

Abstract 21: How do early and lifelong exposure to dietary AGEs affect tissue, gut sensitivity, and microbiota in mice?

M.T. Nogueira Silva Lima¹, **C. Delayre-Orthez**², **M. Howsam**¹, **P. Jacolot**², **C. Niquet-Léridon**², **A. Okwieka**³, **P.M. Anton**², **M. Perot**², **H. Matthieu**², **A. Ghinet**^{1,5}, **C. Fradin**¹, **E. Boulanger**¹, **S. Jaisson**^{3,4}, **P. Gillery**^{3,4}, **F.J. Tessier**^{1*}

¹ U1167-RID-AGE-Facteurs de Risque et Déterminants Moléculaires des Maladies Liées au Vieillissement, Institut Pasteur de Lille, University Lille, Inserm, CHU Lille, F-59000 Lille, France, ² Institut Polytechnique UniLaSalle, Université d'Artois, ULR 7519, Equipe PETALES, 60000 Beauvais, France, ³ University of Reims Champagne-Ardenne, Laboratory of Biochemistry and Molecular Biology, CNRS/URCA UMR 7369 MEDyC, Faculté de Médecine, 51095 Reims, France, ⁴ University Hospital of Reims, Laboratory of Biochemistry-Pharmacology-Toxicology, 51092 Reims, France, ⁵ Junia, Health and Environment, Laboratory of Sustainable Chemistry and Health, 59000 Lille, France

Introduction:

Diet plays a crucial role in triggering deleterious physiological responses. Dietary Advanced glycation end-products (dAGEs) are suggested to lead to chronic low-grade inflammation (CLGI), oxidative stress, and alter gut bacteria. Studies investigate how glycation products like dietary carboxymethyl-lysine (dCML) and the Receptor for Advanced Glycation End-Products (RAGE) affect cellular responses, but it is unclear if early-life or lifelong exposure to dAGEs could contribute to the consequences of AGE intake, and whether these effects can be reversed.

Materials and methods:

Our study employed standard and an in-house prepared protein-dCML model to enrich mice food and explored how a high (13-times) dCML-enriched diet affects Wild-Type (WT) and RAGE KO mice from birth to 6, 35, and 70 weeks. We also investigated if switching to a standard diet at 6-weeks of age could reverse the potential dCML effects in the "Switch group". We assessed outcomes at systemic and local levels using quantitative (LC-MS/MS) and molecular biology methods (qRT-PCR, Metagenomics) to quantify dCML and physiological changes, respectively, in multiple organs.

Results:

We confirmed the accumulation of free dCML in kidneys (3x), ileum (17x), and colon (20x) from 6 to 70 weeks of diet, regardless of RAGE expression. Switching diets lowered dCML comparable control conditions. The dCML-enrich diet did not notably affect endogenous glycation, inflammation, or senescence. *TNF α* , *VCAM1*, *IL6*, and *P16* gene expression roughly doubled with age, especially in WT kidneys. There were notable increases in *TNF α* expression detected in the intestinal tract of the Switch group, suggesting an increased inflammatory reaction that could be related to timing of dietary shifts. Minor alterations in gut microbiota communities were observed.

Discussion and conclusion:

While persistent intake of dCML resulted in increased free dCML levels within tissues, there were no notable increases in parameters associated with inflammation, oxidative stress, or significant microbial community shifts. However, early-life diet switching seemed to contribute with greater sensitivity to intestinal inflammation and increased *TNF α* expression. In addition, the lack of RAGE seemed to lower age-related *TNF α* increase in a healthy rodent model. It provides a potential avenue for future research to delve into understanding the influence of dAGEs on the onset of different diseases and health conditions.