

Immune responses to cancer: Friend or foe?

Colorectal cancer



Colorectal cancer

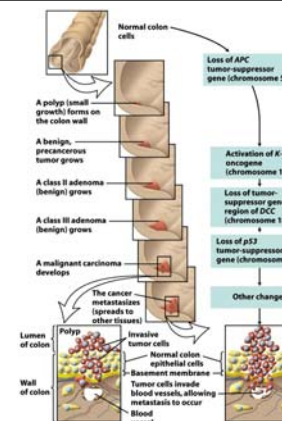
- Cancer of the colon and rectum
- Colon cancer is an adenocarcinoma
 - Carcinomas – ectoderm or endoderm (as opposed to sarcomas – mesoderm)
 - Epithelial in nature – columnar
 - 90% of cancers are carcinomas
- Known mutations in families account for 3-6% of CRC but up to 35% is “familial”
- 65-70% of CRC sporadic

Two major genomic defects result in colorectal cancer

- Chromosomal Instability – CIN
 - Chromosome breakage, translocations, rearrangements
 - Aneuploidy
 - Loss of Heterozygosity
 - FAP – mutation in APC
- Microsatellite Instability – MSI
 - Results from defects in DNA mismatch repair
 - Replication errors in repeats (RER)
 - Hypermutable phenotype
 - Lynch Syndrome or HNPCC – hmlh1 or hmlh2

Fig. 18-22

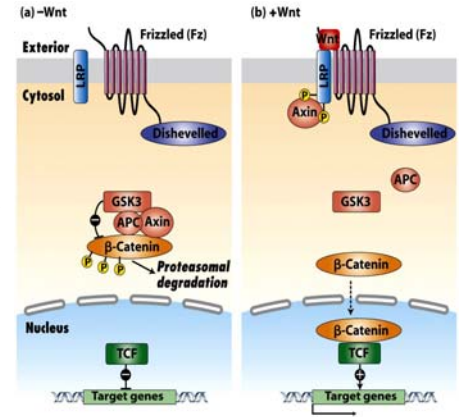
The mutations in CIN



Features of CIN

- Loss of heterozygosity – loss of normal alleles due to chromosome loss, rearrangement, deletions
- Mutation in APC, then LOH – found in very early polyps
- Other evidence of genomic instability is observed in early polyps – related to APC mutations? or starts before APC mutations?
- 80% of sporadic CRC

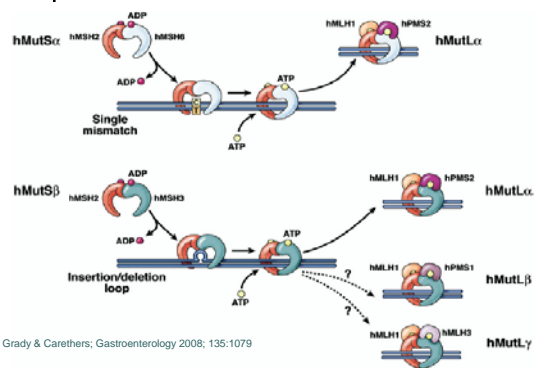
The Wnt pathway: important in cell growth




Features of MSI

- Sporadic tumors have hypermethylation of *hms2* or *hmlh1* promoters – 15% of sporadic CRC
- Microsatellite instability results from DNA polymerase slippage
- Results in frame-shift mutations that prematurely terminate gene products
- Tumors are associated with lymphocyte infiltration and an improved prognosis
- Frameshifted peptides may be recognized as novel Ags for IR


MMR






Genes mutated in MSI

- APC mutations or deregulation of Wnt signaling
 - Still the gatekeeper
- TGF β superfamily (activin, BMPs)
- Bax (pro-apoptotic; inhibits bcl-2)
- E2F4 (cell cycle control)
- pTEN negative regulator of PI3K/AKT




Immunity to CRC: the studies of Jerome Galon et al.

- Patients with IR characterized by Th1, CTLs, NKT cells have a better prognosis and significantly more disease free survival
- Memory T cells appear to be very important to this response
- 90% of cancer deaths due to metastasis
- Appears to have more prognostic value than traditional staging methods
- Independent of MSI status



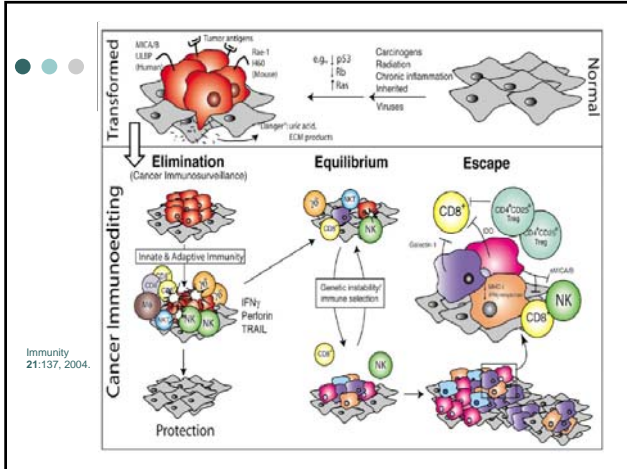
Adaptive immune responses are important to patient prognosis in colon cancer

But what about other cancers or cancer in general?



The history of immunosurveillance

- Proposed by Ehrlich in 1909 and expanded by Burnet and Thomas in the 50's
- Fell out of favor – no evidence
- But specific immune deficient animal models – more susceptible to development of multiple tumor types
- Led to the development of the Immunoediting hypothesis by Schreiber et al



- ### Elimination:
- γ IFN: $\gamma\delta$ T cells, $\alpha\beta$ T cells, NKT, macs
 - promotes Th1, CTL, cytotoxic (M1) macrophages
 - increases tumor susceptibility and immunogenicity
 - the ability to kill
 - perforin, granzyme B, granulysin, TRAIL, FAS
 - consistent with importance of CTLs, NKT, M1 macrophages
 - tumor Ags (???)
 - differentiation Ags, mutation Ags, frameshift peptides, etc.
 - NKG2D ligands (stress molecules)

- ### Equilibrium (most hypothetical)
- Three possible outcomes:
- elimination
 - life-long suppression (best exemplified by transplant examples)
 - escape

- ### Escape:
- Adaptations in Tumor
 - Decreased Ag presentation
 - defects in Class I and/or Ag processing components
 - decreased responsiveness to γ IFN
 - Loss of tumor specific Ags
 - seen in response to immunotherapies
 - consistent with importance of CTLs, NKT, cytotoxic macrophages
 - Immunosuppressive environment
 - cytokines – TGF β , IL-10
 - Indoleamine 2,3-dioxygenase (IDO), arginase

The pro-tumor effects of immunity:

- Inflammation associated with the development of cancer (subverted wound healing)
- Inflammatory microenvironment essential for tumor growth and metastasis
- Th2 cells (IL-4, -10, -13) induce TAMs (tumor associated macrophages) to become M2 cells
- TAMs/MDSC – most abundant immune cell types – promote angiogenesis, tumor growth, EMT, and immunosuppressive environment
- Secretion of TGF β , IDO, arginase, inflammatory cytokines, MMPs, VEGF and other mediators

Immune/inflammatory cells are also required for metastasis

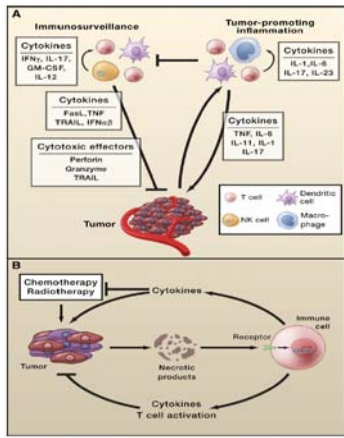
Epithelial to mesenchymal transition

- Cells lose epithelial markers
 - E-cadherin, claudin, occludin
 - Lose tight and adherens junctions
- Cells gain mesenchymal markers
 - N-cadherin, fibronectin, vimentin, collagen
 - Increase MMP production and secretion
- Stimulated cell migration – process is important in normal wound healing
- Increased invasive characteristics in small % of tumor cells - reversible
- Activated by both WNT and TGF β signaling

Metastasis: a collaboration between tumor and inflammatory cells

- Epithelial to mesenchymal transition (EMT)
- Intravasation into blood and lymphatic vessels
- Survival (inflammatory cytokines) and travel through the body
- extravasation into new tissue (site of inflammation as well – mediated by chemokines)
- Metastatic precursors interact with environment (inflammatory cells) to establish new tumor

The interplay between immunity, inflammation and tumor growth



Cell 140:883, 2010