

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC)

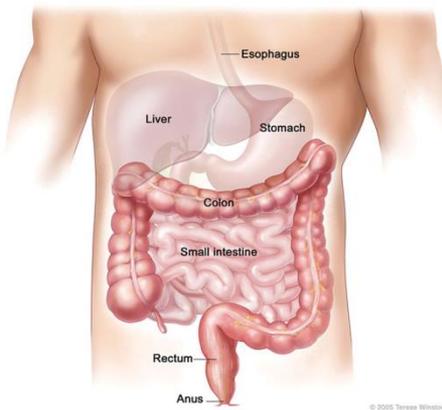
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pd 6 #13



Fig. 1

Physiology

- Aka Lynch Syndrome, causes ~5% of all colorectal cancers
- 80~90% of HNPCC patients develop colorectal cancer and/or stomach, pancreatic, endometrial, ovarian, and kidney cancers.
- Autosomal dominant, one mutated gene causes an effect, but requires homozygosity to be truly expressed.
- Occasionally arises from spontaneous mutation, otherwise is inherited.
- Distinct from FAP (Familial Adenomatous Polyposis)
- Increased risk of developing carcinomas, not increase in adenomas
- Late onset: 50 or younger, which is 10-15 years younger than general population.



← Fig 2

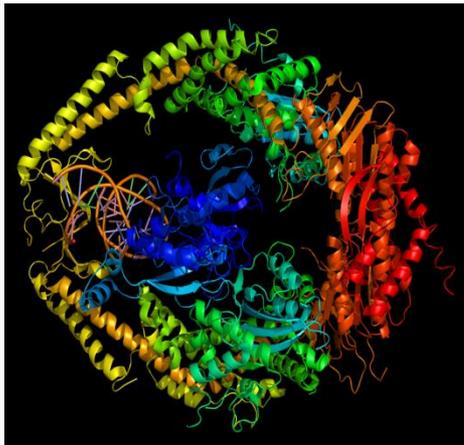
Fig 3 →



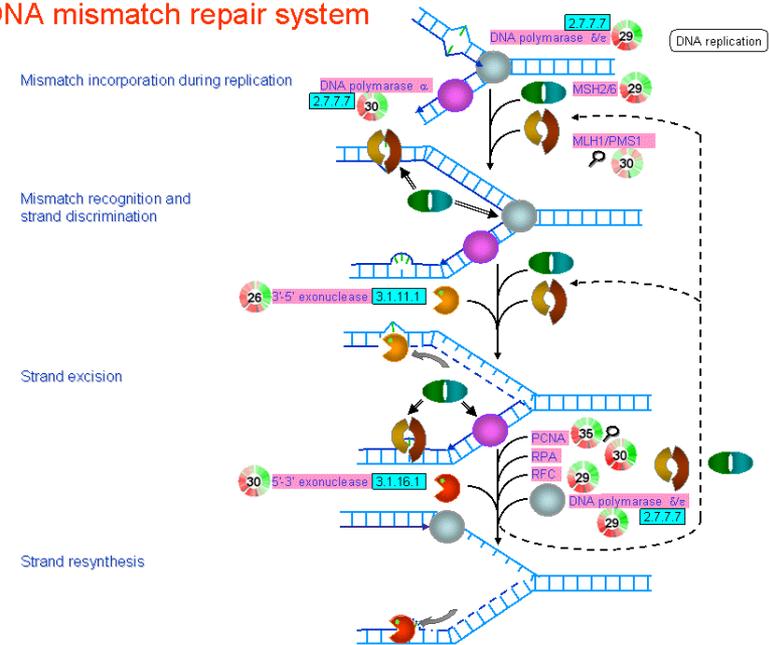
Molecular Cause

- Caused by mutations in DNA mismatch repair (MMR) genes, most commonly MSH2 and MLH1, but also MSH6, MLH3, PMS1 and PMS2
- Any number of mutations in MMR genes (point deletions, insertions, rearrangements, etc.) can cause the loss of functionality of MMR proteins (Fig. 4 →)

(Fig. 5 : Msh2 ↓)



DNA mismatch repair system



- The MMR mechanism in cells regulates DNA repair after replication. MSH2 and MSH6 form MSH α , which identifies errors. MLH α breaks the DNA (single-stranded break), so that it can be resynthesized.
- Defects in MMR lead to microsatellite instability (MSI): damage to repetitive sequences.
- MSI in genes like transforming growth factor receptor II gene (TGFB2) lead to loss of tumor suppressors, which leads to increased cancer risk.
- Knockout of MMR creates a cascade effect.

Treatments/Risks and Limits

- The standard of care for HNPCC focuses on tumors.
- Pre-diagnosis of risk for colorectal cancer and regular screening.
- Because of its hereditary nature, HNPCC can be diagnosed from a pedigree and additional tests (biopsy, sequencing, colonoscopy).
- Chemotherapy and surgery are resorted to once tumors have manifested.

- 5-Fluorouracil (5-FU), a thymidilate synthase inhibitor, and anti-angiogenesis drugs are some of the more interesting chemotherapies.
- However, the efficacy of both of these is currently being debated.
- Radiation therapy is also recommended for metastasized tumors.

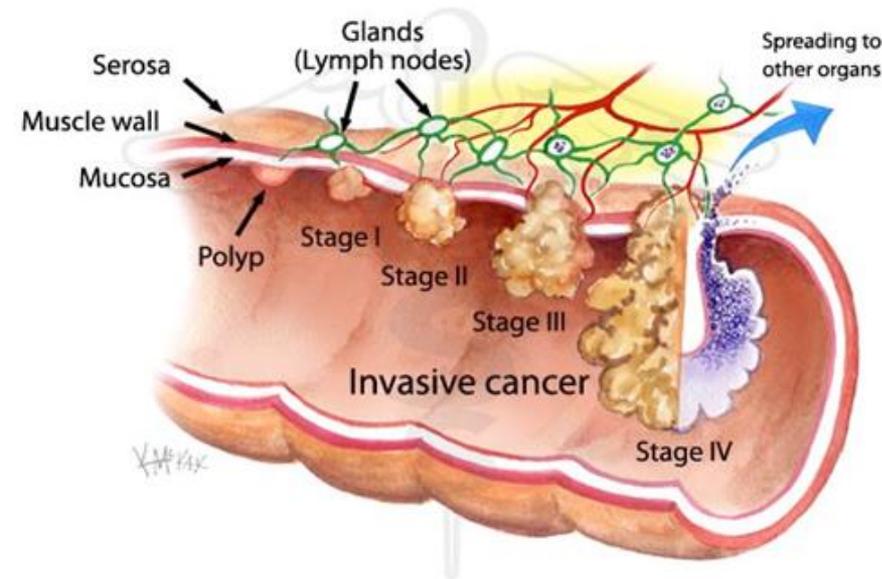


Fig. 6

Proposal

- microRNA (miRNA) is part of the RNA interference (RNAi) system, which naturally regulates gene expression.
- miRNA binds to an Argonaute protein. This complex binds to mature polyA mRNA, blocking RNAase from completing translation. The single-stranded miRNA is the part that binds directly to the single-stranded mRNA, through specific complementarity.
- miRNA expression in HNPCC-related cancers is irregular. Eleven miRNAs are overexpressed, nine are underexpressed.
- I would introduce extra amounts of the nine underexpressed miRNAs to completely shut down the mutated MMR genes that they are associated with.
- Then I would introduce polyA mRNA transcripts of normal MMR genes, taken from yeast. These would be translated in the cytoplasm and the cells would have functioning MMR proteins.
- The delivery mechanism would be a 2-stage gelatin pill carrying liquid containing vesicles with these macromolecules inside of them. The pill would be targeted at the colon, which absorbs water (liquid) and salts. These vesicles would be absorbed too, and the vesicles taken up in endocytosis.
- There are several limitations to this proposal. There is no mechanism to prevent the miRNA from silencing the proper mRNA transcripts. The delivery mechanism may also fail to reach the colon or to be taken in by cells.

References

Title Slide:

Fig. 1 "SCOPE Run and Fun to Beat Colorectal Cancer". Fight Colorectal Cancer.

- http://fightcolorectalcaner.org/research_news/2010/02/scope_run_and_fun_to_beat_colorectal_cancer

Physiology Slide:

Fig. 2 "Colorectal Cancer: Symptoms, Diagnosis and Treatment". NIH Medline Plus.

- <http://www.nlm.nih.gov/medlineplus/magazine/issues/spring09/articles/spring09pg7-8.html>

Fig. 3 "Colon cancer 2"

- https://commons.wikimedia.org/wiki/File:Colon_cancer_2.jpg

Content:

"Hereditary Nonpolyposis Colorectal Cancer" . Cleveland Clinic.http://my.clevelandclinic.org/disorders/inherited_colon_cancer/dd_hnpcc.aspx

"Hereditary Nonpolyposis Colorectal Cancer". Genetics in Medicine. Thompson and Thompson.

Molecular Cause Slide:

Fig. 4 "DNA mismatch repair system" PubMed

- <http://priweb.cc.huji.ac.il/malaria/maps/DNArepair.html>

Fig. 5 "Protein MSH2"

- <http://en.wikipedia.org/wiki/Msh2>

Content:

"Hereditary Nonpolyposis Colorectal Cancer". Genetics in Medicine. Thompson and Thompson.

"Molecular Basis for HNPCC." *National Center for Biotechnology Information.*

- <http://www.ncbi.nlm.nih.gov/pubmed/9259192>

Treatments/Risks and Limits Slide:

Fig 6: "Colorectal Cancer" Colorectal Surgeons Sydney.

- http://colorectalsurgeonssydney.com.au/?page_id=418

Content:

"Hereditary Nonpolyposis Colorectal Cancer" . Cleveland Clinic.http://my.clevelandclinic.org/disorders/inherited_colon_cancer/dd_hnpcc.aspx

Genetics in Medicine. Thompson and Thompson

Proposal Slide:

Contents:

Association of MicroRNA Expression with Microsatellite Instability Status in Colorectal Adenocarcinoma

- <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2893627/>