Gut microbes and the cancer macroenvironment

Origins of Cancer
Van Andel Research Institute
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Healthful longevity

Th-1  Th-2  Th-17  T_{REG}
Why use animal models?
Gut microbe-triggered systemic events

(modified from Coombs, et al 2005; Fiona Powrie lab)
Adoptive Cell Transfer Paradigm

Transplantable anti-inflammatory CD4+CD45RBloCD25+ lymphocytes

Adoptive cell transfer

Cells extracted from immune-competent donor mouse

Cells injected into recipient without its own lymphocytes

Wild type mouse donor

Rag2-KO mouse recipient
Innate immunity is sufficient for IBD and carcinoma

Cells of adaptive immunity suppress IBD and carcinoma

(Erdman et al 2003)
Invasive colonic carcinoma in *H. hepaticus*-infected Rag2-/- mice

Blocking inflammation leads to total remission of established invasive colonic carcinoma.
Interleukin-10

$T_{REG}$

Pro-inflammatory cells & cytokines

Tumor growth
gut bacteria \rightarrow \text{inflammation} \rightarrow \text{cancer}

\text{Interleukin-10} 

\text{T}_{\text{REG}}
A Dominant Mutation That Predisposes to Multiple Intestinal Neoplasia in the Mouse

Amy Rapaich Moser,* Henry C. Pitot, William F. Dove

In a pedigree derived from a mouse treated with the mutagen ethylnitrosourea, a mutation has been identified that predisposes to spontaneous intestinal cancer. The mutant gene was found to be dominantly expressed and fully penetrant. Affected mice developed multiple adenomas throughout the entire intestinal tract at an early age.
Luminex (serum protein) assay reveals that serum levels of cytokine TNFα and IL17 were significantly increased in aged Min mice at high risk of intestinal polyposis. Serum cytokine levels in pg/ml. Statistics using 2-tailed Student’s t-test; ns, not significant *=p>0.05. **=P>0.01.

we thank Werner Olipitz
*H. hepaticus*-infected \(Apc^{\text{Min}/+}\) mice rapidly develop mammary tumors.
Innate Immune Inflammatory Response against Enteric Bacteria *Helicobacter hepaticus* Induces Mammary Adenocarcinoma in Mice

Varada P. Rao,¹ Theofilos Poutahidis,¹,³ Zhongming Ge,¹ Prashant R. Nambiar,¹ Chakib Boussahmain,¹ Yan Yan Wang,² Bruce H. Horwitz,² James G. Fox,¹ and Susan E. Erdman¹
Breast Cancer: Should Gastrointestinal Bacteria Be on Our Radar Screen?

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Cancer Res 2007; 67: (3). February 1, 2007
Do intestinal bacteria modulate breast cancer?

**INTESTINE**  
**BREAST**

**Systemic inflammatory response**

*Translocation of bacteria or antigens?*

*Systemic elevation in cytokines or activated cells?*

**In health**

- **IL-10**
- **T<sub>REC</sub>**

**In pathogenic gut infection**

- **Bowel epithelia**

**Breast epithelial injury & dysregulation**

- **carcinoma**
- **normal**
Modern Hygiene Practices

From the above discussion, it is clear that pathogenic gut bacteria may pose a trigger for breast cancer. However, this seems to be only half the story. It does not explain why breast cancer risk is increasing in developed countries with more rigorous hygiene practices, or answer how chronic use of prescribed antibiotics enhances the risk for breast cancer in women (4). The “hygiene hypothesis” is based on the observation that early childhood infections reduce the incidence of allergies (24). A later counter-regulatory model of the hygiene hypothesis, forwarded by Wills-Karp et al. (24), postulates that microbial infections have a beneficial role in the developing immune system and that the anti-inflammatory cytokine interleukin 10 (IL-10), produced by cells of both innate and adaptive immune...
Can a beneficial ‘probiotic’ microbes of the perinatal window induce host immune stability later in life?
Skin wounds heal twice-as-fast when mice eat beneficial microbes

Biopsy

1 day

2

3

4

5

6

7

8

Wound Closure

day 3

day 6

day 12

Wound Histopathology

day 3

day 6

day 12

Control

L. reuteri
Skin wounds heal twice-as-fast

Poutahidis et al 2013
Microbe-induced benefit in wound repair requires oxytocin

Biopsy

1 day 2 3 4 5 6 7 8 days

a. oxt-WT + L. reuteri (D6) oxt-KO + L. reuteri (D6) Morphometric Analysis

Wound Closure

Wound Area Size

Oxt-WT + L. reuteri Oxt-KO + L. reuteri

Wound Area, pixels

p=0.007

b. Histopathology

Day 6 Re-epithelization

Oxt-WT + L. reuteri Oxt-KO + L. reuteri

Wound Area, pixels

p=0.004
Physical, mental & social fitness

“my bacteria made me do it”
Gut microbe-induced phenotypes are transplantable

Probiotic-fed donor

Ingestion

adoptive cell transfer

Cells extracted from gfp donor mouse

Transplantation of CD4+Foxp3+gfp lymphocytes

Cells injected into Rag-KO recipient without its own lymphocytes

Rag2-KO recipient

Probiotic benefits
Pilot Study in Human Subjects

Human Skin Wound Closure

![Graph showing wound closure for Group A (n=7) and Group B (n=7).]

Scale (in every photo)

Boundary of wound for area determination

A

B
Wound healing capacity

MICROBES

OXYTOCIN

IMMUNITY

Thymus
Oxytocin
Vagus nerve
Brain
Hypothalamus
Oxytocin
Thymus
Spleen
Central and peripheral immunity

Bone marrow
Intestine
Importance of wound healing capacity

Stages of Normal Cutaneous Wound Healing

Improved wound healing $\rightarrow$ longevity
Feeding of probiotic microbes inhibits intestinal polyposis in Min mice
Healthful Longevity

MICROBES

BRAIN

IMMUNITY

Thymus
Oxytocin
Vagus nerve
Brain
Hypothalamus
Oxytocin
Bone marrow
Intestine
Spleen
Thymus
BRAIN
MICROBES
IMMUNITY
Harnessing microbes for public health
Thank you!

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