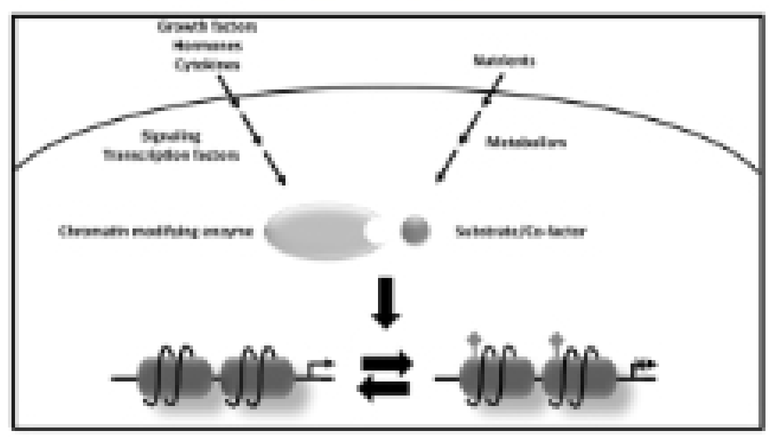
Main Ideas
- Epigenetic modifications are regulated by dietary, hormonal, genetic, and environmental factors
- Epigenetic modifications regulate the cell cycle, DNA damage, apoptosis, cell invasion and metastasis, X-chromosome inactivation, imprinting, and aging
- Key enzymes: DNA methyl transferases, histone methyltransferases, histone acetylases/ deacetylases
- Key epigenetic changes include site-specific hypermethylation, hhistone modifications, and global hypomethylation
- Maternal diet and obesity can affect offspring both metabolically and psychologically for at least 2 generations. Paternal diet can also assert similar affects, but less well investigated.
- The epigenome is sensitive throughout life.
- Epigenetic changes appear to be among the earliest events in cancer progression, leading to activation of oncogenes and inactivation of tumor suppressors.
- Testing for epigenetic modifications is moving into mainstream oncology.

Objectives
1) Describe environmental influences that may have epigenetic consequences.
2) Discuss intergenerational and transgenerational epigenetic inheritance.
3) Discuss how epigenetic mods may initiate and/or promote tumor progression.
4) Describe how manipulating epigenetic alterations may be useful in medicine.

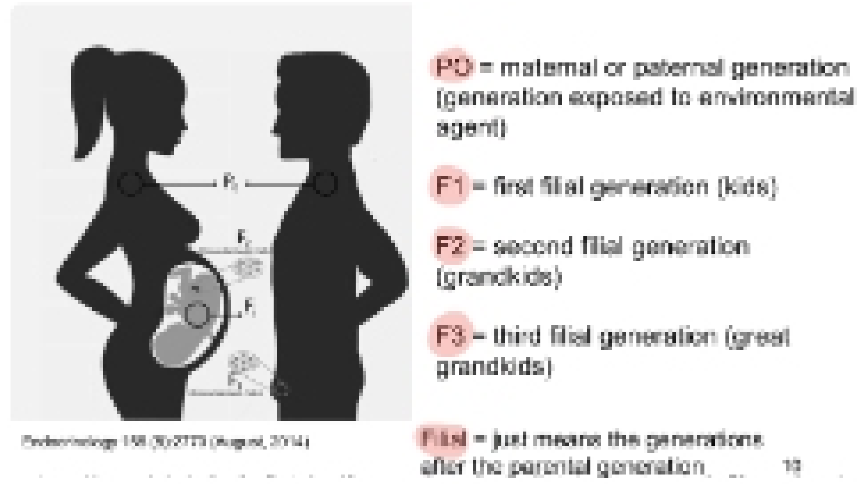
1) Describe environmental influences that may have epigenetic consequences.
- Epigenetic deregulation
    - DNA methylation and epigenetic marks are usually maintained for life
    - Deregulation can result from disturbances in epigenetic control mechanisms or when the marks are changed
        - **epimutation** results from an aberrant erasing, establishing, or maintenance of epigenetic marks
    - Regulating factors: diet, hormonal, envi (ex. stress, chemicals, assisted reproduction)
    - Regulated enzymes: HATs/HDACs, histone methyltransferases, DNA methyltransferases/ demethylases
    - Changes that contribute to disease:
        - **Site specific DNA methylation**: silence tumor repressor genes
        - **Global DNA hypomethylation**: activate oncogenes or mobile elements
        - changes in histone mods



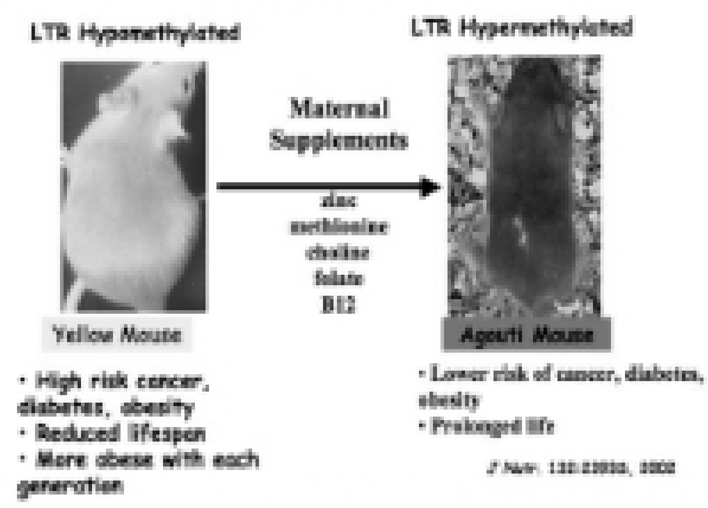
envi-->series of events-->change the chrom. mods enzymes

2) Discuss intergenerational and transgenerational epigenetic inheritance.
- **Metabolic epigenetic marking (Metabolic imprinting)**
    = The programming of an offspring's future metabolic responses by a stimulus that occurs during critical embryological periods.
        - reprogramming right after fertilization and thru to blastocyst, reprogramming of the PPGs before gamete formation
        - whatever the parent is doing is affecting the future metabolic response of the child
    - it's thought to be a quicker adaptation to the envi than evolution. Enhance offspring survival by programming energy balance so that available nutrients are used more effectively.
    - clinical and exp. studies suggest that early life experiences, perhaps spanning multiple

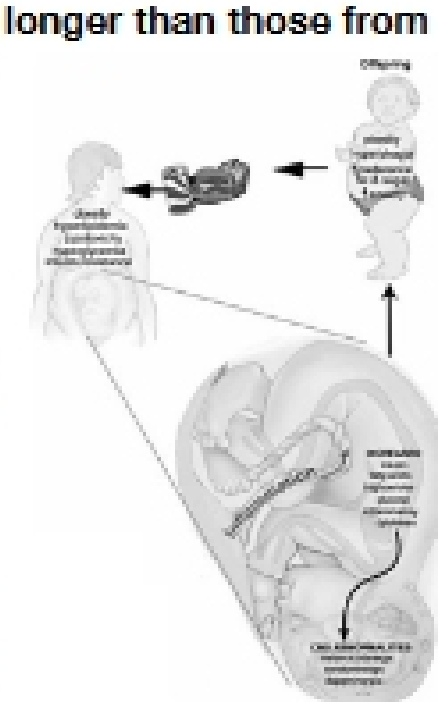
generations, afffect lifelong risk of metabolic dysfunction thru epigenetic mechanisms
    - epigenotype at birth and later adiposity, maternal nutrition and offspring epigenotype



- **Transgenerational Inheritance**= the pheno persists for at least 2 generations after the initial exposure
  - E.g. The mom is smoking--> baby is directly affected and its germ cells are directly affected-->have to go to the F3 generation to see transgenerational effect
  - E.g. For a dad, if F2 shouws a pheno affected by the dad's smoking, it's a transgenerational affect.
  - Differs between maternal and paternal transmission
  - **Maternal Transmission:** her embryo and the embryo's germ cells are directly affected. Transmission of the epigenome/phenotype must be shown in the F3 generation.
  - **Paternal Transmission:** germ cells of F1 are exposed, but not of F2. Transgen pheno in F2.
  - Diet can affect transgenerational traits: The Agouti Mouse



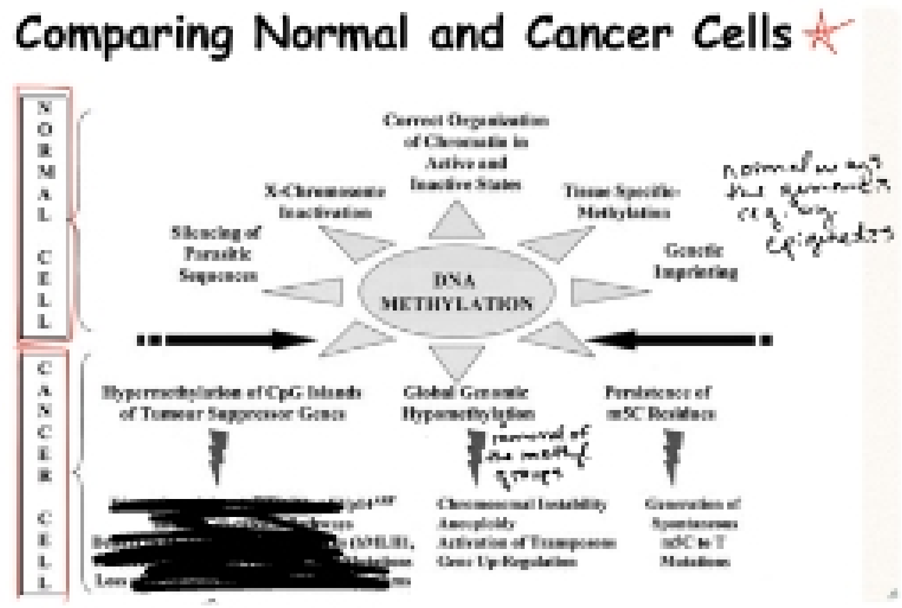
    - Expression from promoters differs on whether or not the mouse parent had enough methyl ground around. If IAP prom. methylated (normal), normal prom. is used, mice are back and normal. If hypomethylated (mouse had diet low in methyl groups), the IAP prom. is active and the mice are yellow and obese.
    - Agouti mouse is used to investigate the effects of the envi on the epigenome
      - Yellow pheno could be reversed in offspring if you give the mom supplments (molecules with methyl groups)
    - **Offspring from mice fed a high fat diet (HFD) were significantly longer than those from mice fed a regular chow diet.**
      - Trans to 3rd gen. by males and females, offspring= basically look diabetic



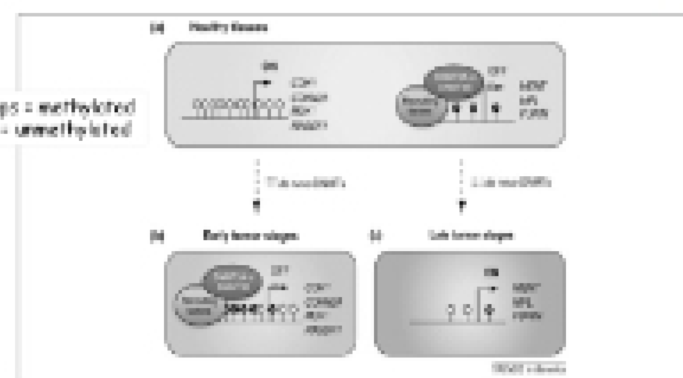
    - Maternal diet can also affect behavior (Macaque mothers HFD-->behavioral disorders in kids. Showed **intergenerational effects**, not transgen.)
    - Maternal diet (in humans) can affect their children's metabolism (ex. women pregnant during famine-->offspring has increased BMI, diabetes, etc. less DNA methylation than sibs. Still just intergenerational)
    - Evidence indicates that perinatal diet program affect many aspects of physiology and behavior: metabolism, diet preferences, body weight set pt, predisposition to mental health issues...
    - **Bottom line:** Maternal obesity and HFD have an enduring impact on the developing fetal brain and the child
  - Paternal diet can also have intergenerational and transgenerational phenotypic effects

3) Discuss how epigenetic mods may initiate and/or promote tumor progression.

- How do both hypermethylation and hypomethylation occur in cancer? It's not at the same time, it's sequential. Confusing hypo we don't need to memorize.
- Frequent epigenetic changes in tumors
    - **Genome wide hypomethylation increases with tumor progression (20-60% decrease)**
        - --> activation of repetitive DNA seq, decreased methylation of introns, activation of genes normally silenced
        - -->increased genomic instabability, mitotic recomb., loss of appropriate imprinting, activation of gene involved in promoting cell proliferation
    - **Hypermethylation of tumor suppressor genes**
        - --> increased cell proliferation and survival, decreased repair of mutations
    - **Persistance of 5MeC residues**
        - --> increased mustation rates of 5MeC to T
        - --> more mutations and disruptions



Filled in lollipops = methylated
Open lollipops = unmethylated



4) Describe how manipulating epigenetic alterations may be useful in medicine.

Don't need to know. Didn't get to rest of slideshow.