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α-Linolenic acid metabolism in human CD3+ T cells is dependent on n-6/n-3 ratio and age

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The essential dietary fatty acid α-linolenic acid (ALA) can be oxidised into 18 carbon oxylipins or metabolised into longer chain n-3 polyunsaturated fatty acids (PUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Oxylipins from n-3 PUFAs are generally acknowledged as less pro-inflammatory or capable of resolving inflammation compared to n-6-derived oxylipins[(1)]. The regulation of the partitioning of ALA between PUFA synthesis and oxidation to oxylipins is not yet understood and might be impaired in human T cells by age-related immune dysregulation; namely immunosenescence.

To address this, peripheral blood $CD3^+$ T cells from healthy younger adult volunteers (18–30 years; *n = 10*) and older adult volunteers (58–74 years; *n = 6*) were cultured for 48 h, with or without concanavalin A (10μg/mL) in 10% (v/v) pooled donor plasma with an 8:1 or 5:1 linoleic acid (LA) to ALA ratio (n-6/n-3 ratio). ALA metabolites were detected either by gas chromatography-mass spectrometry for cellular PUFA or by LC-MS/MS for oxylipins in cell culture supernatants. Metabolite to ALA ratios were calculated for the primary PUFA synthesised from ALA in T cells, eicosatrienoic acid (20:3n-3 / ALA), and the most abundantly oxidised metabolites of ALA, 9- and 13-hydroxyoctatrienoic acid (HOTrE / ALA). Multiple t-test (unpaired, two-tailed) with Holm-Sidak correction was performed for statistical analysis (GraphPad Prism 8.4.3). Results for stimulated and unstimulated cells were similar; only results for stimulated cells are reported here.

In younger adult T cells, HOTrE / ALA was significantly higher than 20:3n-3 / ALA for 5:1 n-6/n-3 (0.44±0.09 vs 0.11±0.01, P = 0.005) and 8:1 n-6/n-3 (0.20±0.02 vs 0.13±0.02, P = 0.019). Further, there was significantly higher HOTrE / ALA in cells treated with 5:1 n-6/n-3 compared to 8:1 n-6/n-3 (0.44±0.09 vs 0.20±0.02, P = 0.041), but 20:3n3 / ALA did not differ between n-6/n-3 ratios.

Likewise, HOTrE / ALA from T cells treated with a 5:1 n-6/n-3 were significantly higher compared to 20:3n-3 / ALA in both younger (0.49±0.09 vs 0.11±0.01, P < 0.001) and older (0.45±0.05 vs 0.28±0.02, P = 0.018) adults. The ratio of 20:3n-3 / ALA was significantly higher in older adults compared to younger adults (0.28±0.02 vs 0.11±0001, P < 0.001), but there was no difference in HOTrE / ALA comparing older and younger adults.

These findings show that ALA is used preferentially by mitogen-stimulated T cells for constitutive production of anti-inflammatory lipid mediators rather than synthesis of longer chain PUFA in both younger and older adults. The lipid mediator production in younger adults is greater with a lower (5:1) n-6/n-3 ratio. Further, elongation of ALA is higher in older than in younger adults. This has implications for understanding the effects of dietary PUFA on immune function and healthy aging.

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