Neoplasia

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Robbins and Cotran Chapter 7

pp. 269-339

Definitions

- **Neoplasia** - new growth
  - Abnormal mass of tissue with growth that exceeds and is uncoordinated with that of the surrounding normal tissues; autonomous
- **Tumor** - synonymous with neoplasm
- **Cancer** - common term for malignant neoplasm
- Neoplasms have **parenchyma** and **stroma**
- Benign and malignant tumors each have their own nomenclature

Benign tumors

- Based on parenchymal component
- Mesenchymal tumors add **-oma** to cell of origin
  - Fibroblasts = fibroma
  - Cartilage = chondroma
  - Osteoblasts = osteoma
- Epithelial tumors can be named for cell of origin, microscopic architecture, or macroscopic appearance
  - **Adenoma** = glandular appearance OR from glandular tissue

Malignant tumors

- Mesenchymal tumors usually called **sarcomas**
  - Fibrosarcoma, liposarcoma, leiomyosarcoma, rhabdomyosarcoma
- Epithelial tumors usually called **carcinomas**
  - Adenocarcinoma = glandular growth pattern
  - Squamous cell carcinoma = squamous pattern
  - Can either be named for organ of origin, or "poorly differentiated" or "undifferentiated"
- **Many exceptions**

Liver tumors

- Focal nodular hyperplasia - spontaneous
- Nodular regenerative hyperplasia - portal hypertension
- Hemangiomas - benign blood vessel tumors
- Liver cell adenomas - rarely become malignant
- Hepatocellular carcinoma (HCC) - common
- Cholangiocarcinoma - much less common

Biology of tumor growth

1) Malignant change in target cell (transformation)
2) Growth of the transformed cells
3) Local invasion
4) Distant metastases

- Generally, morphologic criteria can be used to distinguish benign and malignant tumors, but not always

Differentiation and anaplasia

- Differentiation = extent to which neoplastic cells resemble normal cells
- Anaplasia = lack of differentiation
  - Hallmark of transformation
  - But cancer is not "reverse differentiation"
- In general, benign tumors are well differentiated
- Malignant tumors range from well differentiated to undifferentiated

Features of anaplasia

- Pleomorphism
- Abnormal cell morphology (atypia)
- Abundant and/or atypical mitoses
- Loss of polarity
- Dysplasia = "disordered growth"
  - In epithelia, represents a state between hyperplasia and carcinoma in situ (preinvasive neoplasia)
  - Does not necessarily progress to cancer

Rates of tumor cell growth

- From 1 transformed cell to smallest clinically detectable mass (1 gm) of 10^9 cells = 30 doublings
- To reach 10^{12} cells (1 kg) requires only 10 additional doublings
  - Doubling time of tumor cells
  - Fraction of tumor cells replicating
  - Rate at which cells are shed/lost
- Total cell cell-cycle time is typically normal

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Source: Figure 7-12 in [RC]
Kumar, V., A. K. Abbas, and N. Fausto. *Robbins and Cotran Pathologic Basis of Disease*, 7th ed. Philadelphia PA: Elsevier, 2005. ISBN: 0721601871.

Local invasion and metastasis

- Growth of cancer is usually accompanied by progressive infiltration, invasion, and destruction of surrounding tissue
- Next to metastasis, invasiveness is the most reliable feature that distinguishes malignant tumors from benign tumors
- Metastasis (tumor mass discontinuous with the primary tumor) unequivocally marks a tumor as malignant

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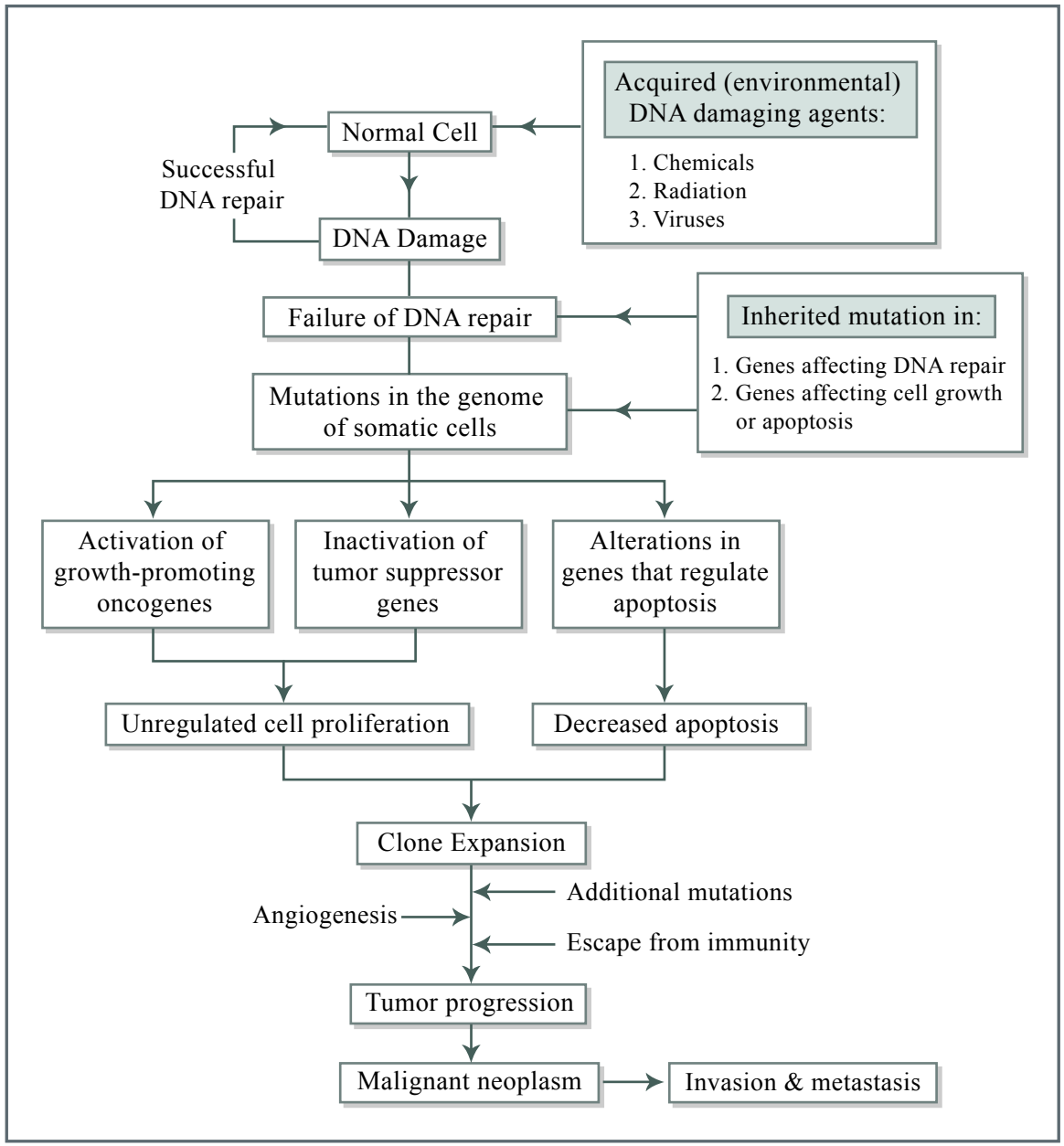
Source: Figure 7-22 in [RC]

Molecular basis of cancer

- Nonlethal genetic damage
- Clonal expansion of a precursor cell
- Main classes of genes involved
    1) Oncogenes
    2) Tumor suppressor genes
    3) Genes regulating apoptosis
    4) DNA repair genes
- Carcinogenesis is a multistep process



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Source: Figure 7-31 in [RC]

Oncogenes

- First recognized in acute transforming retroviruses (v-*onc*)
- Most known oncogenes do not have viral counterparts
- Function as growth factors, receptors, signal transducers, transcription factors, and cell-cycle components
- Have similar functions as protooncogenes, but lack regulation/are constitutive

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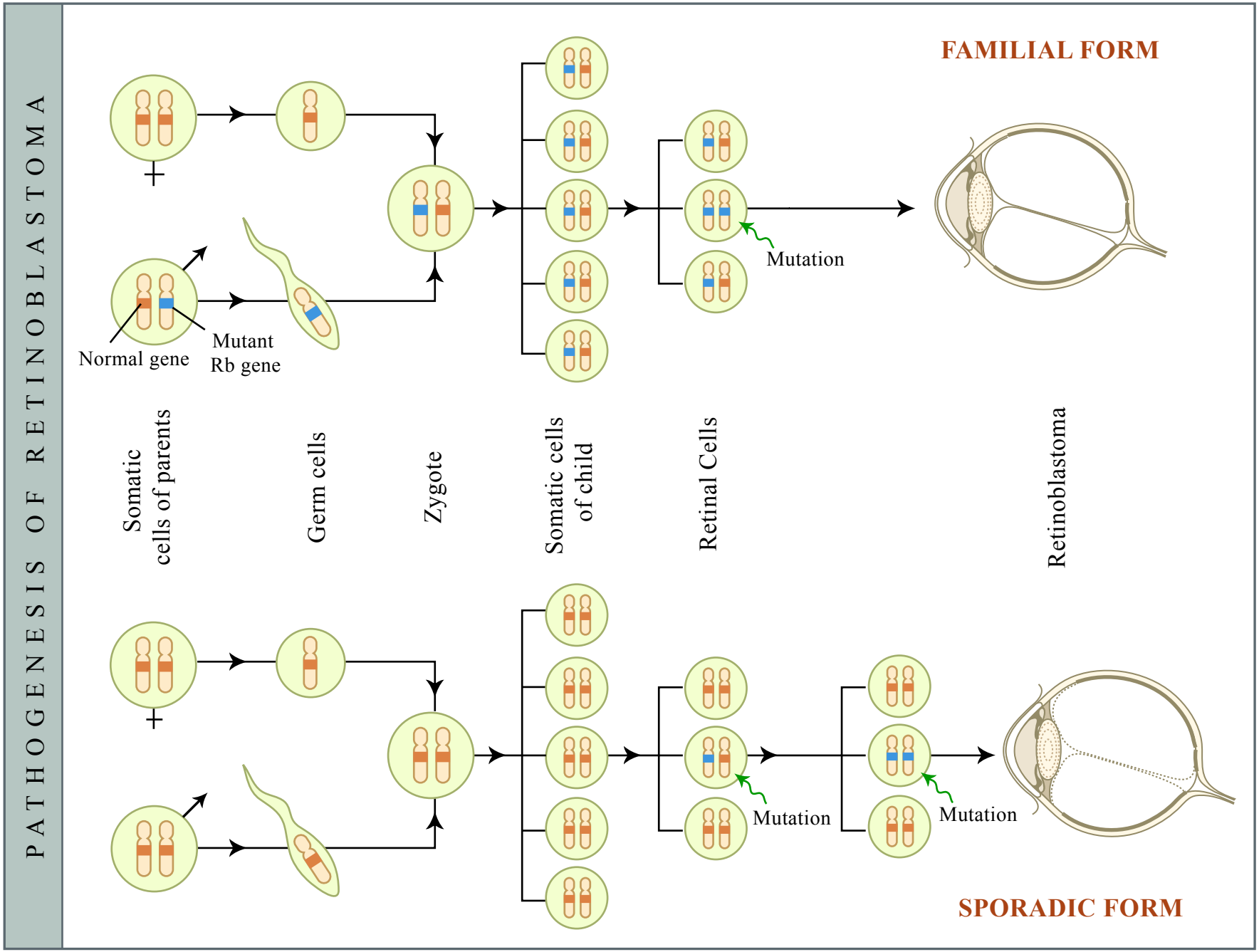
Source: Figure 7-32 in [RC]

RAS oncogene

- 15-20% of all human cancers have a RAS mutation
- Normally, RAS is activated by receptors to exchange GDP for GTP
- Activated RAS returns to ground state by its intrinsic GTPase activity
- GTPase activating proteins (GAPs) augment this process
- Mutant forms of RAS bind GAP but their GTPase activity is not augmented

Tumor suppressor genes

- Normally serve to inhibit cell proliferation
- First recognized in retinoblastoma, rare pediatric tumor of the eye
- RB tumor suppressor gene is a nuclear phosphoprotein that regulates cell cycle
  - Active, hypophosphorylated state in non-dividing cells
  - Inactive, hyperphosphorylated in G_1/S transition
- Many cancers have mutations in the RB pathway (i.e. INK4a, Cyclin D, CDK4)



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Metastasis

- Invasion of ECM
  - Detachment from cells
  - Attachment to ECM
  - Degradation of ECM
  - Migration of tumor cells
- Vascular dissemination
  - Adhesion molecules
  - Chemokines

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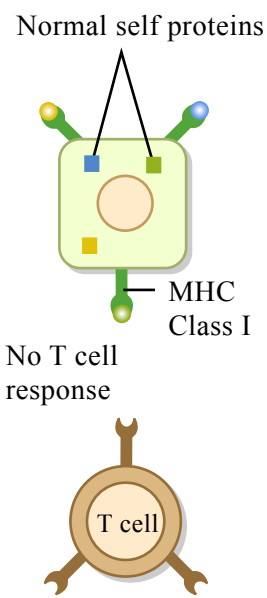
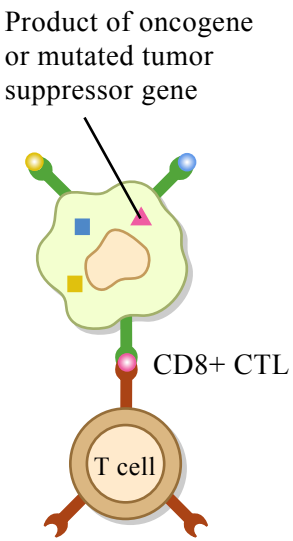
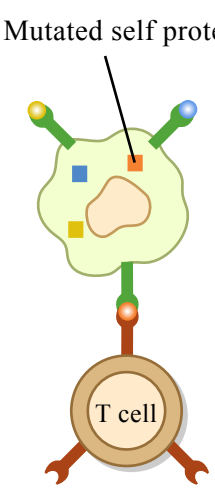
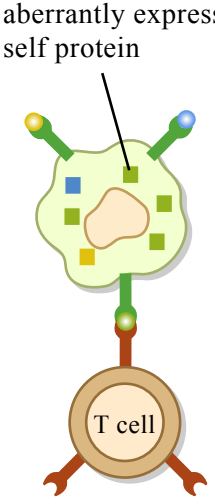
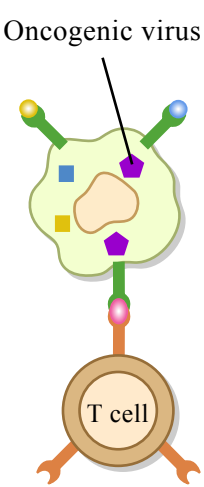
Source: Figure 7-42 in [RC]

Tumor immunity

- Immune surveillance
  - Cancer immunoediting
- Tumor-specific antigens
- Tumor-associated antigens
- Anti-tumor effector mechanisms
  - CTL
  - NK cell
  - Macrophages
  - Antibodies

Normal host cell displaying multiple MHC-associated self antigens	Tumor cells expressing different types of tumor antigens			
				
Examples	Oncogene products: mutated RAS, Bcr/Abl fusion proteins Tumor suppressor gene products: mutated p53 protein	Various mutant proteins in carcinogen, or radiation, induced animal tumors; various mutated proteins in melanomas	Overexpressed: tyrosinase, gp100, MART in melanomas Aberrantly expressed: cancer-testis antigens (MAGE, BAGE)	Human papilloma virus E6, E7 proteins in cervical carcinoma: EBNA proteins in EBV induced lymphoma

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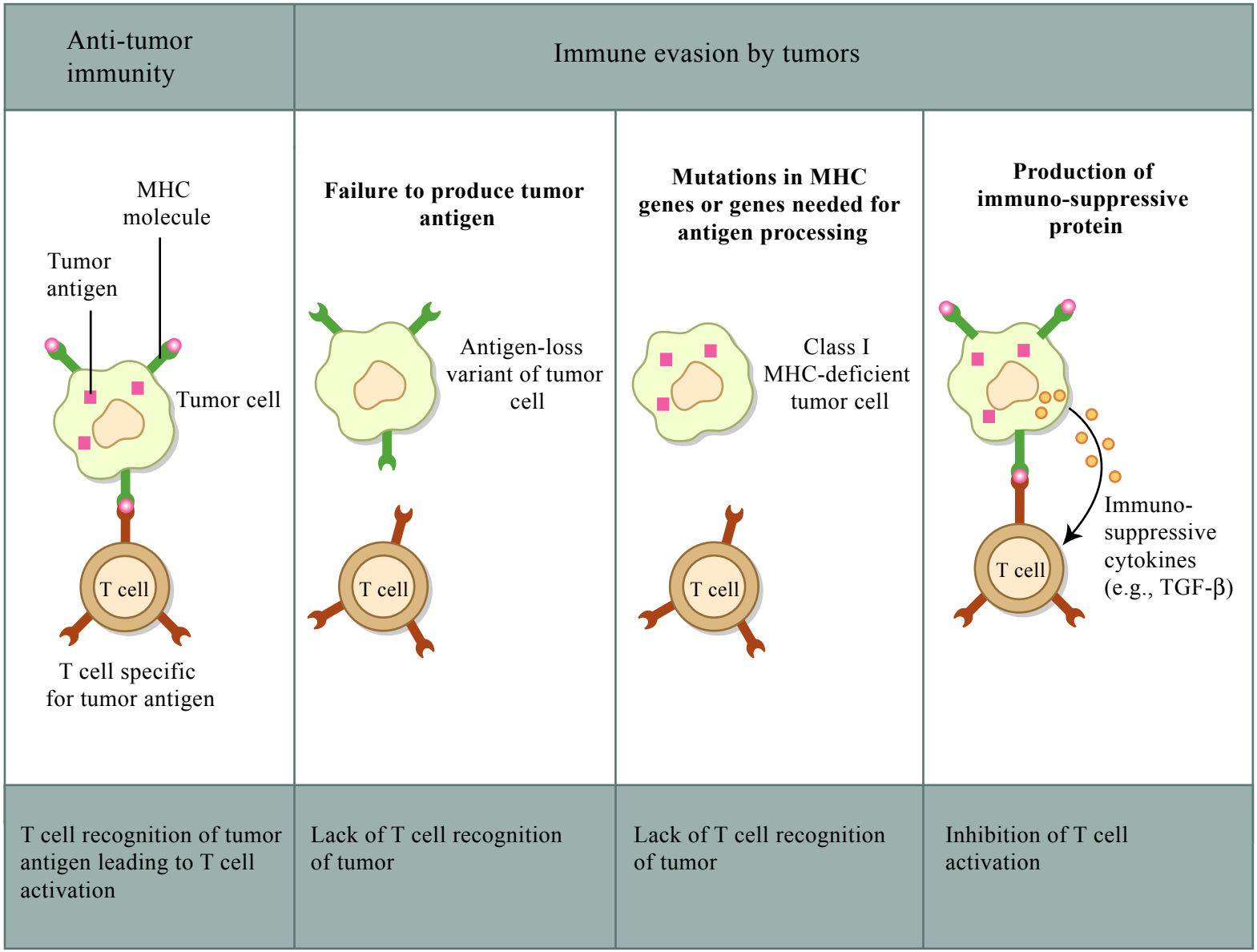

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Special topics

- Epidemiology
- p53
- Epigenetic changes
- Chemical carcinogenesis
- Microbial carcinogenesis
- Molecular profiling
  - Genomic
  - Proteomic