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Title: LIPIDOMIC PROFILING AND PARTIAL LEAST SQUARE ANALYSIS IN LDLR-/- MICE GIVEN INCREASING DOSE OF OMEGA 3 PUFA: F4-NEUROPROSTANES AS A MAJOR PREDICTIVE VARIABLE OF ATHEROSCLEROSIS REGRESSION

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Abstract: Objective. Consumption of long chain n-3 PUFA is associated with reduced risk of cardiovascular disease but the role of their oxygenated metabolites is still unclear. We hypothesized that metabolites issued from the non-enzymatic oxidation of docosahexaenoic acid (DHA, C22:6 n-3) could play a role in the prevention of atherosclerosis.
Methods and Results. LDLR-/- mice (n=30/group) received for 20 weeks an atherogenic diet (10% lard and 0.045% cholesterol) together with daily oral gavages of a mixture of sunflower and tuna oils providing 0%, 0.1%, 1% and 2% of energy as DHA (Control, DHA1, DHA2 and DHA3 groups respectively). Supplementation with DHA dose-dependently reduced atherosclerotic plaque size ($R^2=0.97$) as well as most cardiovascular risk factors such as plasma triglycerides and cholesterol ($R^2=0.97$ and 0.96 respectively). Targeted lipidomic analyses were used to determine plasma and liver profiles of PUFA and their oxygenated metabolites. As expected, DHA supplementation induced dose-dependent increase of long chain n-3 PUFA ($R^2=0.95$ and 0.99 in plasma and liver respectively) but was also associated with an increased production of n-3 PUFA's oxylipins and F4-Neuroprostanes, a major peroxidation metabolite of DHA. Finally, correlation, hierarchical cluster and partial least square analysis of the overall dataset revealed that the liver content of F4-Neuroprostanes was both the variable the most negatively correlated with plaque progression and one of the two major predictive variables of plaque regression.
Conclusion. This study shows the antiatherogenic effect of DHA could in part be achieved by one of its major peroxidation metabolites, the F4-Neuroprostanes.