Mechanism of Action of Probiotics

Patricia Conway (Prof)

School of Chemistry and Biomedical Engineering, Nanyang Technological University, Singapore
(NTU Food Technology Centre)
&
School of Biological, Earth and Environmental Sciences, The University of New South Wales, Australia
Conflict of Interest Statement

No conflict of interest for material in this presentation

- Given lectures sponsored by companies commercialising probiotics eg Nestle Nutrition Institute, Danone and Yakult
- Developed probiotic based products eg supplements and foods for food and biotech companies
- Currently Chief Scientist for ProBiOz P/L
Overview

- Historical perspective
- Gut microbiota
- Concept of probiotics?
- Probiotics for infections
- Probiotics for non-infectious diseases
- Limitations with identifying mechanisms
Historical Perspective

Lactobacillus used for a HUGE range of conditions

Conflicting outcomes; Poorly defined products/preparations; controversy

Antibiotics developed; probiotics not needed

Probiotics for digestive tract uses only
Eg Lactobacillus and Bifidobacterium

Improved methods for studying gut microbes; Probiotic applications increase dramatically with defined studies and models for testing.

Gut microbes and health; long list of potential benefits; gut focus

Reduce intestinal putrefaction; Eat yoghurt
Increase longevity (1907) Nobel prize – macrophages
Microbiota and the emerging pandemic of NCDs (Non-Communicable Diseases)

Early life exposures
- Mode of delivery
- Infant diet
- Antibiotic usage
- Environmental factors

Life style choices
- Diet
- Medications
- Stresses

Gut microbiota
- Dysbiosis
  - Disease
    - Immune atopy, asthma, multiple sclerosis, respiratory
    - Intestinal inflammatory bowel disease, diarrhoea; IBS, necrotising enterocolitis, colon cancer
    - Metabolic; Liver diabetes, obesity
    - Mental; neurological

- Symbiosis
  - Health
    - Immune tolerance, intestinal homeostasis, healthy metabolism
Overview

• Historical perspective
• Gut microbiota
• **Concept of probiotics**
  • Probiotics for infections
  • Probiotics for non-infectious diseases
  • Limitations with understanding mechanisms

Not just targeting the microbiome
Possible actions of some probiotic strains.

- **Improved digestive health**: Less infection, disease, constipation, diarrhea.
- **Reduced metabolic disorders**: Less obesity, diabetes.
- **Improved immune modulation**: Reduced infection, inflammation.
- **Neurological improvement**: Improved function, new nerve cell growth, less anxiety.

**Stress**: emotional, dietary, medications, physical, ageing.

**Probiotics**

**Diet**

**Host**

**Bacteria**
Probiotics

Most common genera:
- Lactobacillus
- Bifidobacterium

Most common species:
- Lactobacillus acidophilus

Genus species STRAIN:
- e.g. Lactobacillus acidophilus GG

Different preparations – different mechanisms of action
What is a probiotic?

• FAO/WHO definition
  (live, survive low pH and bile, colonize by adhesion; beneficial)
  • Predominately lactobacillus and bifidobacteria
  • What about *Saccharomyces boulardii*?
  • What about spore forming *Bacillus* spp or *Clostridium* spp?
  • What about heat killed bacterial preparations?
  • Single strains or mixed strains
  • Next generation probiotics eg *Faecalibacterium prausnitzii*
  • Faecal homogenates?
Mode of action
Prophylactic or therapeutic?

Direct effect on:
- a pathogen (bacterial/viral/protozoal)
- the host immune system
- the host physiology
- enzymatic capacity
- drug metabolism

Indirect effects on:
- Gut microbiome
- Host immune modulation
- Host physiology
- Respiratory conditions
- Metabolic diseases
- Neurological conditions
- Cancers
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Benefits: impact on infection
(bacterial; viral; protozoal)

Inhibition of pathogen growth
- pH, organic acids, H₂O₂, peptides (AMPs)

Inhibition of pathogen adhesion
- block receptor (steric hindrance; specific receptor)

Competition for nutrients
- outcompete pathogen for essential nutrients

Immune triggering
- Trigger IgG and IgA secretion

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<thead>
<tr>
<th></th>
<th>Salmonella</th>
<th>Probiotic A</th>
<th>Probiotic B</th>
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</thead>
<tbody>
<tr>
<td>Growth inhibition</td>
<td>6%</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>Adhesion inhibition</td>
<td>6 times</td>
<td>100 times</td>
<td></td>
</tr>
<tr>
<td>Weight change of mice</td>
<td>-7%</td>
<td>+0.8%</td>
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</table>

Inhibition of *E.coli* ETEC

Weight change of mice
-7% to +0.8%
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Benefits: non-infectious (non-communicable diseases)

Modulation of inflammation
– immune receptor cascade signalling

Neurological signals to and from the gut

Enhanced barrier function of the gut epithelium
- Enhanced mucin production
- Enhanced integrity

Reduced risk of cancer
- apoptosis related enzymes;
- prevent enzymatic co-carcinogen conversion
- Immune responses

Outcompete antimicrobial resistant (AMR) bacteria
- Microbiome targets
Gut-associated lymphoid tissues (GALT)
Adaptive Immunity

Mucosal Site
- Digestive tract
- Respiratory tract
- Nasal cavity
- Vaginal tract
- Urinary tract
- Mammary glands
- Skin

Activation of T cells and B cells
Less IgE (less allergy); More IgA and IgG (less infection); Altered cytokines (less inflammation)
Modulation of lipopolysaccharide (LPS) inflammation

- Gut inflammation commonly caused by LPS
- Attenuated TNF-α production in both prophylactic and therapeutic models

Specific strains not included, but are defined

Esvaran (2011)
Innate Immunity
(responds to pathogen associated molecular patterns ie PAMPs)

Pattern recognition receptors PPRs
eg Toll-like receptors (TLRs and NOD 2)

Bermudez et al
Ann Nutr Metab 2012;61:160-174
DOI: 10.1159/000342079
Gut–brain axis (GBA).
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**Limitations with identifying mechanisms**
Methods for studying mechanisms

- “Omics” – who is there and what are they doing (metagenomics; transcriptomics; metabolomics; proteomics)
- Host physiology (biological sampling)
- \textit{In vitro} and \textit{ex-vivo} models
- Tissue culture (2D and 3D) and organoids
- Animal models (germ free, knock-out mice and SPF)
- \textit{In vivo} data correlations with \textit{in vitro} studies
Factors Impacting on Probiotic Actions

- Medications
- Diet
- Stressors
- Age
- Dental health
- Infection
- Hygiene
- Sanitization
- Urban/rural
- Genetics
- Environment
- Exercise
Cautions & Limitations

- Need to define strains
- Models for studying mechanisms (in vitro assays, animals)
- Models provide evidence of mechanism (pathways affected)
- Extrapolation from models has limits
- Need measurable effects
- Understand limitations of clinical studies (number and diversity of subjects)
- More than just fixing the microbiome (host physiology and immune aspects)
Understanding modes of action: 
– allows understanding outcomes
Conclusions

- Strain dependant effects
- Benefits can be direct or indirect
- Can impact on infection agents
- Can influence non-infectious diseases (immune triggering)
- Can have prophylactic and/or therapeutic effects
Thank you