American Institute of Integrative Oncology
RESEARCH & EDUCATION

Foundations of Integrative Oncology
COURSE

GRAND ROUNDS CALL
With Dr. Nalini Chilkov
May 10th, 2017
Second Wednesday of Every Month
5:30 PM Pacific / 6:30 PM Mountain / 7:30 PM Central / 8:30 PM Eastern

Clinical Pearl: The Estrobolome and Malignancy

TAKE HOME PEARL:
A woman's lifetime exposure to estrogen is influenced by her microbiome.
Lowering beta-glucuronidase in the intestines is one key to lowering estrogen exposure.

See slides below for overview.

Primary References
Microbiome and Malignancy
Plottel, Claudia S. et al. Cell Host & Microbe, Volume 10, Issue 4, 324 - 335

Evolving Concepts: How Diet and the Intestinal Microbiome Act as Modulators of Breast Malignancy
Juliana Shapira, Keith Sultan, Annette Lee, and Emanuela Taioli, ISRN Oncology Vol 2013 Article ID 693920, 10 pages

The Intestinal Microbiome and Estrogen Receptor-Positive Female Breast Cancer.
Kwa M, Plottel CS, Blaser MJ, Adams S. J Natl Cancer Inst. 2016 Apr 22;108(8)

Diet, the Gut Microbiome, and Epigenetics
Meredith A, et al Cancer J. 2014 May-Jun; 20(3): 170–175.

Questions & Answers

Denny Thompson, D.C.:
What is the best source of Chinese herbs?

- Evergreen Herbs https://www.evherbs.com John Chen
- Golden Lotus Herbs http://www.goldenlotusherbs.com/ Dave Ehrlichman
- Health Concerns https://www.healthconcerns.com/ Andrew Gaeddart

Judy Pruzinsky, L.Ac.:
What is of most important in managing the terrain of basal cell carcinomas? Although one of the most benign forms of cancer, after 13 Mohs surgeries, the patient doesn't feel that way.

Most basal cell carcinomas: DNA damage occurred 10-20+ years prior

- Assess Tumor Microenvironment: ALWAYS assess factors identified

- Consider new immune therapies-
  - Topical - such as ZYCLARA Imiquimod which can also reveal subclinical lesions (approved for Actinic Keratoses and HPV Skin lesions (warts but also many studies on BCC) increases Interferon-*a,* CD3, CD4, CD8, CD11c, and CD68 T cells
  - Oral-Systemic Therapy Odomzo® (sonidegib) Tyrosine Kinase inhibitor: inhibits Hedgehog signaling pathway involved in BCC (many adverse SE) ***Resveratrol and Curcumin and Oridonin from

Rabdosia rubescens also inhibit HedgeHog Signaling Pathway***

- Nutraceutical-Botanical Systemic Therapy must include inflammation control. Decrease NFkB (curcumin, boswellia, Scutellaria baicalensis, O3FA), inhibit Hedgehog signalling pathway (Yu Jin Curucma longa>curumin, resveratrol, Rabdosia rubescens), immune modulation (ganoderma, astragalus, coriolus, cordyceps), support for epithelial repair (Vit A), and specific targeted botanicals and phytochemicals (Parthenolide -Tanacetum parthenium -Feverfew), EGCG from Green Tea (Camelia sinensis, Tanshinones and Salvionolic acid: Salvia Milthiorhizza-Dan Shen), Scutellaria baicalensis-Huang Qin

- Acupuncture LI 4, LI 11, Sp10, St 36, GB 41, SJ5 (Lu 1, Lu 10)

- Example of Custom Compounded Formula from CHILKOV CLINIC

240ml	480ml	
20	40	**Salvia Red Sage** (Dan Shen)
40	80	**Tumeric Yu Jin** Curcuma longa
40	80	**Scutellaria baicalensis** Huang Qin
10	20	Oldenlandia(aka Heydotis) Bai Hua She She Cao
30	60	Gotu Kola Centella asiatica
10	20	**Green Tea** Camelia sinensis Cha Ye
10	20	**Tangerine peel** Citrus Reticulata Chen Pi
20	40	**Rabdosia rubescens Dong Ling Cao (oridonin)**
20	40	Cordyceps fungus Dong Chong Xia Cao
20	40	Ganoderma lucidum fungus Ling Zhi Reishi
10	20	Astragalus membranaceus Huang Qi

Judy Pruzinsky, L.Ac.

Do you have a breakdown of different cancers and which hallmarks and/or cancer terrains are most important for each? For example: cancer of the x, tends to be respond especially well to addressing apoptosis, and proliferation signaling and/or inhibiting angiogenesis and working with detoxification.

Yes and No.

Basic Principles: The tumor cell line and the tumor microenvironment are a ***constantly changing biosystem -ecosystem.*** This is what makes cancer challenging.

Best to use what can be known from pathology reports, tumor profiling and assessment of tumor microenvironment.

- Understand Tumor Cell line (always changing) Look at pathology report, molecular and genetic traits of tumor cells (eg Ki67: rate of replication-fast dividing, slow dividing), p53 mutations: more aggressive cancers, do not undergo apoptosis, BRCA positive: poor DNA repair: more aggressive, more vulnerable to RT and oxidative stress, PTEN (tumor suppressor) expressed not expressed?, Estrogen Receptor status?
- Understand Tumor Microenvironment
- Understand Hx of Toxic Exposures (including cancer tx) see QEESI questionnaire for in resources library for quick overview of pt toxic exposures
- Understand Detoxigenomics and Methylgenomics of patient
- Stage (advanced > more coagulopathies, more inflammation, more angiogenesis, more inhibition of apoptosis)
- Some cancers ARE more inflammatory such as the leukemias with leukocytosis, inflammatory breast cancer
- Some ARE more prone to coagulopathies: Breast, Ovarian, Prostate, pt on CT and hormone therapy
- Obese cancer patients already have higher levels of cytokines and adipokines (inflammation), and higher aromatase (more estrogenic effects), increased risk of thromboembolism
- Large masses that produce physical obstruction: more risk of embolism
- Pts with Cachexia: super inflamed, sarcopenic

Case Study

Patient "SS" - Submitted by Judy Pruzinsky, L.Ac.

53 yo female - Dx: Breast cyst and mass - Diagnosed Aug 2015
Biopsy: DCIS HER2-/ER-/PR- (triple negative), high nuclear grade and non-comedogenic
Blood chem: low: hematocrit, hemoglobin, lymphocytes %, Abs Lymphocyte, RBC
High: MCV, MCH, Neutrophil %, Glucose

- 09/15 - Diet/lifestyle changes (see last page of submission)
- 02/16 - Surgery: Sentinel lymph node removed; invasive cancer 2.8, DCIS 4.4, clear margins.
- 04/16 - Adriamycin/Cytoxan (2 months every other week; 4 total) then Taxol (3 months every week; 12 total) residual side effects: chemo brain (i.e., forgetfulness, can't multi-task, have to write everything down) and fatigue.
- 09/16 - Back to work PT, then FT
- 12/16 - MRI with contrast: clear
- 01/17 - Reinitiated alcohol on weekends, THC/CBD at night

Current S&S: Tired, hot flashing wakens her, swollen joints, runny nose and eyes

Cancer Terrain: Tumor MicroEnvironment > BioMarker Monitoring
CA 15-3, CA 27.29, CEA, CTC/BREAST, Cu, Cp, Zn, CRP, Fibrinogen Activity, D Dimer, CBC+Diff, CMP, HgbA1c, Insulin, IGF-1, 25 OH VIT D

Chemotherapy Related Cognitive Impairment (CRCI="Chemo Brain")
Considerations:
Brain Inflammation: Curcumin, O3FA Lion's Mane
Cognitive Impairment Lion's mane (*Hericium ernaceus*) 2-3g/day improves Neurotropic Growth Factor, Inflammation Control, Depression/Anxiety

References

- Li K et al. Protective effects of Hericium erinaceus mycelium and its isolated erinacine a against ischemia-injury-induced neuronal cell death via the inhibition of iNOS/p38 MAPK and nitrotyrosine. *Int J Mol Sci*. 2014;15(9):15073–15089.

- Mori K et al. Improving effects of the mushroom Yamabushitake (Hericium ernaceus) on mild cognitive impairment: a double-blind, placebo-controlled clinical trial. *Phytother Res.*2009;23(3):367–372.

- Nagano M. Reduction of depression and anxiety by 4 weeks Hericium erinaceus intake.*Biomed Res*. 2010;31(4):231–237.

Acetyl L Carnitine and CRCI 2-4g/day (Vital Nutrients ALC Powder added to shake or DFH ALC Capsules) - Memory, promote neurotrophins, neuroprotection

References

- Pisano C et al. Paclitaxel and Cisplatin-induced neurotoxicity: a protective role of acetyl-L-carnitine. *Clin Cancer Res*. 2003;9(15):5756–5767.

- Vivoli E et al. Acetyl-L-carnitine increases artemin level and prevents neurotrophic factor alterations during neuropathy. *Neuroscience*. 2010;167(4):1168–1174.

- Malaguarnera M et al. Acetyl-l-carnitine improves cognitive functions in severe hepatic encephalopathy: a randomized and controlled clinical trial. *Metab Brain Dis*. 2011;26:281–289.

Curcumin and CRCI
References

- Mishra S, Palanivelu K. The effects of curcumin (turmeric) on Alzheimer's disease: an overview. *Ann Indian Acad Neurol*. 2008;11(1):13–19.

- Nam SM, Choi JH, Yoo DY, et al. Effects of curcumin (Curcuma longa) on learning and spatial memory as well as cell proliferation and neuroblast differentiation in adult and aged mice by upregulating brain-derived neurotrophic factor and CREB signaling. *Med Food*. 2014;Apr 8.

- Sanmukhani J et al. Efficacy and safety of curcumin in major depressive disorder: a randomized controlled trial. *Phytother Res*. 2014;28(4):579–585.

Therapeutic Foods and Brain Health - Tart Cherry Extract and Walnuts
References

- Shukitt-Hale B, et al. Antioxidants (Basel). 2016 Sep 22;5(4). Tart Cherry Extracts Reduce Inflammatory and Oxidative Stress Signaling in Microglial Cells.

- Rajaram S et al Front Aging Neurosci. 2017 Jan 10;8:333. The Walnuts and Healthy Aging Study (WAHA): Protocol for a Nutritional Intervention Trial With Walnuts on Brain Aging.

(NB: in Traditional Chinese Medicine walnuts are considered a "brain nourishing food" due to the Doctrine of Signatures)

Menopausal Sx: add Maca rhizome powder (*Lepidium meyenii)* to your Tx Plan (3 g/day),
Consider Yin Tonics: Schizandra (2-3g day),

Acupuncture: Sp6, K6, Lu 7, St 36, H7, H6, CV17, CV4

References:

- Depypere HT, Comhaire FH. Maturitas. 2014 Feb;77(2):191-4. Herbal preparations for the menopause: beyond isoflavones and black cohosh.

Swollen Joints, Runny Nose Eyes...determine etiology

Myelosuppression (2' to CT??)
Acupuncture - Moxibustion St 36, Sp3, LI4, Sp6 (CV12, CV6)

Health Concerns Marrow Plus (Subhuti Dharmananda) (SP-Digestive Qi, Blood, Yin, Blood Stasis) **Traditional Chinese Herb Formula**

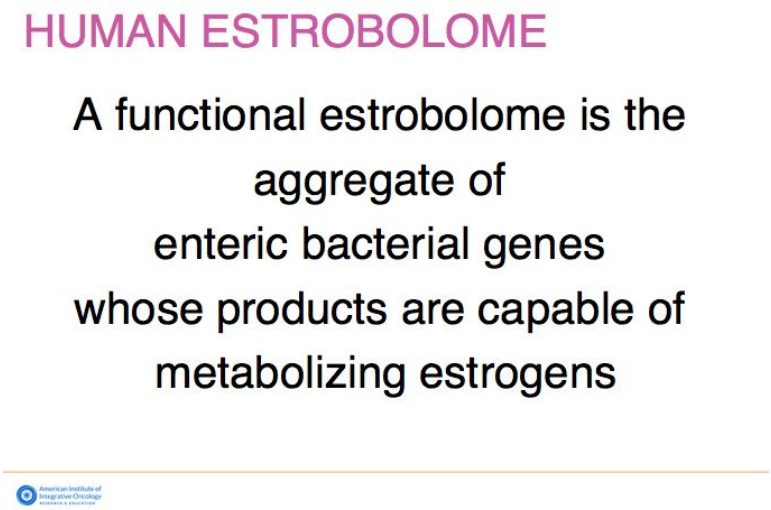
Milletia (Ji Xue Teng),
He-shou-wu (Ho Shou Wu),
Salvia (Dan Shen),
Codonopsis (Dang Shen),
Astragalus (Huang Qi),
Ligusticum (Chuan Xiong),
Raw Rehmannia (Sheng Di Huang),
Cooked Rehmannia (Shu Di Huang),
Lycium (Gou Ji Zi),
Tang-kuei (Dang Gui),
Lotus Seed (Lian Zi),
Citrus (Chen Pi),
Red Date Extract (Da Zao),
Oryza (Gu Ya),
Gelatinum (E Jiao)

NATURA HEALTH PRODUCTS Immucare One (Donald Yance) (Sp_Digestive Qi Qi, Blood, Yin, Inflammation)
Chinese Herbs + Western Herbs

Astragalus membranaceus Root 15:1 Ext. 180 mg
Millettia reticulata Stem 12:1 Ext. 90 mg
Cordyceps sinensis 4:1 Ext. 40% Polysaccharides 80 mg
Atractylodes macrocephala Rhizome 15:1 Ext. 76 mg
Echinacea purpurea Root Ext. 4% Phenolic 74 mg
Ligustrum lucidum Fruit 15:1 Ext. 60 mg
Panax ginseng (white) Root Ext. 80% Ginsenosides 60 mg
Cat's Claw (Uncaria tomentosa) Bark Ext. 3% Pentacyclic Alkaloids 60 mg
Peony (Paeonia lactiflora) white Root without Bark Ext. 10% Paeonol 44 mg

Polygonum multiflorum Root 10:1 Ext. 44 mg
Cured Rehmannia (Rehmannia glutinosa) Root & Rhizome 4:1 Ext. 41 mg
Licorice (Glycyrrhiza glabra) Root and Rhizome Ext. 26% Glycyrrhizic Acid 35 mg
Lycium (Lycium chinense) Fruit Ext. 10% Polysaccharides 35 mg
Dong Quai (Angelica sinensis) Root Ext. 1% Ligustilide 31 mg
Deer Velvet Antler (Cornu cervi parvum) 30 mg
Tangerine (Citrus reticulata) Peel 4:1 Ext. 30 mg
Cinnamon (Cinnamomum cassia) Bark Ext. 20% Polyphenols 9 mg
Luo Han Guo (Siraitia grosvenorii) Fruit Ext. 9 mg
MSM (Methyl Sulfonyl Methane) 7 mg
Long Pepper (Piper longum) Fruit Ext. 1.5% Piperine 5 mg

Clinical Pearl Summary: The Estrobolome



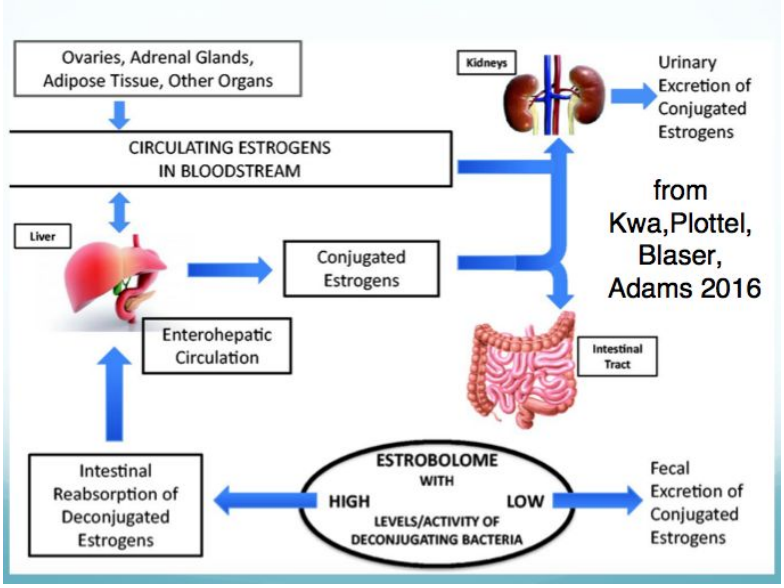
- Direct effects (*H. pylori*)
- Hyperinsulinism
- Obesity
- Inflammation (via metabolic endotoxemia, elevated serum LPS)
- Hyperestrogenism (via β-glucuronidase)
- Cancer cell proliferation (via low SCFAs)
- Anxiety
- Depression
- GI distress
- Immune function
- *C. diff* risk (via competitive exclusion)
- Intestinal wall integrity/bacterial translocation (neutropenic fever, sepsis)

3 Modifiable Microbial Biotransformations Influencing Cancer Prevention & Treatment

1. **De-Conjugation:** Reversal of Liver Detoxification by **Microbial Deglucuronidation** Enzyme β-glucuronidase

2. **Production of Toxic Secondary Bile Acids** by Microbial Dehydroxlyation Enzyme 7-α-dehydroxylase (CYP7A1)

3. **Production of Butyrate from Dietary Fiber to AcetylCoA to Butyrate** by Butyrogenic Pathway (6 microbial enzymes)



Hormone-dependent breast, ovarian, and endometrial cancer

- **The gut microbiome modulates estrogen metabolism** and contributes to the proportion of re-circulated and excreted estrogen and estrogen metabolites
- Reduction in the population of specific gut bacteria in humans causes increased fecal excretion of conjugated estrogens and decreases in urinary estrogens
- **Deconjugation may result in greater reabsorption of free estrogens, & development of estrogen-driven cancers such as breast, ovarian, and endometrial cancers.**

Dietary Interventions for Lowering Beta-Glucuronidase

INCLUDE
Cultured or Fermented dairy or non-dairy products

Cruciferous Vegetables

Foods High in Soluble PreBiotic Fiber

A Multi-Species Probiotic Supplement with L.GG

Scutellaria baicalensis Huang Qin Root
rich in BG Inhibitor baicalin

Dietary Interventions for Lowering Beta-Glucuronidase

Plant Based Vegetarian Diet or plant based diet low in animal proteins. **High meat diets increases BG** Vegetarian diets are associated with reduced concentrations of Clostridial cluster XIVa bacteria

Raw Vegan Diet Change from standard diet rapidly and significantly reduces BG activity

Avoidance of Heterocyclic Amines from Charred Grilled Animal Proteins plus ingestion of Lactobacillus and Bifidobacterium

Lower Incidence of Breast Cancer in Vegetarian Women

- Vegetarian women excrete 2 to 3 times more estrogens in feces than do omnivores
- Omnivores have about 50% higher mean plasma level of unconjugated estrone and estradiol than vegetarians
- In vegetarians a greater amount of the biliary estrogens escape reabsorption and are excreted with the feces

Cancer Res. 1981 Sep;41(9 Pt 2):3771-3. Effect of diet on excretion of estrogens in pre- and postmenopausal women. Goldin BR, et al

Laboratory Assays

Created by Vectors Market from Noun Project

Fecal Beta-glucuronidase

Microbiota Profiles

http://ubiome.com/

Summary

- A woman's lifetime burden of estrogen exposure may reflect the metabolic functioning of her Estrobolome (the aggregate of enteric bacteria that metabolize estrogens)
- Enteric Bacteria influence enterohepatic circulation of estrogens
- The composition of the Estrobolome is linked to the enteric microbiome and estrogen driven cancers

Summary

- Bacterial Beta Glucuronidase deconjugates conjugated estrogen metabolites reversing liver detoxification and estrogen metabolite excretion
- Dysbiotic intestinal ecology produces increased amounts of beta-glucuronidase in the Estrobolome
- Entero-PhytoEstrogens, intestinal metabolites activated by microbiota, act as SERMS, exerting both estrogenic and anti-estrogenic effects

Primary References

Microbiome and Malignancy
Plottel, Claudia S. et al.
Cell Host & Microbe , Volume 10 , Issue 4 , 324 – 335 October 2011

Review Article:Evolving Concepts: How Diet and the Intestinal Microbiome Act as Modulators of Breast Malignancy
ISRN Oncology
Volume 2013 (2013), Article ID 693920, 10 pages
http://dx.doi.org/10.1155/2013/693920
Iuliana Shapira, Keith Sultan, Annette Lee, and Emanuela Taioli

The Intestinal Microbiome and Estrogen Receptor-Positive Female Breast Cancer.
J Natl Cancer Inst. 2016 Apr 22;108(8)
Kwa M1, Plottel CS, Blaser MJ, Adams S.