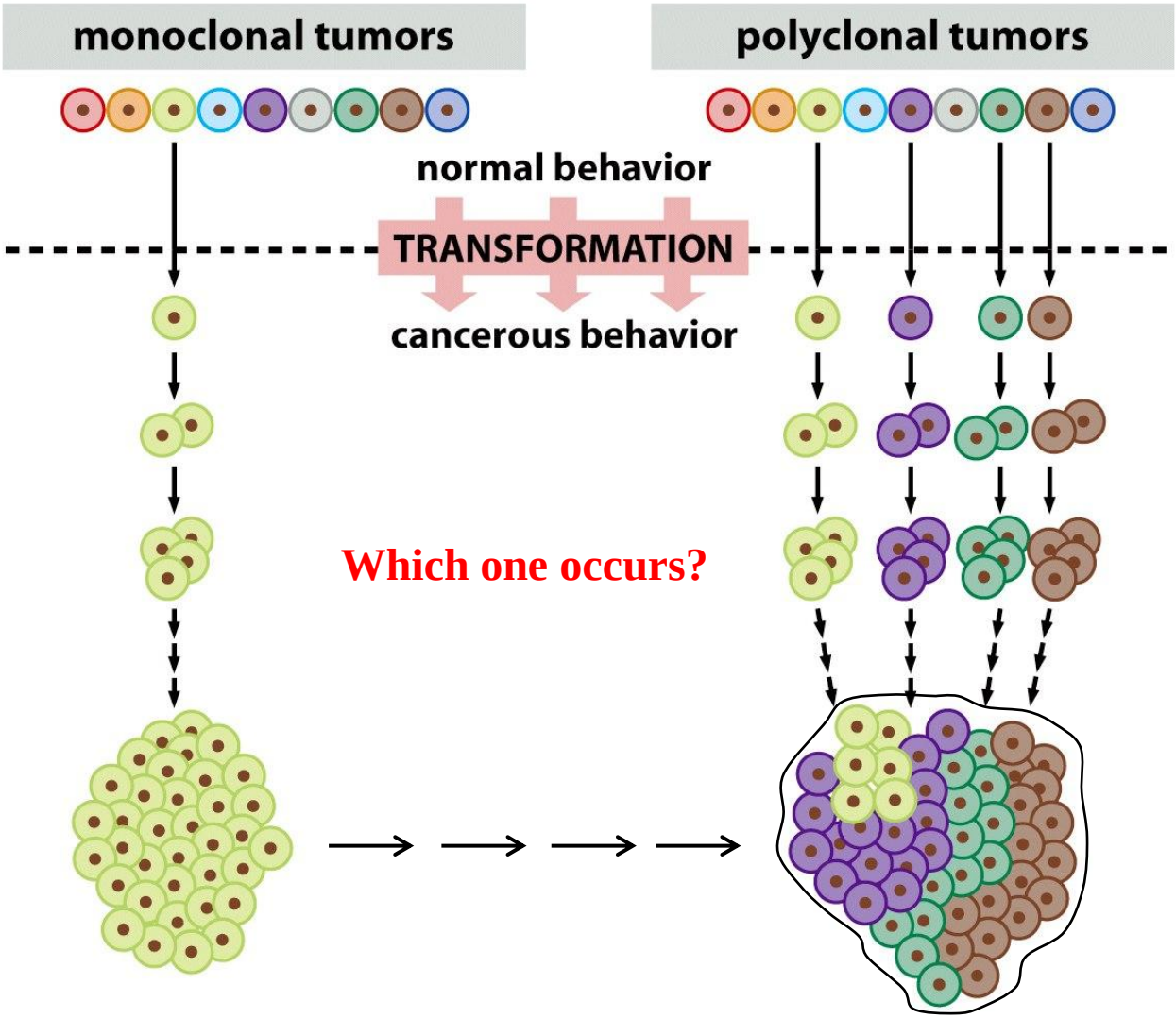
Synopsis 1

1. Cancer is a disease of old age
2. Cancer seems to develop progressively
3. Tumor microenvironment
4. Genetic heterogeneity of cancer cells
5. Common characteristics (Hallmarks)

2
Mechanism of Carcinogenesis: Initiation, promotion & progression


Normal cell
?
Metastatic
cancer

Cancer Arises from single or multiple cells?

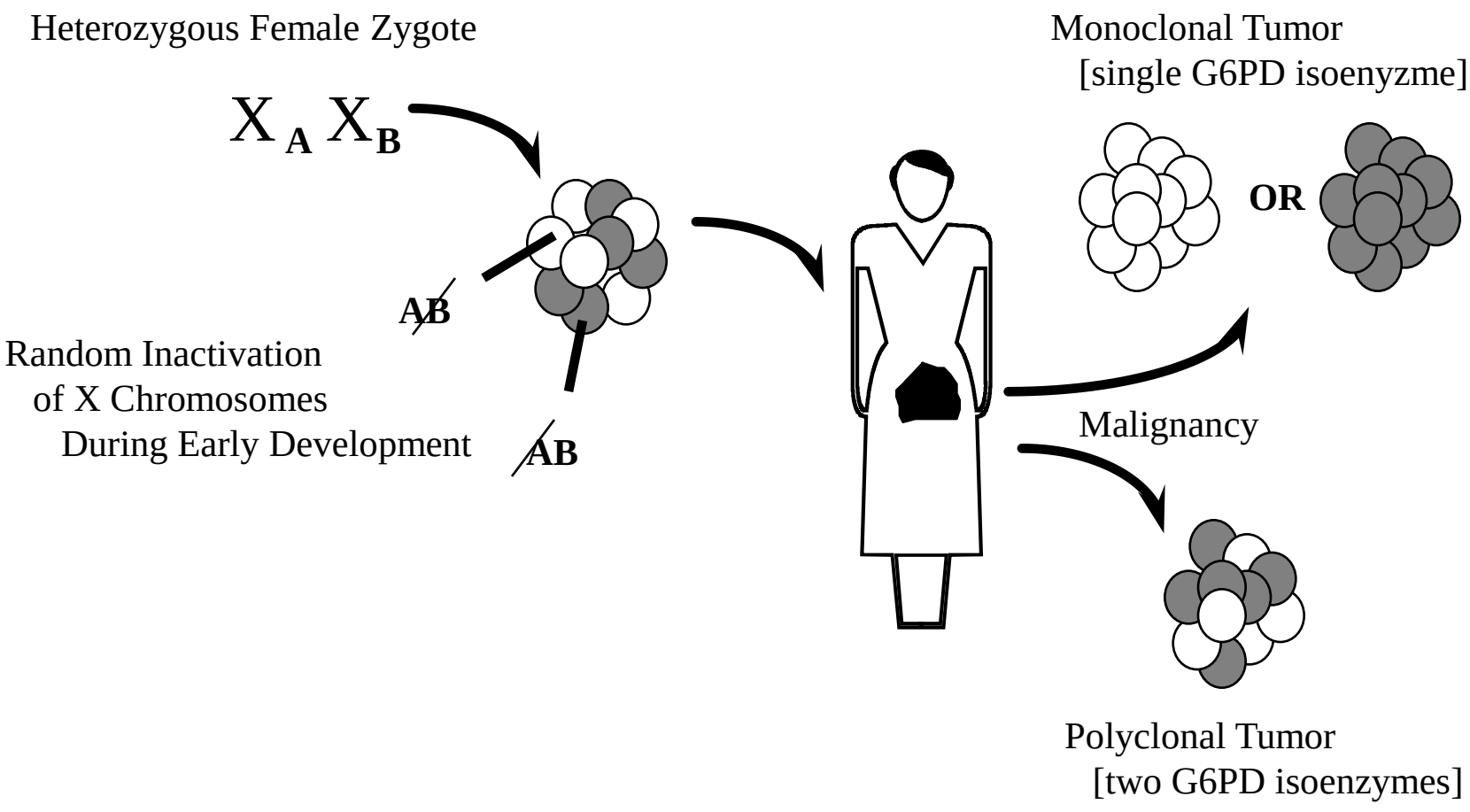


Cancer Arises from Single Cells

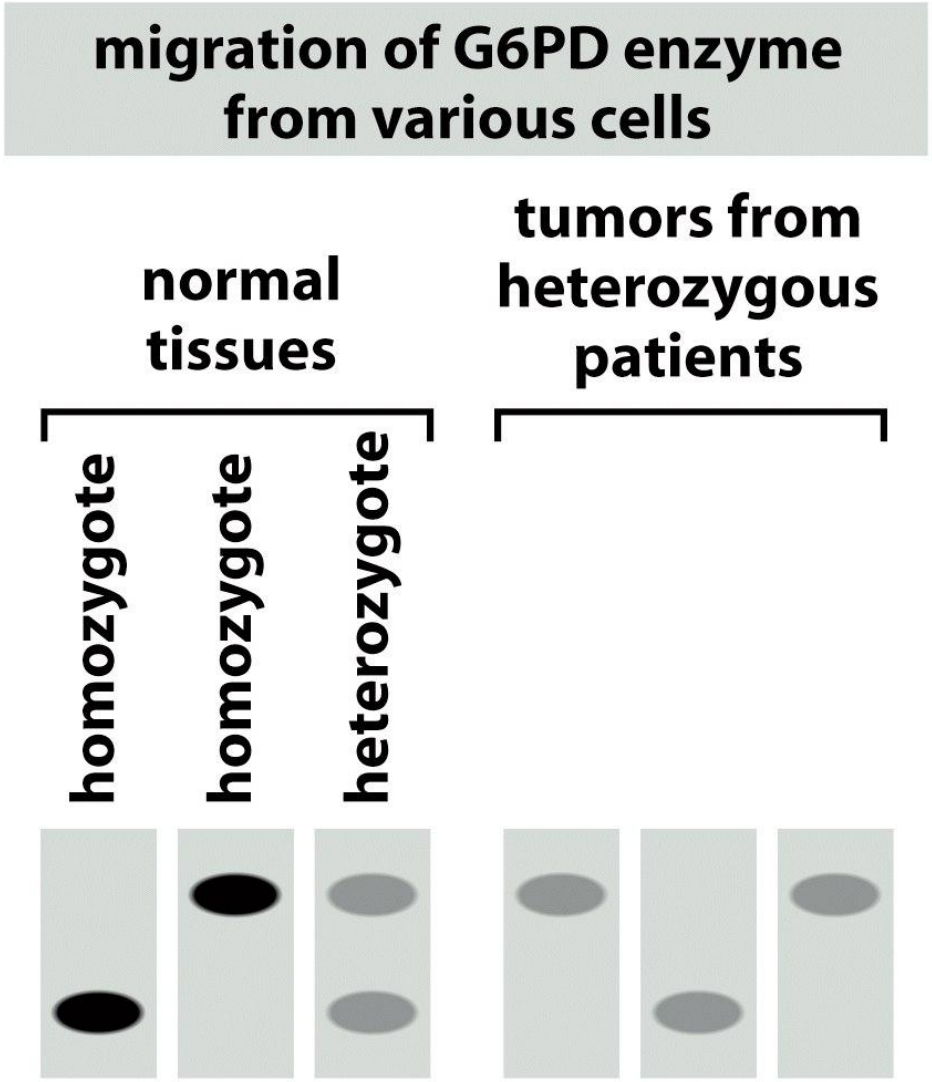
- Cancers are usually clonal in origin.

  [X-inactivation studies in human cancer]

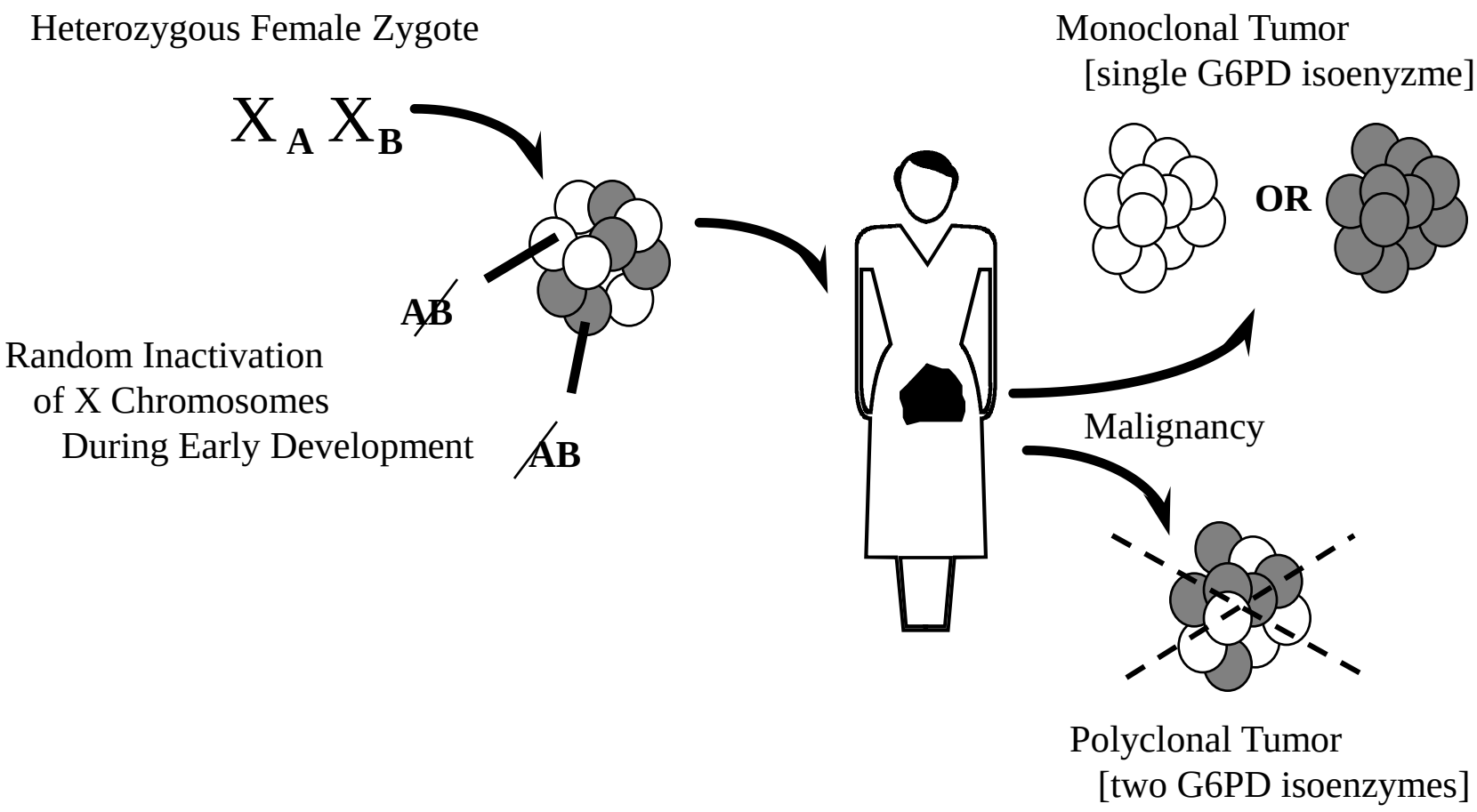
Tumor Clonality by X-Inactivation



Tumor Clonality by X-Inactivation



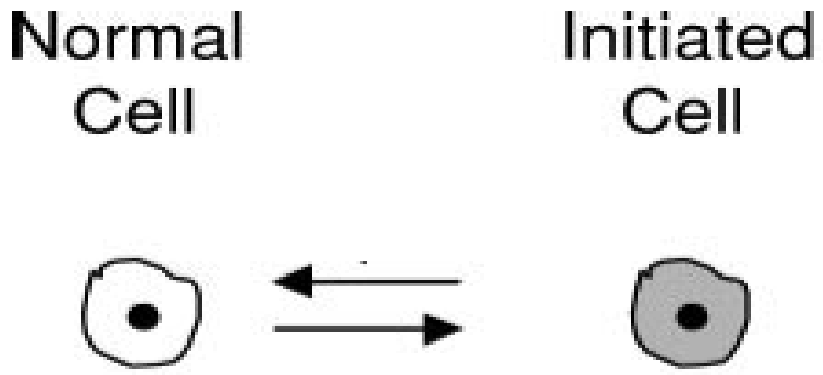
Tumor Clonality by X-Inactivation



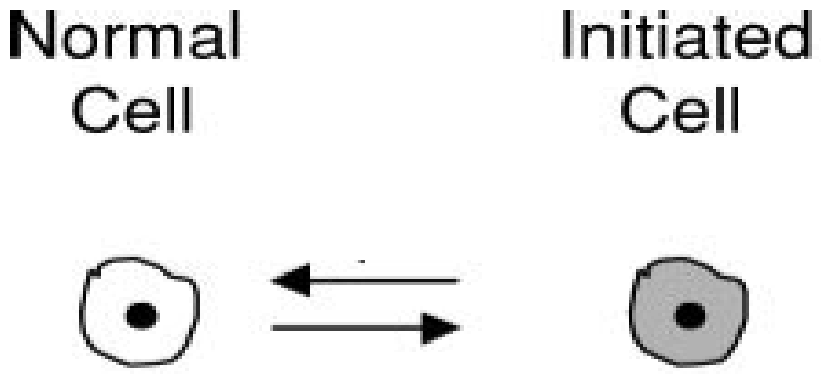
Clonality of Lymphoid Proliferation

Cell Type	Normal	Malignant
B Lymphocyte	Ig Light Chain Heterogeneity	Ig Kappa or Lambda Only
Plasma Cells	Heterogeneous Ig Electrophoresis	Monoclonal Ig Spike
T Lymphocyte	Heterogeneous Variable Regions	Homogeneous Variable Regions

Cancer Arises from Single Cells – **HOW??**



Cancer Arises from Single Cells – **HOW??**



1. Naturally occurring mutations because of faults during replication (mistakes will increase under conditions that cause replication stress).
2. Exogenous mutagens (radiation, diet, tobacco chemicals, etc.)

Mutational Targets

Loss of TGF function in colon cancer by defective Mismatch repair (MMR)

Hallmarks mostly affected: anti-growth signals

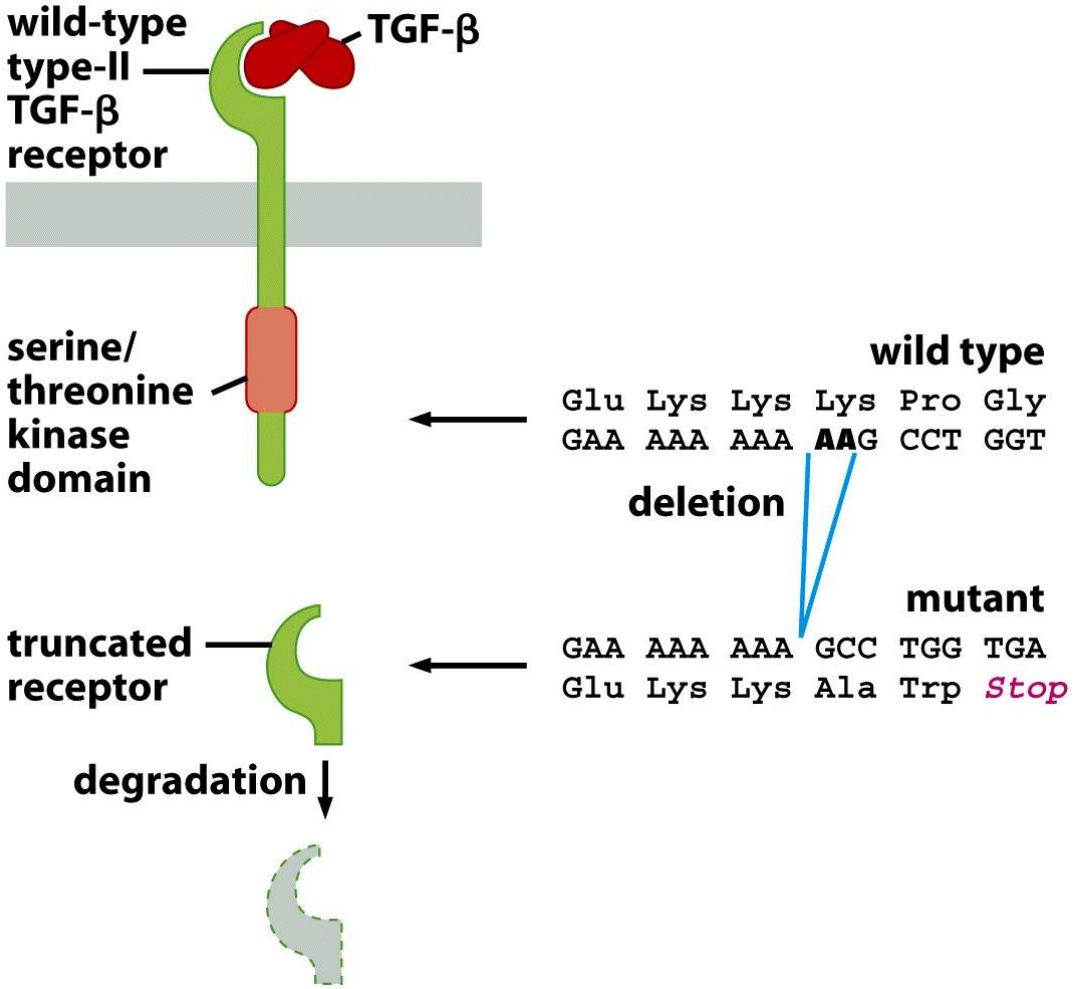
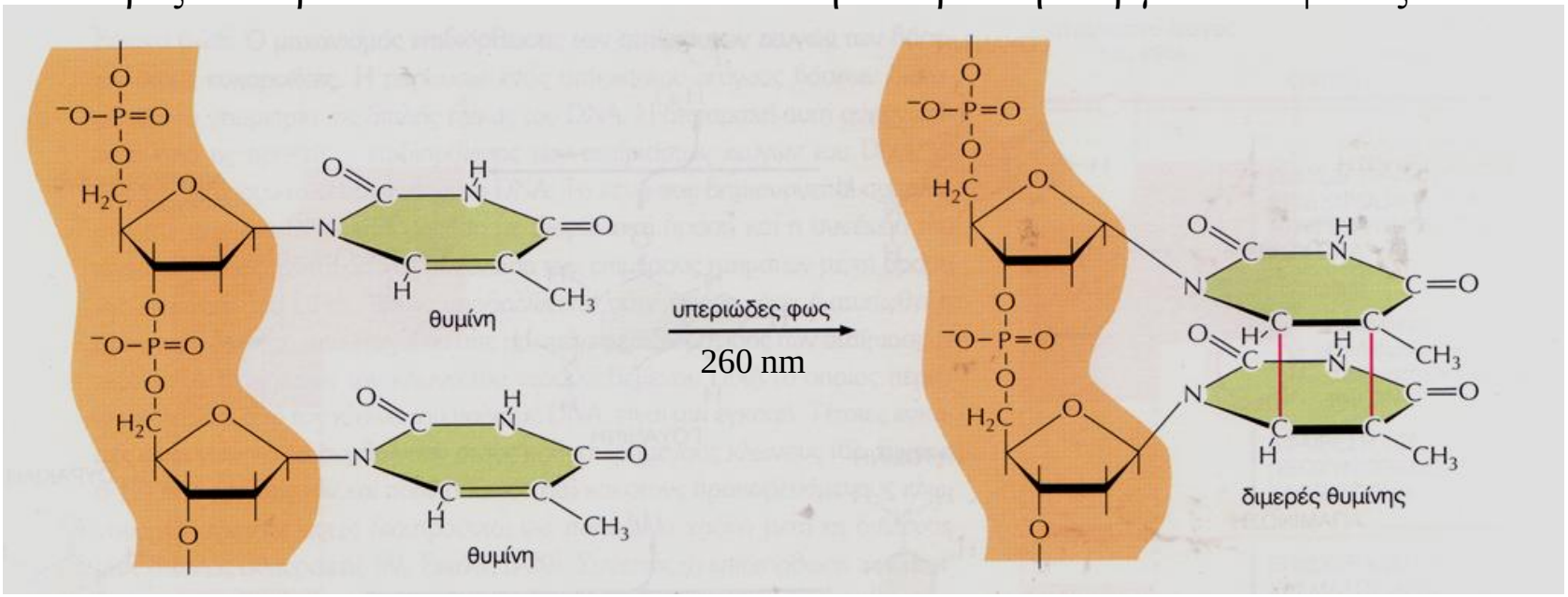


Figure 12.28 *The Biology of Cancer* (© Garland Science 2007)

Mutational Targets

The example of P53

Βλάβες που προκαλούνται στο DNA απο την υπεριώδη ενέργεια του φωτός



Mutational Targets

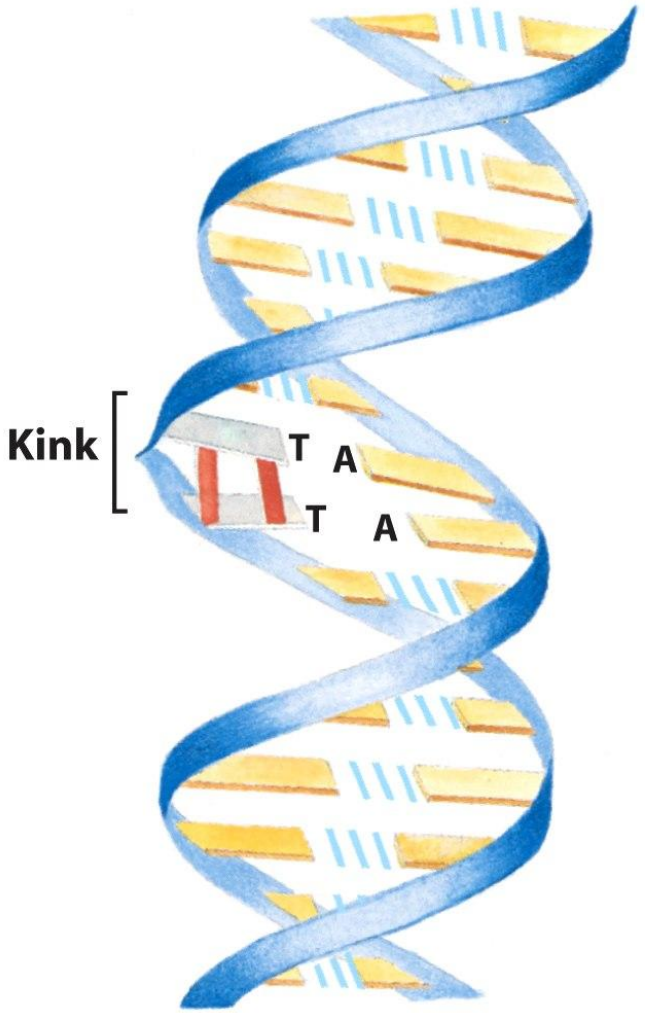
The example of P53:

- 50-100 τέτοιες διμερή θυμίνης δημιουρ-γούνται στο δέρμα κάθε δευτερόλεπτο έκθεσης στον ήλιο!

- Οι περισσότερες αναγνωρίζονται και διορθώνονται αμέσως.

- Αν δεν διορθωθούν, μπορεί να μεταπέσουν σε μόνιμη μετάλλαξη, συνήθως CC λόγω ταυτομέρειας (όπως στο P53)

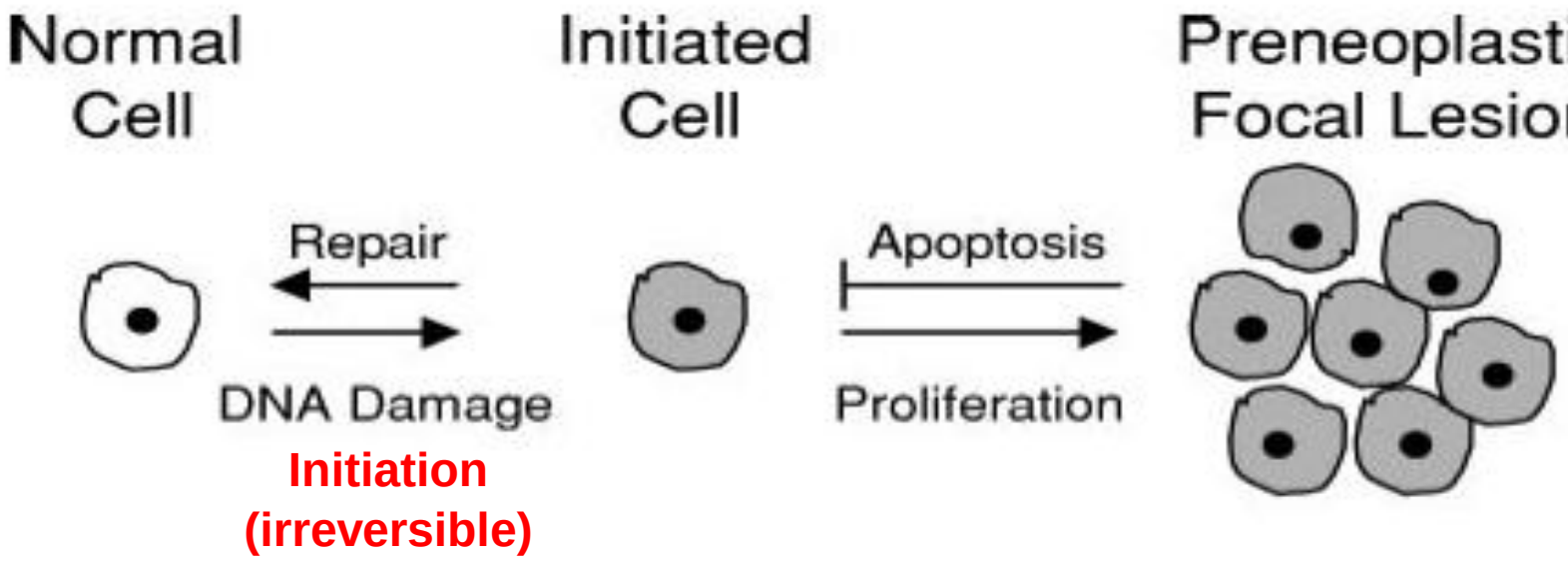
- Hallmarks mostly affected by p53 mutations: apoptosis, replicative potential

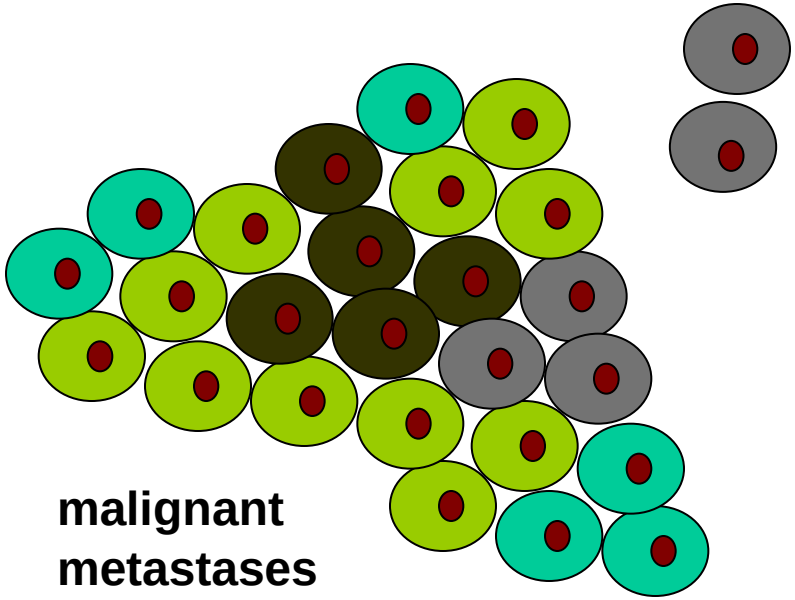


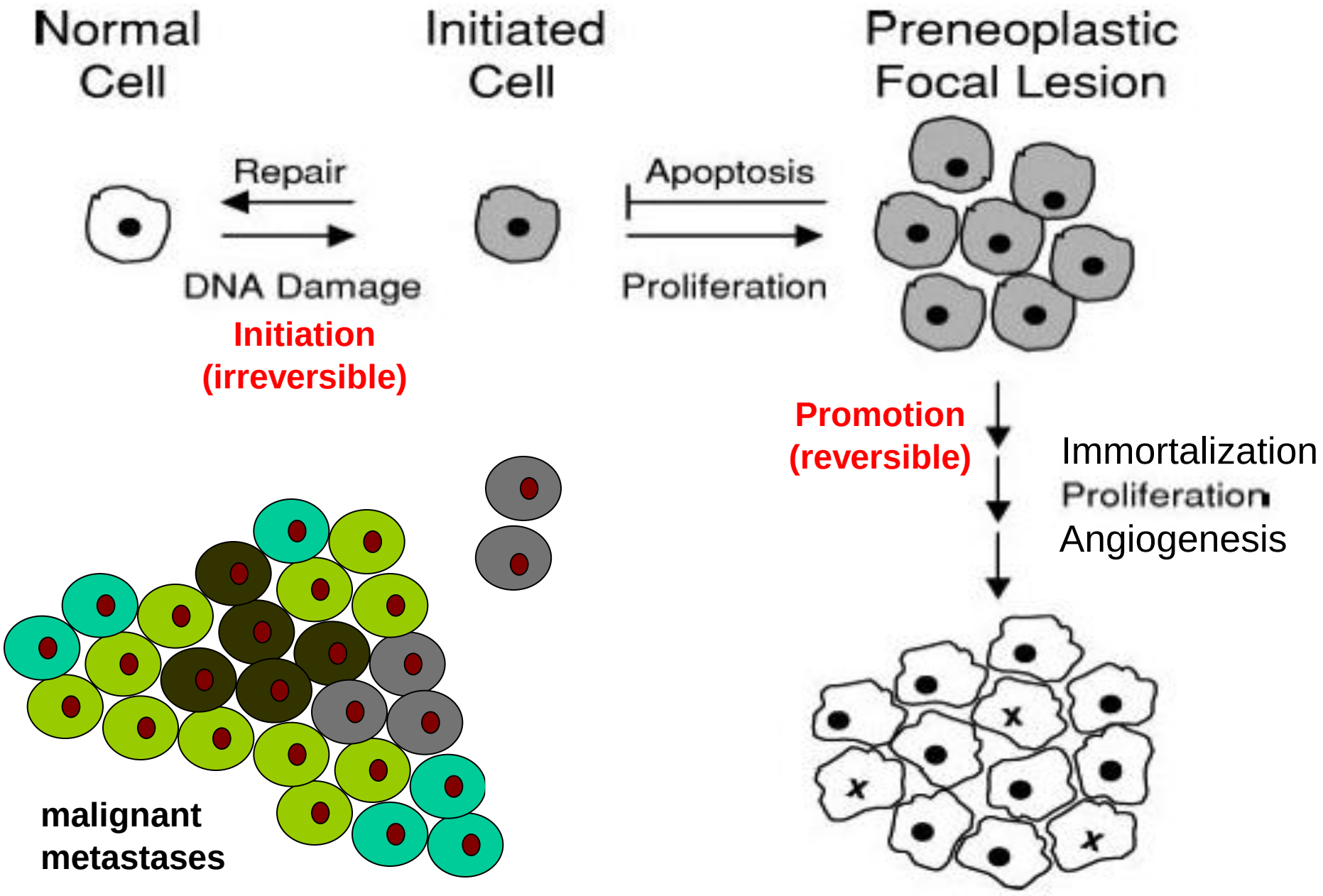
Mutational Targets

Cancer initiation via:

1. Mutational activation of oncogenic (proliferative) pathways (e.g. growth factor receptors and downstream signaling proteins, proteins involved in cell cycle checkpoints.
2. Mutational inactivation of apoptotic (cell death) pathways (e.g. growth inhibitory receptors, proteins involved in apoptosis, tumor suppressors).
3. Mutational inactivation of DNA repair mechanisms (e.g. BER, NER, etc).
4. Mutational inactivation of antioxidant response (e.g. SOD).

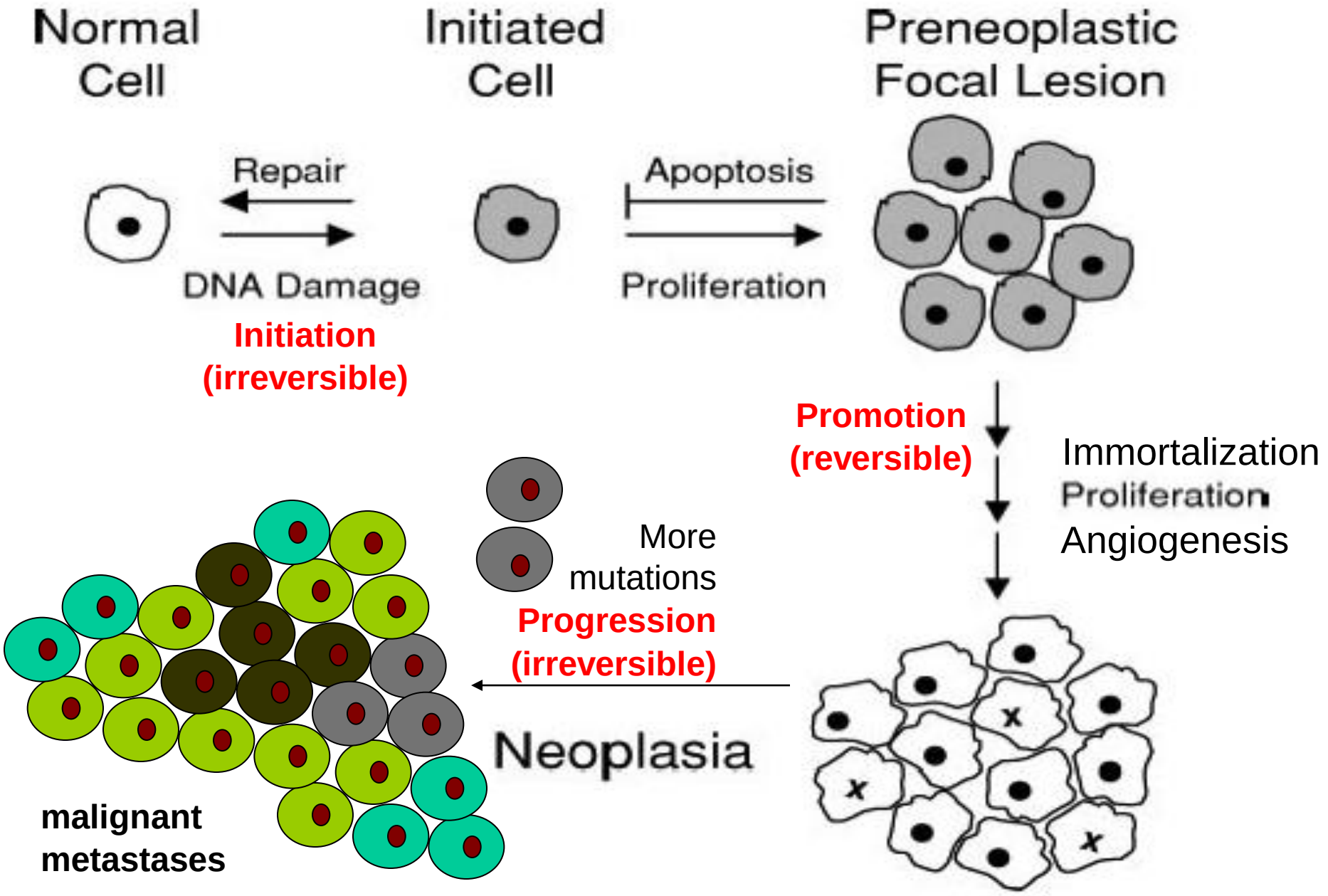

Normal Cell
Initiated Cell
Preneoplastic Focal Lesion
Repair
DNA Damage
Apoptosis
Proliferation
Initiation (irreversible)


malignant metastases


Normal Cell
Initiated Cell
Preneoplastic Focal Lesion
Repair
DNA Damage
Initiation (irreversible)
Apoptosis
Proliferation
Promotion (reversible)
Immortalization
Proliferation
Angiogenesis
malignant metastases

Promoters

1. Reactive Oxygen Species (ROS) and redox active xenobiotics and metals
2. Phorbol esters (e.g. TPA)
3. Polycyclic aromatic compounds (e.g. Dioxin)
4. Peroxisome Proliferators (oxidized fats)
5. Endocrine Disruptors (estradiol)
6. **Chronic inflammation** (e.g. Colitis, pancreatitis, etc.)


Normal Cell
Initiated Cell
Preneoplastic Focal Lesion
Repair
DNA Damage
Initiation (irreversible)
Apoptosis
Proliferation
Promotion (reversible)
Immortalization
Proliferation
Angiogenesis
More mutations
Progression (irreversible)
Neoplasia
malignant metastases

Three strikes to Cancer

Initiation: Mutation in one or more cellular genes controlling key regulatory pathways of the cell (irreversible).

Promotion: selective growth enhancement induced in the initiated cell and its progeny by the continuous exposure to a promoting agent.

Progression: results from continuing evolution of unstable chromosomes; further mutations from genetic instability during promotion—results in further degrees of independence, invasiveness, metastasis, etc.

Colon tumor progression: Vogelstein, Fearon et al.
(Science 1989)

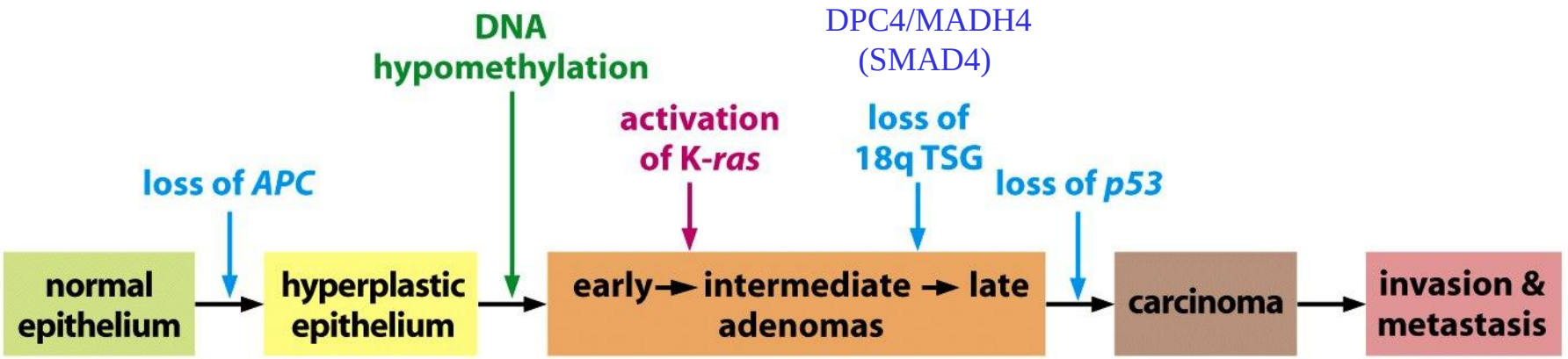
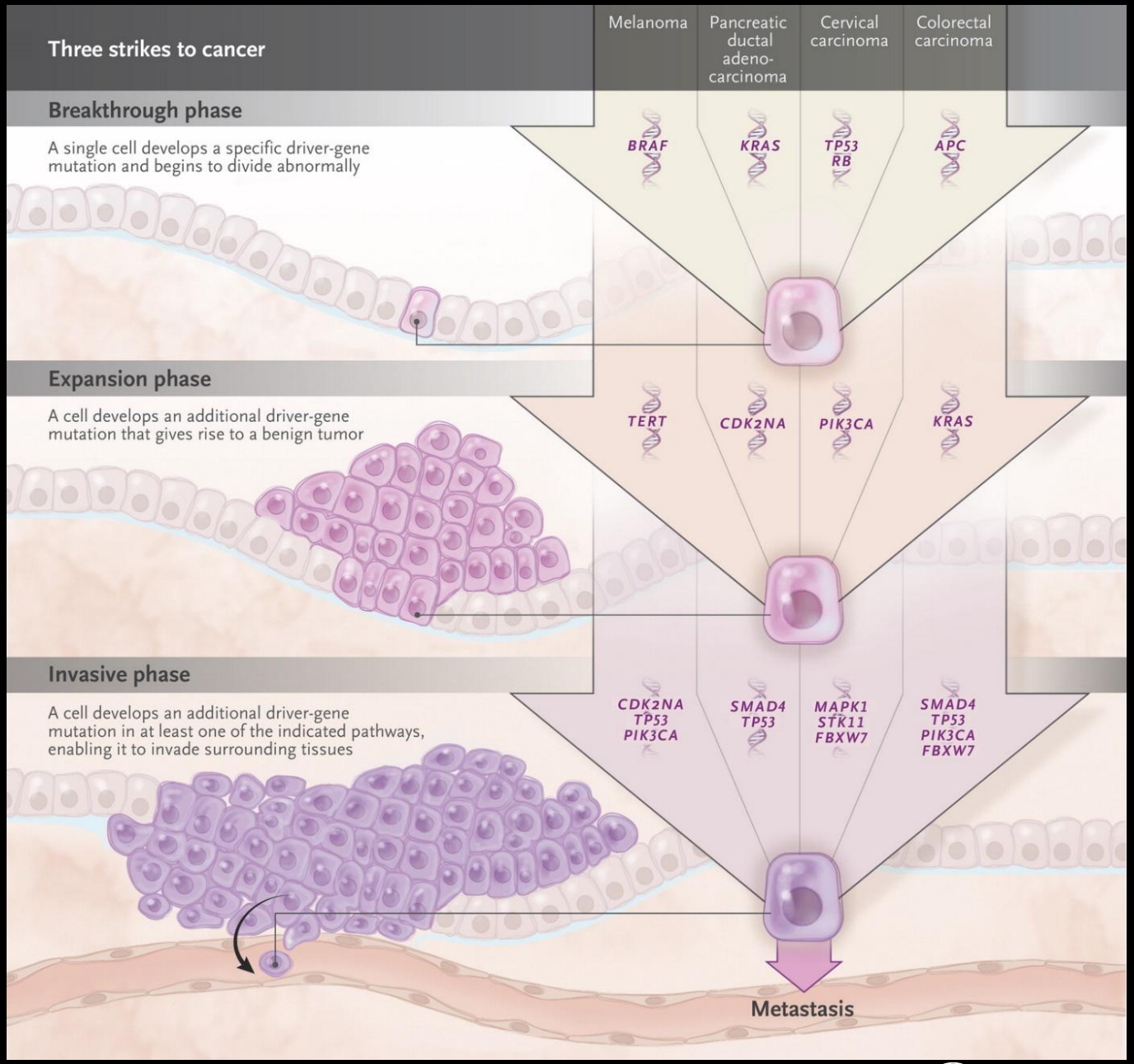


Figure 11.10 *The Biology of Cancer* (© Garland Science 2007)

Three Strikes to Cancer.



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Cancer Evolution

Growth signal self sufficiency

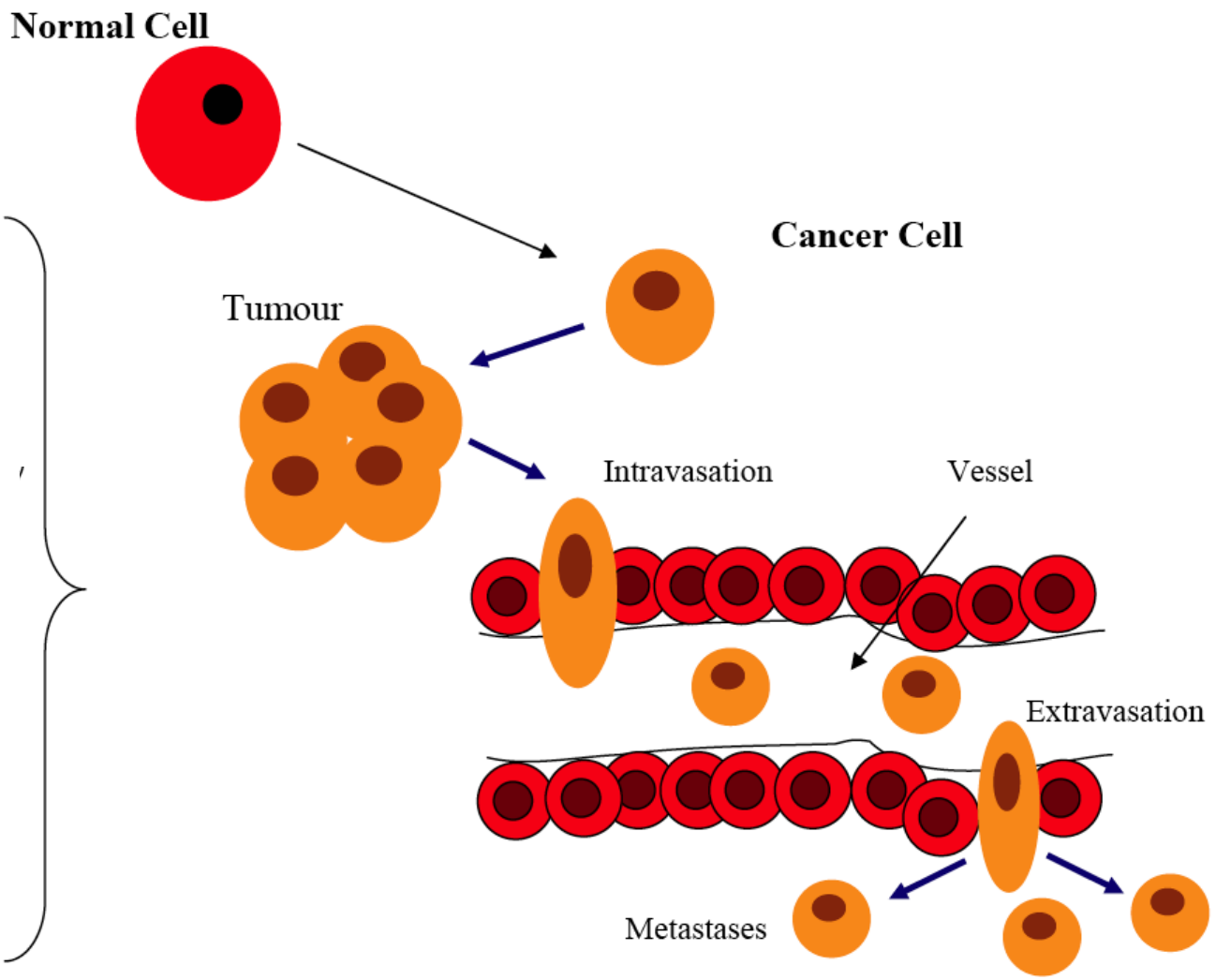
Insensitive to anti-growth signals

Ability to evade apoptosis

Potential to infinitely replicate

Angiogenic capability

Ability to invade tissues and metastasis



Synopsis 2

1. Ο καρκίνος είναι μια μικρο-εξελικτική διαδικασία μετασχηματισμού ενός φυσιολογικού κυττάρου σε μια κοινότητα κυττάρων που αυξάνει ανεξέλεγκτα.
2. Πολυσταδιακή διαδικασία: έναρξη, προαγωγή, εξέλιξη.
3. Κάθε στάδιο προκαλείται από μεταλλαγές που προσδίδουν στο κύτταρο πλεονεκτήματα επιβίωσης.
4. Οι μεταλλαγές προκαλούνται από φυσικά λάθη του συστήματος αντιγραφής-επιδιόρθωσης (συνεπικουρούμενων μικρο-περιβαλλοντικών παραγόντων), ή από εξωγενείς περιβαλλοντικούς παράγοντες.
5. Μεταλλαγές επιτρέπουν σε ορισμένα γονίδια να αποκτήσουν νέες ή αυξημένες λειτουργίες (ογκογονίδια) ενώ μπορεί να καταστείλουν τις φυσιολογικές λειτουργίες άλλων (ογκο-κατασταλτικά γονίδια).
6. Στα τελικά στάδια της ογκογένεσης, τα κύτταρα χάνουν παντελώς τους ρυθμιστικούς μηχανισμούς ελέγχου της αντιγραφής και επιδιόρθωσης και αποκτούν εξαιρετικά ασταθή γονιδιώματα (γενετική ετερογένεια).