Diet, Inflammation, and Cancer Prevention

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What is Cancer Prevention?

- Cancer Prevention
- Cancer Treatment
- Survival with Cancer
- Survival without Cancer


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Hallmarks of Cancer: A Genomic Disease

- Sustained Proliferation
- Resist Apoptosis
- Avoid Growth Suppression
- Inducing angiogenesis
- Achieving Immortality

Hanahan and Weinberg, 2006
The Molecular Signature of Colon Cancer

Distal Colon and Rectum

- APC → ACF → KRAS → Adenoma → Carcinoma
  - p16, GSTP1
  - COX2
  - DCC, SMAD3/4, p53
  - CIN

Proximal Colon

- Normal Mucosa → Hyperplastic Polyp → Serrated Adenoma → Carcinoma
  - Mutagens → MLH1 promoter methylation
  - BRAF
  - MSI
  - MHC class I or β2 microglobulin
  - hypermutation

>80% with mutations in:
- TGFbr2
- TAF1B
- TBP
- PTHL3
- MACS
- ACVR2

Fearon and Vogelstein, 1990, Cell  61:759

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“If genetic damage is the match that lights the fire (of cancer), inflammation may provide the fuel that feeds the flames.”

Dr. Fran Balkwill
Barts Cancer Institute
Queen Mary University of London
New Hallmarks of Cancer

Involvement of the Immune System

Emerging Hallmarks

Deregulating cellular energetics

Avoid Immune Destruction

Genome instability and mutation

Tumor Promoting Inflammation

Enabling Characteristics

Hanahan and Weinberg, 2011
Innate Immunity
Non-specific, Rapid

Adaptive Immunity
Specific, slower

Colitis Stimulates Intestinal Immunity

Gut microbiome

Mucosal Layer

Epithelial Layer

Damage

Bleeding

Immune cell infiltration and cytokines

Colitis-Enhances Tumorigenesis in Mice

CAC; APC\(^{\Delta580/+}\)
20 wk, 10% Incidence

CAC; APC\(^{\Delta580/+}\)
2% DSS, 5 or 7 d @ 10 wks
50% Incidence


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Inflammation-Induced Cancer is “Different”

Sporadic Cancer of the Distal Colon and Rectum

Colitis Associated Colon Cancer

Terzic et al. (2009) Gastroenterology 138:2101

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How Does Inflammation Induce Carcinogenesis?

Possible Mechanisms:

- ROS or RNS-induced DNA damage
- Release of bacterial genotoxins
- Cytokine-induced
  - Disruption of barrier
  - Proliferation
  - Suppression of apoptosis
Severe Vitamin D Deficiency Enhances DSS-Induced Colitis

Colitis examined 10 d after a 6 d course of DSS

Many other dietary agents suppress colitis

Lagishetty et al. (2010) Endocrinology 151:2423
How Does Nutrition Block Inflammation or its Effects?

Monday Morning Split Session A: Dietary Modulation of the Microbiome and Cancer Risk

Terzic et al. (2010) Gastroenterology 138:2101
Dietary Interventions that Reduce Colitis-Associated Cancer Change the Gut Microbiome

Curcumin

Eicosapentanoic Acid (EPA)

McFadden et al. 2015 Inflamm. Bowel Dis. 21:2483

How Does Nutrition Block Inflammation or its Effects?

Direct effect on epithelial cells:
- Anti-proliferative
- Pro-apoptotic
- Regulate tight junctions
- Protect from ROS
- Protect from cytokines

Terzic et al. (2010) Gastroenterology 138:2101
1,25(OH)$_2$D Suppresses Pro-Inflammatory Cytokine Signaling in PEC

- RWPE1
- “Normal” prostate cells
- 100 nM, 1,25(OH)$_2$D
- microarray

Kovalenko et al. 2010 BMC Genomics 11:26
$1,25(\text{OH})_2 \text{D}$ Induces Antioxidant and DNA Protective Mechanisms in PEC

= ChIP-seq peak

**GSA c2. 6h NRF2 TFs**
- MAFB 4.68
- MAFF 1.94
- MAFK 1.27

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- GADD45a 2.1 x
- RAD9A 1.7 x
- VRK3 1.6 x
- SULT1A3 1.7 x

Protection from DNA Damage

<table>
<thead>
<tr>
<th>Glucose -6-P</th>
<th>6-phosphogluconon δ lactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSH</td>
<td>NADP</td>
</tr>
<tr>
<td>GSSG</td>
<td>NADPH</td>
</tr>
<tr>
<td>G6PD 3.4x</td>
<td></td>
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</tbody>
</table>
Dietary Lipids Can Be Anti-Inflammatory

Linolenic acid

ω3FA family

5LOX

EPA

15LOX

COX1

COX2

TXA

PGE3

PGI3

GPCR

PPAR

GPCR PKA/cAMP

Inflammation

Membrane composition

DHA

5LOX

COX2

Resolvins Protectins

Hou et al. (2016) Annu Rev Nutr 36:543

Greene et al. (2011) Prostagl Other Lipid Mediat 96:27

Barbalho et al. (2016) Ann Gastroenterol 29:37
How Does Nutrition Block Inflammation or its Effects?

Direct effect on Immune cells:
- Multiple cell targets

Terzic et al. (2010) Gastroenterology 138:2101
Increased DSS Effect with Loss of Vitamin D Signaling

n=8/group
8 wk M + F
C57BL/6j

Body Weight

1.35% DSS
5 days

Colon Inflamm.

Vitamin D Deficiency

Increased DSS Effect with Loss of Vitamin D Signaling

Fleet 2015
Nutrients Regulate Immune Cells

Hewison (2011) Vitamin Horm. 86:23
1,25(OH)$_2$ D Influences MΦ Biology

Bone Marrow
- HSC
- M-CSF
- PU.1
- MDP
- M-CSF
- PU.1
- MoP

Blood
- Monocyte
- MCP-1/CCR2

Colon
- Th1
- IL-12
- IFN-γ
- IL-4
- IL-10
- IFN-γ+LPS
- Pro-inflammatory
- M1
- Tolerogenic
- M0
- M2
- Th2/Treg

Hematopoietic Stem Cell (HSC)
Monocyte and Dendritic Cell Progenitor (MDP)
Monocyte Progenitor (MoP)
Monocyte
CCR2
MCP-1
Positive Regulation by Vitamin D
Negative Regulation by Vitamin D

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1,25(OH)\(_2\) D Influences MΦ Biology

**Figure A**
- DSS
- Time (wks)
- AOM
- Sacrifice

**Figure B**
- CD68 staining
- VDR\(+/-\)
- VDR\(-/-\)
- 2.5X

**Figure C**
- Tumor incidence (%)
- Adenoma + Ca
- VDR\(+/-\)
- VDR\(-/-\)
- p=0.001
- p=0.1

**Figure D**
- Tumor size (mm)
- VDR\(+/-\)
- VDR\(-/-\)
- IL6
- TNFα
- IL1β

*Dougherty et al. (2014) Clin Cancer Res 20:5848*
A Healthy Immune System Can Clear Transformed Cells
A Healthy Immune System is Needed to Fight Cancer

Immunodeficient

Carcinogen

200 days

Immunocompetent

Carcinogen

200 days

Schreiber et al. (2011) Science 331:1565
The Tumor Microenvironment is Complex

Immune Inflammatory Cells
Fleet Lab

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How Does Inflammation Promote Cancer?