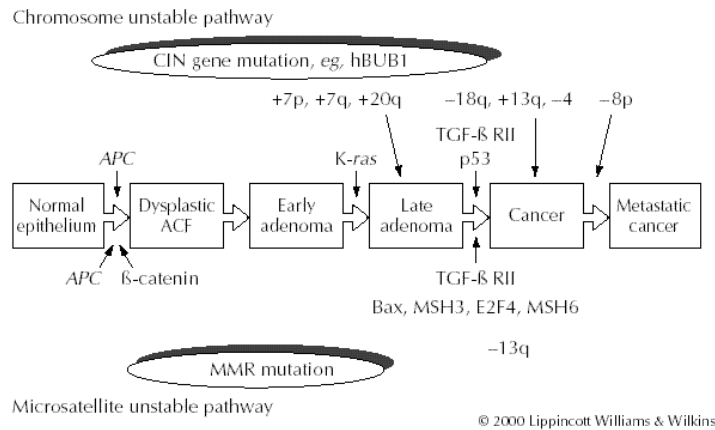


BIOLOGY OF COLORECTAL CANCER

- A genetic disorder with multiple pathogenetic pathways
- Genetic instability as a prerequisite for neoplastic evolution
- DNA damage – cease replication and initiate repair, or undergo apoptosis. Failure to recognize this damage is the basis for the potential growth advantage.
- Two types of genetic instability:
 - Chromosomal instability
 - Microsatellite instability
 - Poly A, poly CA in nonencoding segments
- DNA mismatch repair (MMR) genes – hMSH2, hMSH3, hMSH6, hMLH1, hPMS2
- Targets for mutations: TGFβR2, IGF2R, BAX
- The adenoma carcinoma sequence:



Frequency of genetic alterations in colorectal tumor stratified on the basis of DNA anomaly:

Mutation	MSI-H	MSI-L	CIN
APC	39%	51%	58%
K-ras	11%	47%	35%
TP53	18%	47%	52%
LOH			
5q	3%	35%	57%
17p	15%	67%	71%

More data that support alternative pathways to the adenoma carcinoma sequence:

- Genetic alterations are more common in adenomas compared to carcinomas
- Adenoma removal in 3 controlled trials failed to reduce incidence of cancer

Four alternative pathways to cancer:

Aggressive adenomas, example: HNPCC

Flat or depressed adenomas
De novo carcinomas
Rapidly progressive serrated pathway

From molecular characterization to clinical application

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Chen Rubinstein MD
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