Archaea: neglected components of the human microbiome

Christine Moissl-Eichinger[1], Guillaume Borrel[2], Jean-François Brugère[3], Ruth Schmitz-Sreit[4], Holger Heine[5], Paul W. O'Toole[6], Simonetta Gribaldo[2]

[1] Medical University of Graz, Department for Internal Medicine, Auenbruggerplatz 15, 8036 Graz, Austria, BioTechMed Graz, Austria
[2] Department of Microbiology, Unit Evolutionary Biology of the Microbial Cell, Institut Pasteur, Paris, France
[3] Université Clermont Auvergne, Clermont-Ferrand, France
[4] University Kiel, Germany, Institute for general and applied Micorbiology
[5] Research Center BorstelDivision of Innate Immunity, Borstel, Germany
[6] School of Microbiology and APC Microbiome Institute, University College Cork, Cork, Ireland

Background

On the occasion of the fortieth anniversary of their discovery by Carl Woese and colleagues, the Archaea are currently in the limelight. However, Archaea have meanwhile become of age. Initially considered extremophilic anomalies, they are now recognized as organisms of universal environmental importance. One specific aspect of archaeal biology is still largely ignored: their presence and role in the microbiome of holobionts, including humans, forming the so called "archaeome".

Methanogenic archaea are amongst the most abundant microorganisms in the human gastrointestinal tract, sometimes outnumbering even the most abundant bacterial species, and of key relevance for the human ecosystem. However, due to their fundamentally different biology, they often remain undetected due to insufficient methodology.

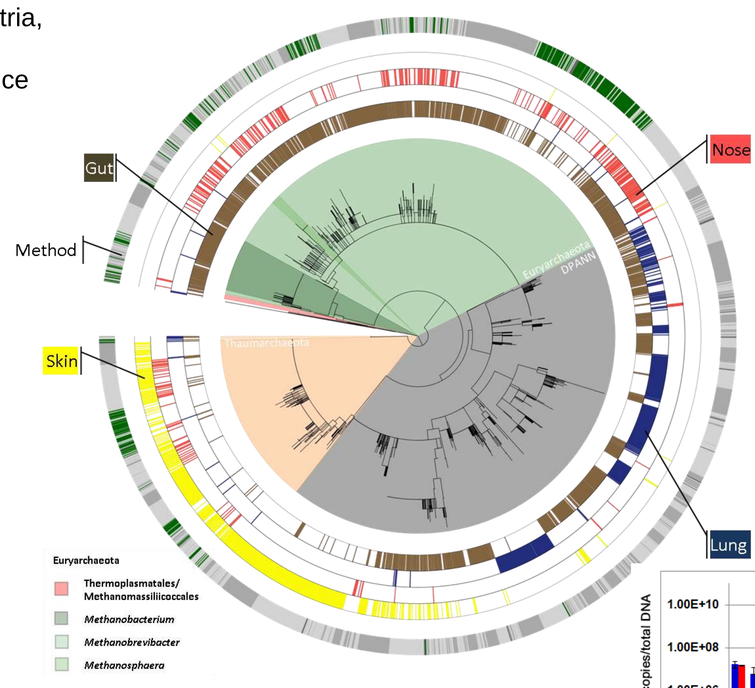

Fig. 1: **Novel insights into the human archaeome.** Phylogenetic tree of novel retrieved archaeal signatures from gut, nose, lung and skin samples. Signatures were affiliated to Euryarchaeota, Thaumarchaeota and DPANN superphylum. The four inner circles display the origin of the respective OTU/RSV: skin (yellow), nose (red), blue (lung), gut (brown)[1].

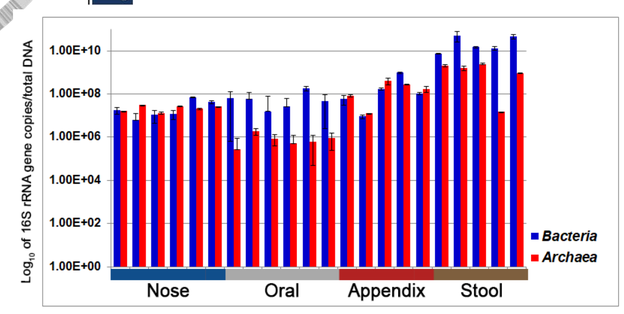

Fig. 2: **Quantitative detection of archaeal signatures in human samples by optimized qPCR.** Ratios Bacteria/Archaea:
Stool samples: 20:1 (0.1 to 21.3%).
Appendix: 1:1 (21.8 to 70.7 %)
Nose: 1:1 (22.8 to 82.8%)
Oral: 77:1 (0.3 to 5.3 %)[2]

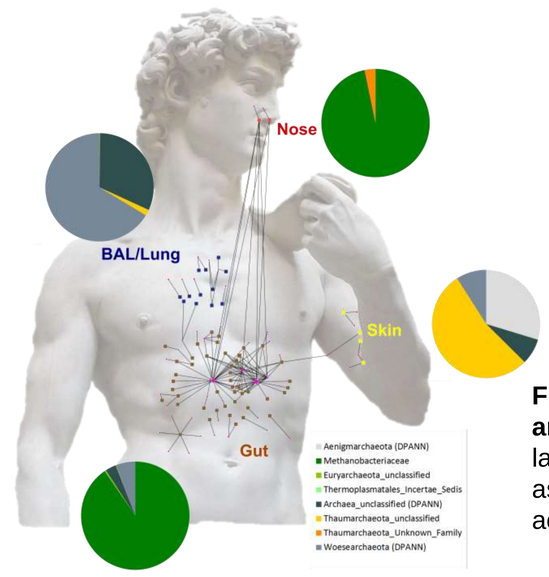

Fig. 3: **The biogeography of the human archaeome.** The archaeal taxonomic landscape of the human body visualised as a network, plotted and arranged according to the sampling origin[1].

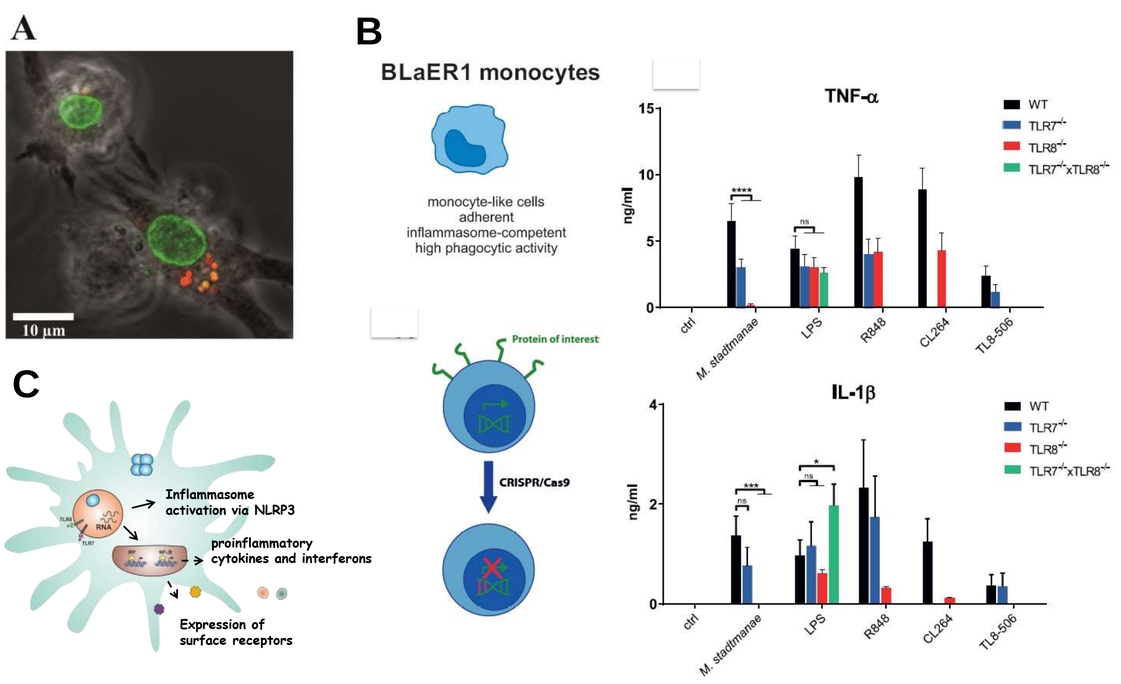

Figure 5. Immune response of human immune cells to methanoarchaea
A DCs were stimulated with *M. stadtmanae* to determine phagocytosis. Formed phagolysosomes in moDCs were stained with LysoTracker Red DND-99, and cells were labeled with Hoechst for DAPI-staining. **B** *M. stadtmanae* is recognized through TLR7 and TLR8 in monocyte-like BLaER1 cells. Clonal BLaER knockout cell lines were stimulated and cytokine release was determined after 20 h. Synthetic antagonisists: R848: TLR7/8; CL264: TLR7; TL8-506: TL8. **C** Schematic simplification of immune cell activation. After phagocytosis, archaeal RNA recognition by TLR7 and TLR8 lead to intracellular signaling cascades, finally resulting in the release of pro-inflammatory cytokines, antimicrobial peptides and the expression of modulatory surface molecules in order to active adaptive immune responses. Additionally the NLRP3-inflammasome is activated.5, [6]

→ ***M. stadtmanae* appears to have the potential to be involved in inflammatory processes (directly or indirectly).**

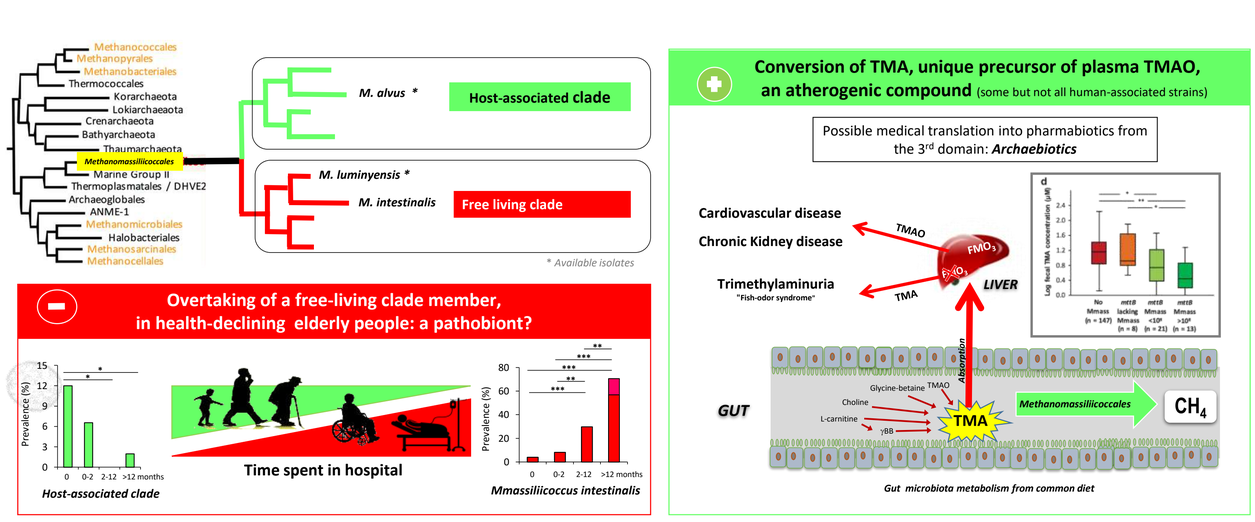

Fig.4: Gut *Methanomassiliicoccales*: some as pathobionts, some as unique beneficial microbes?
Methanomassiliicoccales are euryarchaeal methanogens (phylogeny schematically depicted upper left), that can be divided into two main clades according to their lifestyle. Some of human gut associated *Methanomassiliicoccales* (eg. *Methanomethylophilus alvus*) use trimethylamine (TMA) with H_2 for their methanogenesis, leading to the bioremediation of this deleterious compound (left). Indeed, fecal TMA concentration is lower in subjects carrying high level of *Methanomassiliicoccales*. This property could be used for preventing some important human diseases.[3] However, one species belonging to the free-living clade, but currently retrieved only from gut environment (*Methanomassiliicoccus intestinalis*), is associated with health-declining older people, while it is nearly absent in elderly living in the community (red box, bottom right).[4]

Open questions

With novel methods in place, many basic questions about the contribution of archaea to human microbiomes and health can now be addressed to update our rudimentary and fragmentary knowledge, addressing the most puzzling questions, including:

- How do archaea communicate on intra- and interspecies level, with their hosts or syntrophic partners?
- Are archaea influenced by host parameters?
- When and how are they acquired during life?
- What are the functions of human-associated archaea besides methanogenesis?
- Do archaeal pathogens exist?

Publications

1: Koskinen K, Pausan MR, Perras AK, Beck M, Bang C, Mora M, et al. First insights into the diverse human archaeome: specific detection of archaea in the gastrointestinal tract, lung, and nose and on skin. MBio. 2017;(8(6)):e00824–17.
2: Pausan MR, Csorba C, Singer G, Till H, Schoepf V, Santigli E, et al. Measuring the archaeome: detection and quantification of archaea signatures in the human body. bioRxiv: http://biorxiv.org/content/early/2018/05/30/334748.abstract
3: Brugère et al. (2014). Archaebiotics: proposed therapeutic use of archaea to prevent trimethylaminuria and cardiovascular disease. *Gut Microbes*, *5*(1), 1-5.
4: Borrel et al. (2017). Genomics and metagenomics of trimethylamine-utilizing Archaea in the human gut microbiome. *The ISME journal*, *11*(9), 2059.
5: Bang et al. (2014) The intestinal Archaea *Methanosphaera stadtmanae* and *Methanobrevibacter smithii* activate human dendritic cells, *PlosOne* 9(6):e99411. doi: 10.1371
6: Vierbuchen et al. (2017) The Human-Associated Archaeon Methanosphaera Stadtmanae is Recognized by Its RNA and Induces TLR8-Dependent NLRP3 Inflammasome Activation" *Frontiers in Immunology* 8:1535.

Funding provided by the FWF P 30796 and PhD program MolMed (Medical University of Graz) and DFG (Schm1052/11-2; He 2758/4-2) is gratefully acknowledged.