COLORECTAL CANCER BIOLOGY : MOLECULAR TO CLINICAL TRANSITION

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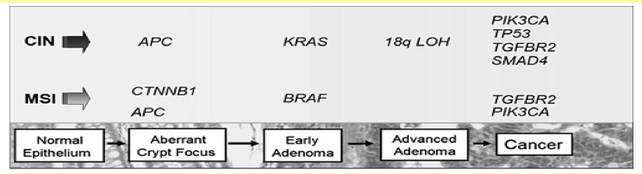
COLORECTAL CANCER PREVALENCE

- Third leading cause of cancer related deaths in western world
- Incidence rated rapidly increasing in economically transitioning countries in the world due to changing dietary and physical activity patterns.
- According to AMERICAN CANCER SOCIETY, in 2008, around 1,50,000 people diagnosed with colorectal cancer and around 50,000 died due to it.
- In the last decade, incidence rate of colorectal cancer has increased from 27% to 51%.

MOLECULAR MECHANISMS OF COLORECTAL CARCINOGENESIS



- The colorectal carcinogenesis progresses by two pathways.

1. CIN pathway (Chromosome Instability)
2. MSI pathway (Microsatellite Instability)
3. CIMP pathway (C_pG Island Methylator Pathway)

CIN PATHWAY	MSI PATHWAY
Most common. Found in 85% of colorectal cancers.	Found in only 15% of colorectal cancers.
Recognized by aneuploidy – Presence of chromosomal changes and multiple structural aberrations.	Recognized by presence of 30% unstable loci (genetic map). Aberrent DNA methylation
Mutations in the KRAF	Mutations in the BRAF
Poor prognosis	Better prognosis
Assessed by DNA flow cytometry	Assessed by mononucleotide markers.

Comparison Between CIN and MSI Pathways

CIMP PATHWAY: Hypomethylation of gene promoters that contain C_pG islands and global DNA hypomethylation. Mechanisms are not well understood but BRAF V600 mutations have been suggested. This pathway has still not impacted clinical care.

PATHWAYS DEREGULATED IN COLORECTAL CANCER AND COMMONLY USED DRUGS IN CLINICAL ARENA

PATHWAY	GENE MUTATIONS AND ALTERATIONS IN THE PATHWAY THAT LEADS TO COLORECTAL CANCER
WNT pathway	Mutations in the APC (Adenomatous Polyposis Coli) gene. Leads to classic tubular adenoma in CIN pathway. Disruption in APC protein leads to increase in WNT signaling through stabilization of β-catenin.
TGF β pathway	TGF β is considered as tumor suppressor pathway in colon. Mutations in the genes of this pathway, especially TGFR B2 leads to colorectal cancer of MSI type. Other important gene associated with this pathway is SMAD 4 gene. It is located in 18q region on chromosome and that region is deleted in colorectal cancer.
18qLOH	Most frequent cytogenetic alteration in colorectal cancer. Observed in upto 70% of tumors. It deregulates TGF β signaling.
EGFR signaling pathway	KRAS, member of RAS family of proto-oncogenes frequently mutated gene in colorectal cancer. KRAS is downstream effector of EGFR that signals through BRAF to activate MAPK pathway which leads to cell growth and survival.
PI3K pathway	Mutations in the p110α catalytic subunit of PI3K CA gene reported in around 30% of colorectal cancers and may promote adenoma-carcinoma sequence. Mutations also observed in PTEN, a tumor suppressor gene that negatively regulates PI3K signaling. PI3K and EGFR both are interlinked pathways.
TP53	Mutations in this gene can lead to colorectal cancer. Key tumor suppressor gene

Pathway	Specific target	Drugs
EGF/MAPK	EGFR (mAb)	**Cetuximab, Panitumumab**
	EGFR (TKI)	**Erlotinib, Gefitinib**
	KRAS	Tipifarnib, Lonafarnib
	BRAF	Sorafenib, PLX4032, XL281
	MEK	Selumetinib
PI3K	PI3K	BKM120, BGT226, XL147, GDC-0941
	mTOR	Everolimus, XL765
	AKT	Perifosine
WNT		Resveratrol
TGFβ	TGFβ2	AP 12009
VEGF	VEGF	**Bevacizumab**
	VEGFR	Vatalanib, AMG706, Pazopanib, Cediranib
HGF	HGF mAb	AMG102
IGF	IGF-1 mAb	AMG479, IMC-A12

- Drugs which are shown in bold letters have been approved by FDA for treatment of colorectal cancer.
- Other drugs are still under clinical trial.
- Most newly approved drugs are anti VEGF antibodies.
- There are certain kinase inhibitor drugs which act on specific pathway of molecular mechanism of colorectal cancer. These drugs are under clinical trial. E.g. Lorafarnib, tipifarnib, sorafenib etc.
- Certain vaccines targeting colorectal cancer are also in research phase.

BIOMARKERS FOR COLORECTAL CANCER

1. Predictive Biomarkers
2. Prognostic Biomarkers

Biomarker	Mutation frequency	Prognosis	Evidence
Microsatellite instability (MSI)	15%	Favourable	Strong
Chromosome instability (CIN)	70%	Unfavourable	Strong
18qLOH/*SMAD4* loss	50%	Unfavourable	Moderate
BRAF V600E mutations	10%	Probably unfavourable	Moderate
KRAS codon 12/13 mutations	40%	Probably unfavourable in advanced disease	Limited
PIK3CA mutations	20%	Possibly unfavourable	Limited

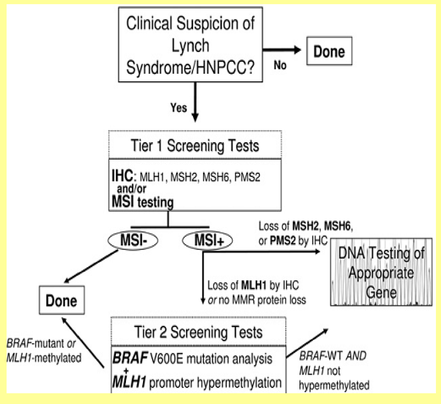
Prognostic Biomarkers

Biomarker	Mutation frequency	Drug selection	Evidence
KRAS codon 12/13 mutations	40%	Predicts resistance to anti-EGFR therapy	Strong
KRAS codon 61/117/146 mutations	1%	Probably predicts resistance to anti-EGFR therapy	Moderate
BRAF V600E mutations	10%	Probably predicts resistance to anti-EGFR therapy, may predict response to BRAF inhibitors	Moderate
PIK3CA mutations	20%	May predict resistance to anti-EGFR therapy	Limited
PTEN loss	30%	May predict resistance to anti-EGFR therapy	Limited
Microsatellite instability (MSI)	15%	May predict adverse outcome with 5-FU and improved outcome with Irinotecan	Moderate
18qLOH/*SMAD4* loss	50%	May predict resistance to 5-FU	Moderate
Topo1 low	50%	May predict resistance to irinotecan	Limited

Predictive biomarkers

LYNCH SYNDROME/HPNCC SYNDROME

- Hereditary Non Polyposis Colorectal Cancer
- Identifying individuals with this syndrome significantly alters their clinical management and can lead to effective colorectal cancer prevention programmes.



Testing Strategies for Lynch syndrome

Biomarker	Frequency: Sporadic	Frequency: Lynch syndrome
Microsatellite instability (MSI)	15%	>95%
BRAF V600E mutations	50% of sporadic MSI	<1%
	5% of MSS	
	10% overall	
Mismatch repair protein loss by IHC	10–15%, mostly MLH1	~90%
MLH1 promoter hypermethylation	~99% of sporadic MSI	<1%
	<1% MSS	
	15% overall	

Biomarkers for Lynch syndrome

FUTURE DIRECTIONS

- KRAS mutational analysis to guide anti-EGFR treatment stands as one of the first success in the era of personalized medicine.
- MSI and BRAF mutations have clear role in genetic testing of Lynch syndrome and these markers are poised to take a much greater role in prognostication and prediction of colorectal cancer.
- Studies are in progress to assess the efficacy of multikinase/BRAF inhibitor sorafinib and inhibitors of PI3K signaling in colorectal cancer.
- Newer selective BRAF inhibitors are also in pipeline.
- The expanding list of drugs designed to inhibit specific oncogenes and oncogenic signaling pathways highlights that molecular mechanisms will play a crucial role in clinical care of patients with colorectal cancer.
- The use of molecular markers for risk stratification and early detection of colorectal cancer also showing promise, and will be a part of era of molecular medicine concept which is rapidly emerging.

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