PERSONALIZED INTERVENTION STRATEGIES TO KEEP A HEALTH PROMOTING GUT MICROBIOTA CONFIGURATION IN THE ELDERLY

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EU population aged 65y is projected to increase from 17.4% to nearly 30% by 2060 while population aged over 80y and is predicted to triple during this period.

Life expectancy continues to rise but healthy life years do not increase at the same rate, and the time spent in ill health will be even longer in future.

**Gap between life expectancy and healthy life years**

- High pressure on public health and care services

Crucial to identify appropriate strategies to help population age healthy
PATHOPHYSIOLOGY OF AGEING

Immunosenescence and inflamm-aging
changes in lifestyle
changes in diet
reduced intestinal motility
increased intestinal permeability

Impact on the gut physiology and functionality affecting the gut microbiota composition and function compromising its symbiotic relationship with the host

AGED-TYPE MICROBIOTA

PRO-INFLAMMATORY CONSORTIUM THAT PROMOTES THE PROCESS OF “INFLAMM-AGING” BY ESTABLISHING A SELF-SUSTAINED INFLAMMATORY LOOP DETRIMENTAL FOR HOST LONGEVITY
PHYLOGENETIC DIVERSITY

> 1000 species

10 (out of 100) bacterial phyla

- Firmicutes, Bacteroidetes: 90%
- Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia: 10%
FUNCTIONAL DIVERSITY

MICROBIOME
(collective genome of the microbiota)

10^6 GENES

58% KNOWN
• carbohydrate metabolism (CAZymes)
• energy metabolism
• amino acid metabolism
• biosynthesis of secondary metabolites
• metabolism of cofactors and vitamins

42% UNKNOWN

Schloissing et al, Nature 2013
MICROBIOTA PLASTICITY

THE INDIVIDUAL MICROBIOTA COMPOSITION CONTINUOUSLY CHANGES IN RESPONSE TO EXTRINSIC AND INTRINSIC VARIABLES

IN A MUTUALISTIC CONTEXT, THE PLASTICITY OF THE HUMAN MICROBIOTA GUARANTEES A RAPID ADAPTATION OF THE SUPER-ORGANISM IN RESPONSE TO DIET CHANGES, AGE, ETC. THERE IS A STRONG SELECTION TOWARDS A READILY CHANGEABLE INDIVIDUAL MICROBIOME PROFILE.
MUTUALISM BREAKDOWN

the GM is a multistable system with a variable fraction at 40% of the total community

MUTUALISM

n different compositional layouts

Switch-like behavior, making sudden jumps from different steady states

RUPTURE OF THE GM-HOST MUTUALISTIC AGREEMENT AND COMPROMISED HOST ENERGY BALANCE AND IMMUNE HOMEOSTASIS

Faith et al, Science 2013
GM AND INFLAMMATION

Susceptible Host
- Genetics
- Env. Factors

Chronic GIT Inflammation

Pro-inflammatory Loop

Microbiota Dysbiosis

Pro-inflammatory Intestinal Microbial Community

Raise in Pathobionts

Decrease of Immuno Modulatory Groups
THE GM DESCRIBES AN ADAPTIVE TRAJECTORY ALONG HUMAN AGING

GUT MICROBIOTA CHANGES ITS PHYLOGENETIC AND FUNCTIONAL PROFILE FROM INFANCY TO ELDERLY PROVIDING THE HOST WITH ECOLOGICAL SERVICES CALIBRATED FOR EACH STAGE OF LIFE

Candela et al., Critical Rev Microbiol, 2013
ELDERLY-TYPE MICROBIOTA

What happens to the human GM with ageing?

When does microbiome start to change in the healthy elderly?

Do the adaptive gut microbiome changes complement human ageing?
HEALTHY ELDERLY (78 Y) SHOW A MICROBIOTA STRUCTURE COMPARABLE TO THE ONE OF YOUNG ADULTS (35 Y)

ONLY FRAIL ELDERLY SHOW A COMPROMISED MICROBIOME STRUCTURE

Claesson et al., Nature, 2012
DIETARY CHANGES AND FRAILTY-RELATED FACTORS FORCE MICROBIOME DYSBIOSIS WHICH COMPROMISES THE HEALTH OF THE ELDERLY
COMPARATIVE STUDY OF THE GM STRUCTURE IN HEALTHY CENTENARIANS, ELDERLY AND YOUNG ADULTS

Genetically unrelated

- **Young Adults**
  - Group Y: 20 Young adults
    - 11 men, 9 women
    - Age 25-40, mean 31

- **Elderly**
  - Group E: 22 elderly
    - 11 men, 11 women
    - Age 63-76, mean 72.7

- **Centenarians**
  - Group C: 21 Centenarians
    - 1 man, 20 women
    - Age 99-104, mean 100.5

Free-living, “good” physical and cognitive health conditions

Biagi et al., 2010, PlosONE, Collino et al., PlosOne 2013
GM CHANGES IN HEALTHY PEOPLE ARE NOT LINEAR WITH AGE

Hierarchical clustering and RDA show that centenarians tend to group together while no separation was observed between elderly and young adults.

Differences in the microbiota fingerprint between C and all the other subjects are greater than the differences between E and Y.
BLOOD PRO-INFLAMMATORY CYTOKINES

8.9% of the total variability of the GM can be related to the pattern of pro-inflammatory cytokines

GM LAYOUT IN CENTENARIANS MATCHES WITH AN OVERALL INFLAMMATORY ASSET
THE CENTENARIAN GM APPEARS AS DYSBIOTIC

TRACES OF STRUCTURAL AND FUNCTIONAL CHARACTERISTICS WITH THE POTENTIAL TO COMPROMISE HOST METABOLIC AND IMMUNE HOMEOSTASIS

dysbiotic structural features

LOW BACTERIAL DIVERSITY ➔ reduction of ecosystem resilience and stability ➔ DISEASE-ASSOCIATED MICROBIOME

INCREASE OF PATHOBIIONTS ➔ high pro-inflammatory potential ➔ IMMUNE ACTIVATION/INFLAMMAGING
THE CENTENARIAN GM SHOWS AN ENRICHMENT IN PROTEOLYTIC FUNCTIONS

dysbiotic functional features

- HIGH TRYPTOPHAN METABOLISM
  - reduction of tryptophan bioavailability
  - increase of indolic metabolites

- HIGH TYROSINE METABOLISM
  - COGNITIVE IMPAIRMENT
  - IMMUNE ACTIVATION
  - CANCER DEPRESSION DIABETES

Rampelli et al., 2013, Aging
GM AND EXTREME LONGEVITY

Semi-supercentenarians (105-109y)

Increasing abundance of subdominant species

Rearrangement in their co-occurrence network

Enrichment of health associated groups which might support health maintenance during aging

Biagi et al., 2016, Curr. Biol.
GM MODULATION STRATEGIES

Improvement of the healthy status in the elderly by modulating the GM functions

Development of elderly tailored intervention strategies to support/recover a balanced health promoting GM compositional and functional layout:

- Prebiotics
- Probiotics (next generation probiotics)
- Functional foods
- Dietary approaches (whole diet, FP7 KBBE NuAGE)
DIETARY COMPONENTS: SYNTROPHIC MICROBIAL NETWORKS

HOST POLYSACCHARIDE

STARCH

PLANT CELL WALL cellulose

AMINO ACIDS

SOLUBLE CELL WALL POLYSACCHARIDES
hemicellulose, xylan, pectin, mannans,
inulin, fructans

Bacteroidetes

Clostridium clusters IV and XIVa
Faecalibacterium prausnitzii,
Butyrrivibrio, Roseburia,
Eubacterium rectale

Ruminococci

ACETATE

proteolytic clostridia and
Bacteroidetes

(Alistipes)

sulfate-reducing bacteria

methanogens
Methanothermobacter smithii,
Bilophila wadsworthia

acetogens
Blautila hydrogenotrophica

H₂ S

CH₄

ACETATE

SCFA

PHENOLIC AND INDOLIC METABOLITES

METHYLAMINES

BUTYRATE

propionate

SUCCINATE

ACETATE

H₂

low CO₂
IMPACT OF DIETARY FAT ON THE GUT MICROBIAL COMMUNITIES

DIETARY FATS → BILE SECRETION → BILE ACIDS IN THE GUT

- BILE ACIDS IN THE GUT:
  - Firmicutes (Clostridia, Erysipelotrichi)
  - Enterobacteriaceae
  - Bacteroidetes
  - sulfate-reducing bacteria (Bilophila wadsworthia)

SECONDARY BILE ACIDS → H₂S
GM-HOST CO-METABOLIC LAYOUTS

diet regulates microbiota composition and metabolic output with a final impact on host physiology

complex polysaccharides → SACCHAROLYTIC METABOLISM

highly diverse community of polysaccharide-degrading Bacteroidetes and Clostridia establishing syntrophy in the gut

amino acids → PROTEOLYTIC METABOLISM

low diverse community enriched in specialized proteolytic Alistipes and Clostridia

animal fat → FAT ADAPTATION

selection of a low diverse community made of bile resistant Erysipelotrichi, Bilophila wadsworthia, Enterobacteriaceae

SCFA

SCFA

PHENOLIC AND INDOLIC METABOLITES

SECONDARY BILE ACIDS

METHYLAMINES

H₂S

Disease associated

Health promoting

SUCCINATE

CH₄

BCFA

SCFA

Succinate

CH₄
PREBIOTICS FERMENTATION IN HUMAN GUT

(A) Insoluble plant cell wall polysaccharides (cellulose, arabinoxylan, xylolglucan, β-glucan, mann, pectins and lignin) are degraded by primary degraders via soluble polysaccharides, resulting in soluble polysaccharides and oligosaccharides. Syntrophic consortia: primary and secondary degraders produce SCFA and other metabolic products.

(B) Inulin FOS and b-fructofuranosidase from Bifidobacterium spp. degrade inulin to FOS. Starch is degraded by a-amylase, pullulanase, amylopullulanase from Bacteroides spp. to produce succinate. Inulin is degraded by Roseburia inulinivorans Faecalibacterium prausnitzii to produce succinate, which is further degraded by Faecalibacterium prausnitzii Clostridium cluster XIVa to produce acetate and butyrate. Xylan is degraded by Roseburia intestinalis to produce H₂ + CO₂, which is then converted by Ruminococcus hydrogenotrophus and other acetogens to butyrate and acetate.
Next Generation Probiotics

Faecalibacterium prausnitzii

Roseburia

Bacteroides
New dietary strategies addressing the specific needs of the elderly population for healthy ageing in Europe

Appropriate DIET +

Gut microbiota -

INFLAMM-AGEING
NUAGE recruited subjects (65-79 years of age)

A total of 1250 individuals categorized as not frail or prefrail were recruited in 5 European countries (Italy, France, UK, The Netherlands and Poland), and divided into 2 groups:

1. followed a whole “mediterranean” ad hoc fortified/modified diet
2. continued its own diet (control group)
Fig. 4. The NuAge modified Food Guide 65+ Pyramid for the elderly has a narrower base (to reflect a decrease in energy needs), while emphasizing nutrient-dense foods, fibre and water. In addition, nutrient-specific supplements are appropriate for many older people.
NUAGE “OMICS”
BEFORE AND AFTER 1Y DIETARY INTERVENTION

A variety of parameters have been measured (hematological profiles, immunology and inflammation, cognition, genetics, body composition)

- Transcriptomics
- Metabolomics, lipidomics
- GM metagenomics
- Genetics
- Epigenetics

Systems biology approach
Database analysis is ongoing
The elderly of today are very different from those of 20y ago: the emerging wave of more educated people over 65y implies a greater % of older adults paying more attention to their diet.

Age-specific and up-to-date dietary and lifestyle recommendations for elderly in EU are not easy to find.

Older adult population is very heterogeneous (simply referring to people aged +65y is not appropriate).

Improving the GM profile in elderly is a target to reduce their risk for inflammation and metabolic disorders.

Design of elderly-tailored innovative functional foods (soups, drinks, dairy and bakery products, finger foods, snacks, 3D printed foods), counteracting the age related increase of pro-inflammatory pathobionts and sustaining the immune homeostasis.

Consolidation of knowledge about the elderly-microbiome interactions, including the gut-brain axis (how inflammatory and metabolic stimuli from the gut can contribute to cognitive impairment).

Longitudinal studies to follow healthy older adults into very old age and validate the outcomes of the dietary intervention.
THANKS FOR YOUR ATTENTION

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