Immune surveillance theory: the body's immune mechanism contains cell populations capable of recognizing and destroying transformed cells before they become tumors
Tumor Associated Antigens and Tumor Specfic Antigens
Causes of Lack of tumor immunogenicity:

(1) Lack of co-stimulation
(2) Immune escape mechanisms: Production of Immunosuppressive cytokines, downregulation of MHC antigens
(3) Obstruction of apoptosis

Immune responses to tumors is superior after depletion of the regulator T-lymphocytes
Growth factor receptors are transmembrane proteins, with an extracellular domain for ligand binding, a transmembrane domain for anchoring to the cell membrane and an intracellular domain with tyrosine kinase activity.
Growth signals are activated by phosphorylation, following ligand binding to receptor and receptor dimerization.
Intracellular growth signaling proteins are tyrosine kinase, serine/ threonine, GTP-binding proteins, phosphatase, etc.
Central part in activation of growth signaling is played by the Ras family of proteins, MAP-kinase proteins and PI3K proteins.

How do cancer cells achieve self-sufficiency?

(1) By modulation of growth factor provision: autocrine or paracrine
(2) Modulation of growth factor receptors:

-Overexpression of growth factor receptor/ associated protein and/ or amplification of gene coding for that receptor, eg HER-2
-Mutations: translocation (eg CMML, PTC-RET) and point deletion (eg AML-Flt3, GIST-cKIT, NSCLC-EGFR)
-Influencing ECM -Integrins

(3) Modulation of intracellular signaling pathways: RAS, RAF, CRK, SRC

k-RAS=carcinomas
n-RAS=AML, MDS
k-RAS, n-RAS, h-RAS= FTC
BRAF=malignant melanoma, PTC, CRC, serous ovarian cancer
CRK=gliomas, lung cancer, breast cancer
SRK= SCLC,RMS, neuroblastoma, colon cancer, breast cancer,

Telomerase (DNA polymerase) is upregulated or reactivated in 90% of cancers.
Teleomeres consists of TTAGGG repeat sequences (upto 150 kb long)

Cancer stem cells
Apoptosis:
Intrinsic pathway (predominant) activated by intracellular stresses, such as an oncogenic virus, reactive oxygen species, DNA damage, etc. Also called mitochondrial pathway.
Extrinsic pathway, activated by binding of extracellular ligand (Fas ligand, TNF) to death receptors: used by NK and K cells to dispose of preneoplastic cells
Caspases are the effectors of apoptosis.

Regulated by bcl-2 family of proteins, along with p53 (pro-apoptotic), ubiquitin-proteosome (pro-apoptotic), PI3K –Akt pathway (anti-apoptotic) & NF-kB (anti-apoptotic).
BCL-2 family→Pro= BX, Bak. Anti=BCL-2, BCL-XL.
P53 is called the gatekeeper of the genome as it can activate pro-apoptotic processes. Normally exists in low quantities in unstressed conditions, bound to inhibitor Mdm-2. Activated by phosophorylation. In damaged cells, the half-life of p53 increases and it accumulates, causing G1-S growth arrest or apoptosis (by transcription of the BAX gene).
Cells cannot survive more than 200 micrometer from a blood vessel & any tumor more than 2-3 cc in size cannot survive without neovascularisation.
Natural promoters of angiogenesis: VEGF, PDGF, EGF, FGF
Natural suppressors of angiogenesis: Angiostatin, Endostatin, IFN-alpha & gamma, Thrombospondin, IL-12, TMPs, Dopamine
Tumor blood vessels are tortuous and dilated. Tumor microenvironment is characterized by interstitial hypertension.

Cell Cycle:
G1-S checkpoint: regulated by pRb, Cyclin D & E, CDK 4 & 6 (Cycline D), CDK 2 (Cyclin E). In its active state, pRb remains bound to E2F-DP.
S-phase progression: Cyclin A and CDK 2
G2-M checkpoint: Cyclin B kinase-cdc2
M-phase progression: Cyclin B degradation

Transcription:
Promoter zones are TATA box and CCAAT.

Ras pathway:
Proto-oncogene
Member of superfamily of G-proteins
Active when bound to GTP, inactive to GDP
Binding of growth factors to receptor tyrosine kinases ultimately causes Ras to bind to GTP. Ras then recruits & activates Raf, which initiates a cascade of phosophoryation of transcription factors, which in turn causes gene transcription.

MHC:
Class I present on all nucleated cells. Exogenous antigens are presented along with class II cells and recognized by helper T cells.
Class II present on antigen-presenting cells. Endogenous antigens are presented along with class I cells and recognized by cytotoxic T cells.
Dendritic cells are the most potent APCs and the only variety that can activate naïve T-cells.