Conclusions from 475 data

* Age and pMS are the primary divers of the differences, with smoking potentially acting as a modifier rather than a direct control for these factors
  + Smoking modifies or interacts with the effects of age and pMS on the microbiome, amplifying differences that might otherwise remain subtle
  + When smoking is not included, variability within groups might be higher, masking the effects of age or pMS
    - Including smoking reduces unexplained variability by accounting for its effects, making the differences due to age and pMS clearer
  + Therefore, smoking is likely a modifier or amplifier of the effects of age and pMS. This highlights the complex relationship in the gut mirobiome
* pMS may influence microbiome changes similar to those seen with aging. Higher abundance when pMS and age interact.
* Without longitudinal data directly tracking microbiome aging in individuals with pMS, we cannot conclusively say that pMS “drives” microbiome aging. More accurate to say pMS may intensify age-associate microbiome changes

Verrucomicrobia

* Mucin-degrading bacteria residing in the intestinal mucosa that contribute to intestinal health and glucose homeostasis
* 2 studies report an increased abundance of Akkermansia, belonging to the Verrucomicrobia phylum in MS patients
  + Role is still increase

[Citation](https://pmc.ncbi.nlm.nih.gov/articles/PMC5730390/#cit0002)- https://pmc.ncbi.nlm.nih.gov/articles/PMC5730390/#cit0002

* Dorea: pro or anti-inflammatory depending on surrounding gut bacteria and/or available nutrients
  + Blautia uses gases produced by Dorea
  + Increased Dorea in MS may promote Blautia growth
* Jangi et al. and Cekanaviciute et al. report higher abundance of Akkermansia
  + Promote expansion of pro-infammatory cytokines, higher abundance in MS studies
  + Dorea and Akkermansia can utilize a common pathway, such as mucin degradation to induce proinflammatory responses resulting in chronic inflammation in MS
* **Mucin Degradation Pathway**: Dorea and Akkermansia may utilize mucin degradation to drive pro-inflammatory responses, contributing to chronic inflammation and MS predisposition.

[Citation](https://pmc.ncbi.nlm.nih.gov/articles/PMC7993679/#:~:text=Interestingly%2C%206%2Dmonths%20old%20mice,Porphyromonadaceae%2C%20Mucispirillum%2C%20and%20Prevotellaceae.)- https://pmc.ncbi.nlm.nih.gov/articles/PMC7993679/#:~:text=Interestingly%2C%206%2Dmonths%20old%20mice,Porphyromonadaceae%2C%20Mucispirillum%2C%20and%20Prevotellaceae.

* Age-dependent increases in akkermansia
* Typically linked to health beneficial and anti inflammatory effects, such as improving glucose homeostasis in diet-induced obecity and slowing progression of dextran sulfate sodium-induced colitis
* Mucin degredation properties may exacerbate certain infection

Citation

* Likely a high concentration of mucin in the BHI medium could stimulate A.muciniphila to produce numerous glycoside hydrolases

1. Release of sialic acid from non-reducing ends is an initial step in the sequential degradation of mucins
2. Mucin pore glycans were exposed to further enzymatic degradation for other glycoside hydrolases (b-hexosaminidase, b-galactosidase, a-L-fucosidase)
3. Bacteria enter the PTS pathway for further energy metabolism and promote cell growth

* High mucin addition induced A. muciniphila to overexpress fucosidase, B-galactosidase, hexosaminidase to degrade mucins into fucose, N-acetylgalactosamine, and N-acetylglucosamine
* Resulting oligosaccharides broken down to monosaccharides 🡪glycolysis
* High mucin addition upregulated genes involving nutrient uptake, cell growth, and cell morphology, probably regulating ATP production. Shows mucin-dependant growth by degrading mucin to maintain energy balance

Caro’s thoughts

* Genetic component that causes an individual to produce excess mucus??
* Immune system activation from something produced by Akkermansia or on the surface that is similar to myelin
* SCFA increases mucin production- [link](https://onlinelibrary.wiley.com/doi/full/10.1111/ane.13045)
  + SCFA can suppress demyelination and enhance remyelination in association with oligodendrocyte differentiation
* <https://www.frontiersin.org/journals/cellular-and-infection-microbiology/articles/10.3389/fcimb.2020.00248/full>

**References**

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Cekanaviciute E, Debelius JW, Singh S, Runia T, Nelson C, Yoo B, et al.. Gut dysbiosis is a feature of MS and it is characterized by bacteria able to regulate lymphocyte differentiation in vitro. 2016 European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). London, 2016:147026.