From Prebiotic Concept to Prebiotic Effects: Metabolic and Health Benefits

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ILSI Europe Prebiotics Task Force

Basic question:

Which data support the hypothesis of a causal relationship between a selective change in gut microbiota composition and health effects/benefits?
Prebiotic effects: metabolic and health benefits

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  &

  Prebiotic effects on:

  - Gut
  - Immune system
  - Paediatrics
  - Gastro-intestinal disorders
  - Mineral metabolism
  - Weight management and obesity-related disorders

- Conclusions and perspectives
Introduction: Prebiotic concept & Prebiotic effects on:

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Conclusions and perspectives
Introduction: the prebiotic concept

Gut microbiota a key player in health and well-being

- A composition in which potentially health promoting dominant microorganisms

- Elevated and/or more active saccharolytic genera/species e.g. bifidobacteria)

- Reduced proteolytic/putrefactive genera/species potentially harmful ones

- Situation: ‘normobiotic’ or ‘eubiotic’.
Introduction: the prebiotic concept

Health beneficial dominant microbiota:

- Genus *Bifidobacterium* plays an important role
- Future Research different genera/species (eg *Eubacterium*, *Faecalibacterium* and *Roseburia*)

Hypothesis:
Increasing these genera/species in gut microbiota, might improve health status and reduce disease risk.
Introduction: the prebiotic concept

Validate and expand the original idea of the prebiotic concept as:

“The selective stimulation of growth and/or activity(ies) of one or a limited number of microbial genus(era)/species in the gut microbiota that confer(s) health benefits to the host”,
Introduction: the prebiotic concept

- “Selectivity”
  the key condition that needs to be demonstrated, *in vivo*, in the complex human (animal) gut microbiota

- “Activity(ies)”
  a metabolic profile(s), molecular signalling, prokaryote-eucaryote cell-cell interaction

- “Confer(s)”
  referring to one or a limited number of selectively stimulated genus(era)/species
Introduction: prebiotic effects

The conceptual approach emphasizes the LINK between

“selective stimulation of growth and/or activity(ies) of one or a limited number of specific bacteria genus/species”

and “health benefit(s)”

by specific food products/ingredients/supplements
Introduction: Prebiotic concept

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Conclusions and perspectives
**Prebiotic effects and the gut**

Reviewing the most recent data:

- Gastro-intestinal microbiology esp. large intestine
- Bacterial fermentation & physiology incl. substrate utilisation & ferment. products (eg SCFAs)
- *in vivo & in vitro* studies on prebiotic effects;

**CONCLUSIONS are:**
**Prebiotic effects and the gut: Conclusions I**

*In vitro test:*
comparaison, selection, identification and quantification
potential ingredients & fermentation products

The multi-stage models are designed
to mimic the different segments of the intestine

*In vivo studies*
essential to prove the prebiotic effect
2. Non-digestible carbohydrates with prebiotic effects selectively stimulate the growth of bacterial genera/species characterized exclusively, or preferably, by saccharolytic fermentation.

3. This is well established today for prebiotic effects favouring the growth of bifidobacteria and lactobacilli. Emerging genera are Eubacterium, Faecalibacterium and Roseburia although more evidence is needed on their physiological properties.
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Prebiotic effects and the immune system

Rationale:

- That modulation of the immune system may result from prebiotic effects is based on the interaction between the intestinal microbiota and the host immune system.

- The microbiota is essential for an optimal structural and functional development of the immune system.
Prebiotic effects and the immune system

Rationale:

- **Interactive co-existence of immune cells and microbiota** is strongest in GI tract: GALT:
  - **optimal defense:** against intestinal pathogens,
  - **tolerance:** dietary and self-antigens, commensal non-pathogenic microbiota.

- **Intestinal cells key intermediates** convey signals from intestinal lumen to mucosal immune system and are target for a prebiotic effect on immune system.
Prebiotic effects and the immune system

Mechanisms:

- **Prebiotic effects may influence the immune system directly or indirectly** via intestinal fermentation and selective promotion of the gut microbiota, thus, that may change the immuno-interactive profile of the microbiota.

- **Through pattern-recognition receptors** (eg. TLR), both immune cells and enterocytes interact with pathogen-associated molecular patterns (PAMPs), (eg. LPS, lipoteichoic acids and unmethylated CpG DNA)
Prebiotic effects and the immune system

Mechanisms:

- These interactions result in a variety of downstream events eventually leading to cytokine production steering towards an appropriate immune response.

- SCFAs may interact with immune cells and enterocytes and modify their activity through binding to G-protein coupled receptors and modulate chemokine expression in intestinal epithelial cells.
Prebiotic effects and the immune system:

Conclusions

- Limited, yet promising, evidence that ingredients showing a prebiotic effect modulate immune markers in humans.

- Important to know whether such an immuno-modulation results in a clinically relevant outcome.

- Preliminary yet promising clinical endpoint studies exist that integrate the measurement of immune markers as possible explanation of prebiotic efficacy.
Introduction: Prebiotic concept

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Conclusions and perspectives
Prebiotic effects in Paediatrics

- One type of oligosaccharide mixture consisting of galactooligosaccharides and high MW inulin (scGOS/lcFOS; ratio of 9:1) has, so far, been extensively evaluated for paediatric applications.

- Directive 2006/141/EC on infant and follow-on formulae specifically allows the addition of GOS/FOS in a ratio of 9/1 and in a quantity of 0.8g/100 ml prepared product
Prebiotic effects in Paediatrics

Conclusions

- GOS/FOS increases, selectively and dose-dependently, the number of bifidobacteria in faeces and modulates stool characteristics (consistency, pH, & SCFAs pattern) similarly to breast fed infants.

- Controlled trials show that GOS/FOS is able to reduce the incidence of atopic diseases, the effect persists beyond the intervention period,

- Reduce the risk of some infectious diseases

- The available data on prebiotic effects do NOT demonstrate adverse effects in infants
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Prebiotic effects and IBS

- To date, two published studies of adequate design report the positive effects of ITF and GOS in IBS.

- Evidence accumulated so far in well-designed clinical studies is limited, but suggests possible benefits at moderate doses.
Prebiotic effects and gastro-intestinal disorders

Prebiotic effects and IBD

- There is convincing evidence that patients with IBD have a GI dysbiosis characterised by lower concentrations of luminal and mucosal bifidobacteria and of SCFAs suggesting a potential for prebiotic intervention.

- Numerous small pilot human studies have been conducted in pouchitis, UC and CD indicating potential benefit in treating active disease.

- Results are substance- and study-specific, but do not warrant a conclusion for prebiotic effects in general.

- No adverse effect has been reported.
Prebiotic effects and gastro-intestinal disorders

Prebiotic effects and gastro-intestinal infections

- **Experimental studies** in different models of IBD have demonstrated beneficial effects of ingredient with prebiotic effects.
- **In humans**, the number of studies on the efficacy a prebiotic effect in the prevention of infectious diseases is limited.
- Clearly, a rationale is present but the measurement of the putative associated effect on the microbiota is not always included in these studies, hindering any conclusions on possible underlying mechanisms.
Prebiotic effects and colon cancer

- **Experimental studies**, in different models of colon carcinogenesis, have demonstrated beneficial effects of ingredient with prebiotic effects.

- These studies show beneficial effects on:
  - incidence & yield of aberrant crypt foci, tumours and cancers
  - changes in gut bacterial enzyme activities,
  - up-regulation of apoptosis & induction of protective enzymes
Prebiotic effects and colon cancer

- **In humans**, up to date, only one study on the efficacy of a prebiotic effect in the reduction of risk is available based on early or intermediate biomarkers of cancer.

- **Data show a reduction in DNA damage, cell proliferation in colon biopsies and genotoxic activity of faecal extracts**
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- Conclusions and perspectives
Experimental studies, in different models, show that ingredient with prebiotic effects increase Ca and Mg (and possibly Fe) absorption & bone min. dens.

A possible mechanism is extension of the site of mineral absorption (through the tight junctions) towards the large intestine.

Clearly, a rationale is present to consider that compounds showing prebiotic effects as a source for putative innovative dietary health intervention for improvement of mineral retention.
Prebiotic effects and mineral metabolism

In humans

- Enhanced calcium absorption, depending on age (e.g., adolescents) or physiological status (no effect in early postmenopausal women).

- In adolescents, the long term benefits translate into benefits to bone health, especially enhancement of calcium accretion in bones, but also bone mineral density.
Introduction: Prebiotic concept

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Conclusions and perspectives
Prebiotic effects in weight management and obesity-related disorders

Regulation of food intake, fat mass and body weight

In experimental studies
- regulate food intake, fat mass and weight gain,
  (possibly via a modulation of GI peptides production)
- modulate metabolic disorders assoc. with obesity,
  eg. liver steatosis, dyslipidemia, diabetes, hypertension.

In humans,
- promote satiety and to reduce hunger ,
  (possibly via a modulation of GLP-1, PYY or Ghrelin)
- to help maintaining an appropriate BMI and fat mass
  in non obese adolescents
- to decrease food intake, body weight gain and fat mass development in obese subjects.
Prebiotic effects in weight management and obesity-related disorders

Glucose homeostasis

In humans

- to decrease basal hepatic glucose production, but had no detectable effect on insulin-stimulated glucose metabolism
- to lower blood lipids in normo- and moderately hyperlipidemic subjects but both positive and negative data have been obtained
Prebiotic effects in weight management and obesity-related disorders

**Obesity-associated inflammation**

**Hypothesis:** obesity and insulin resistance are associated with a low grade inflammation due to circulating bacterial LPS as triggering factor. That situation is known as “metabolic endotoxemia” and is likely to be due to change in gut microbiota composition (especially decrease in bifidobacteria).

In mice, an inverse relationship has been established between the level of faecal bifidobacteria and some features of the metabolic alterations linked to obesity (endotoxemia, fat mass, glucose intolerance).
Introduction: Prebiotic concept

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Conclusions and perspectives
Conclusions and perspectives

As a result of the research activity that followed the publication of the prebiotic concept 15 years ago, it has become clear that specific food products/ingredients/supplements that cause a selective modification in the gut microbiota’s composition and/or activity(ies) and thus strengthens normobiosis could either induce beneficial physiological effects in the colon and also in extra-intestinal compartments or contribute towards reducing the risk of dysbiosis and associated intestinal and systemic pathologies.
Conclusions and perspectives

Prebiotic effects on:

✓ Gut
✓ Immune system
✓ Paediatrics
✓ Gastro-intestinal disorders
✓ Mineral metabolism
✓ Weight management & obesity-related disorders
Key questions I

Which of the physiological and/or pathophysiological well-being and health benefits are causally linked with a particular composition of the gut microbiota or (a) selective change(s) therein?

Which observed benefits, is (are) not linked to a particular composition of the gut microbiota or (a) selective change(s) therein but is (are) the consequence(s) of other mechanism(s) of the product claimed to have a prebiotic effect?

Which protocol(s)/markers are validated to demonstrate change(s) in microbiota composition?
Key questions II

Which protocol(s), methodologies and markers are available and validated to demonstrate links between a particular composition of the gut microbiota or a selective change therein and a particular physiological and/or pathophysiological well-being and health benefit?
Conclusions and perspectives

- Increased intestinal levels of **bifidobacteria** in majority of human studies

- Often associated with improvement in accepted markers of health.

- Strongly associates prebiotic effects with GI and systemic health benefits.

- Consideration of results on PRObiotic bifidobacteria:
  - Compelling evidence: Relationship between **intestinal microbiota** (esp. bifidobacteria) and health might well be causal.
Thank you for your attention