Familial Adenomatous Polyposis Outline

Jonathan Quang

Disease Name: Familial Adenomatous Polyposis

A Deep Probe of FAP

Opening Declaration: I promise to do this assignment authentically

Student Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date:\_\_\_\_\_\_\_\_\_

Yellow highlights are additions or substitutions. Red Os indicate a deletion

**Introduction and Background**

**Basic Genetic Background/Facts**

* Autosomal dominant, 50% chance of passing to a child if the other parent is unaffacted
* According to the American Society of Clinical Oncology, "About 30% of people with FAP do not have any family history of the condition; they have a de novo (new) mutation in the APC gene."
* According to the National Center for Biotechnology Information, the cytogenic gene location of this disorder is from 5q21 to 5q22, which includes the base pairs from 112,707,505 to 112,846,239 (NCBI)
* Classical FAP is caused by mutations on chromosome 5.
* There are numerous subsets of classical FAP: AFAP , Gardner syndrome, and Turcot syndrome
* Usually nonsense or frame shift mutations
* Late onset, symptoms begin showing in the early teens, but do not become a big problem until the late teens
* Affects APC (Adenomatous polyposis coli) gene.
* The gene is a tumor suppressor gene

**Symptoms**

* Causes polyps to grow in the colon, may lead to bloody stool because APC protein works with cell adhesion, replication, and mobility. This disrupts the folding of the stomach lining.
* Polyps, if left untreated, will turn into colonic cancer.
* Other types of cancer found in families with FAP include hepatoblastoma, a type of liver cancer seen in young children; desmoid tumors/desmoid fibromatosis, a locally aggressive tumor that does not metastasize; papillary thyroid cancer; pancreatic, adrenal, and bile duct tumors; and a type of brain tumor called medulloblastoma," (American Society of Clinical Oncology).
* Non cancer related symptoms that might happen: bone related growths in the jaw, gaining or losing teeth, changes in skin, and growths in the adrenal region

**Site of Lesion**

* Frame shift mutations, nonsense mutations, or large sections being duplicated or removed results in the APC protein folding into a shorter protein.
* APC has multiple functions listed below:

**WNT Pathway**

* Works in the WNT pathway when the pathway is off. Pathway off = destruction of β catenin. Pathway on = " cytoplasmic β-catenin forms a complex with Axin, APC, GSK3, and CK1, and is phosphorylated by CK1... and subsequently by GSK3," (MacDonald, Tamai, and He). β-catenin accumulation in cytoplasm. Travels from cytoplasm to nuclear cytoplasm. Works as a coactivator with TCF transcription factor to begin transcribing WNT-activated genes.
* Normally: Destruction complex formed with Axin, GSK3, CKJ, and β-catenin. Results in Ubiquitin, β-Trcp, and a phosphate group being attached to β-catenin. Targets it for destruction by a proteosome.
* With FAP: Destruction complex might not form or form improperly. β-catenin is allowed to accumulate in nuclear cytoplasm, as if pathway was activated.

**Effects on Cell Adhesion and Cytoskeleton**

* Mutated APC proteins have an effect on cell adhesion and the cell's cytoskeleton.
* Normal function: Cells stick to each other tightly.
* Mutated function: Cells stick to each other loosely, leading to growths in wrong directions
* Functional APC gene returned to cancerous colon cells results in this: " . E-cadherin is ... translocated to the cell membrane, where it forms functional adherens junctions. Total cellular levels of E-cadherin are increased in the SW480APC [colon cancer] cells and the altered charge distribution in the presence of full-length APC suggests that APC is involved in post-translational regulation of E-cadherin localization. Changes in the location of adherens junction proteins are associated with tighter cell-cell adhesion in SW480APC cells, with consequent changes in cell morphology, the actin cytoskeleton and cell migration... SW480APC cells have a reduced proliferation rate, a reduced ability to form colonies in soft agar and do not grow tumoursO in a xenograft mouse tumour model," (Faux, Ross, Meeker, Johns, Ji, Simpson, Layton, Burgess).
* Intercellular adhesion in epithelial cells is governed by calcium dependent glycoproteins called cadherins. A cell with cadherins will be joined to other cells via cadherins.
* Cadherins are connected to the interior of the cell by connecting to β-catenin or E-Cadherin. This in turn connects to alpha catenin, which finally connects to the cell cytoskeleton. (Nieset, Redfield, Jin, Knudsen, Johnson, and Wheelock)
* APC has a role in microtubule development.
* Normal APC: " In migrating epithelial cells, microtubules decorated with APC at their plus ends spend increased time in growth and decreased time shortening," (Barth, Caro-Gonzalez, and Nelson).
* Mutated APC: Interacts with microtubules indiscriminately, causes microtubule growth to continue at the wrong places.
* There is some research into APC directly transcribing DNA, though what happens when APC is mutated is not widely known.
* Increased transcription of cell reproduction related genes and messed up cell adhesion and growth = polyps ---> cancer

**Current Therapy**

**Post Birth Therapy**

* Mohmmad Wehbi of the Medscape website recommends "Flexible sigmoidoscopy should be performed every 1-2 years starting at age 10-12 years in patients with FAP to document the onset of polyposis... Once polyps are detected, colonoscopic surveillance is recommended to remove large polyps in patients who have not had an operation," (Wehbi).
* Three possible surgeries: "Ileal pouch-anal anastomosis (J-pouch) surgery, total colectomy, and continent ileostomy." (Mayo Clinic Staff).
* Ileal puch-anal anastomosis = small intestine is curved so it can store waste.
* Limitation: problems reproducing
* Total colectomy = colon completely removed
* Limitation : Fluid absorption is weaker.
* Continent ileostomy = small intestine connected to skin, stoma made, and a bag is attached to the stoma.
* Limitation: Less fluid absorption, stoma must be frequently checked for infection, harder to get drunk
* Surgery followed up by sulindac or celecoxib.
* " Celecoxib is no longer widely used because " of the association between cyclooxygenase 2 (COX-2) inhibitors (celecoxib is a member of this drug family) and coronary artery disease," (Wehbi)."
* Both are COX-2 inhibitors that were intended to reduce inflammation. It was found to also suppress intestinal tumors.
* FAP tumors found to over express COX-2
* Both reduce polyps in the rectum post surgery.
* No palliative care really exists for FAP specifically since removing the colon usually eliminates the main issue with FAP, colonic cancer, by removing the colon.   
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* Though not widespread, freezing of eggs to test for cancer related diseases, such as FAP, is an option (Quinn, Vadaparampil, Jacobsen, Knapp, David, Keefe, Geri).

**Experimental Drugs**

* According to "Can we safely target the WNT pathway?" a drug that interferes with β-catenin interaction with TCF is iCRT3 (Khan).
* iCRT3 = C16H17NO5S2­
* Soluble in DMSO, an organosulfur compound capable of dissolving some polar and non polar compounds.
* Not approved for use in humans, but effective in mice (ABCAM).
* In a clinical trial, Sulindac and Eflornithine " have been shown to significantly reduce polyps in patients with a history of large colon polyps but who did not have FAP. There are also studies that show a reduction in polyps in patients with FAP,"( Hereditary Colon Cancer Foundation).

**Molecular Intervention Therapy**

* Easiest defect to cure: The lack of destruction of β-catenin.
* Symptoms could possibly show in the early teens, intervention should start earlier than puberty.
* Target tissue is epithelial tissue.
* Mainly the colon, but polyps and tumors can occur anywhere from the stomach to the rectum..
* Barriers: Digestive juices, medicine must not be absorbed before the end of the small intestine.
* β-catenin exists in the cytoplasm and nuclear cytoplasm.
* Possible intervention methods: Block molecule from entering the nucleus, destroy the molecule, and blocking the molecule from bonding with the transcription factor TCF in the nucleus.
* Destroying Beta-catenine in the cytoplasm is dangerous because it is needed to maintain cell adhesion.
* Proposed cure: A protein that blocks the binding site of TCF to β-catenin in the nuclear membrane.
* Protein bound to be too large to get across cell and nuclear membrane.
* To get across the cell membrane, put it in vesicle.
* Protein could piggyback on Axin as a shuttle to the nuclear membrane or just let the protein wander to the nuclear membrane.
* Axin also acts as a shuttle for β-catenin to go from cytoplasm to nuclear membrane. If only Axin was blocked, β-catenin's effect in the nuclear membrane could be slowed down.
* Once the protein gets to the nuclear membrane, it should be able to generate a nuclear localization signal to be accepted into the nucleus.
* The protein changes once it gets past nuclear membrane so it binds with β-catenin
* A bunch of these vesicles are loaded into a capsule that reacts to a magnetic field.
* Vesicles and protein produced by genetically engineered bacteria.
* Collect the vesicles into a capsule.
* Put an elastic band on magnet and place magnet somewhere in the abdominal region where the beginning of the small intestine (or other places along the digestive system if problems occur there). This magnet is outside the body.
* Once the capsule passes the magnetic field, vesicles released.
* Previously mentioned iCRT3 is soluble in DMSO at low temperatures, about -20 degrees Celsius (ABCAM).
* Unknown how soluble iCRT3 is in the digestive system.

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