HUVECs and downregulated the expression of genes involved in alloantigen presentation through the class I major histocompatibility complex (IRF1, TAP1, B2M), and reduced the activation and pro-inflammatory polarization of co-cultured allogeneic lymphocytes. Consequently, RNA-Seq analysis of these lymphocytes showed that treatment with MXene nanosheets downregulated genes responsible for transplant-induced T-cell activation, cell-mediated rejection, and development of allograft vasculopathy. Furthermore, gene set enrichment analysis revealed significant negative enrichment of genes involved in interferon alpha/beta and interferon gamma signaling. Finally, in an in vivo rat model of allograft vasculopathy, treatment with Ti3C2Tx MXene nanosheets reduced lymphocyte infiltration and preserved medial smooth muscle cell integrity within transplanted aortic allografts.

CONCLUSION: These findings support the potential of Ti3C2Tx MXene nanosheets for prevention and treatment of allograft vasculopathy and other inflammatory diseases. This research also opens the door to development of Ti3C2Tx MXene technologies for other immune-sensitive regenerative medicine applications.

Canadian Institutes of Health Research - Fellowship, Canadian Institutes of Health Research (CIHR)

P012
INCREASED EICOSAPENTAENOIC ACID TO ARACHIDONIC ACID (EPA/AA) RATIO IN BRAIN ENDOTHELIAL CELLS ASSOCIATED WITH REDUCED EXPRESSION OF NEUTROPHIL DEGRANULATION PROTEINS DURING INFLAMMATION

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BACKGROUND: Endothelial cell (EC) dysfunction results in inflammation and increased atherothrombotic risk, including stroke. The omega-3 fatty acid (FA) eicosapentaenoic acid (EPA) improves arterial compliance in a manner predicted by circulating EPA/AA ratios, an indicator of cardiovascular (CV) risk. Treatment with icosapent ethyl (IPE), a formulation of highly purified EPA, reduced composite CV events, including stroke, in REDUCE-IT that correlated with on-treatment EPA levels. We measured the effects of EPA on the EPA/AA ratio and protein expression in endothelial cells from brain ECs (BECs) following cytokine challenge.

METHODS AND RESULTS: BECs were challenged with IL-6 (12 ng/mL) for 2 hours and then treated with EPA (40 μM) or equivolume vehicle and incubated for 24 hours. Samples were allocated for FA analysis or proteomic analysis. Total cellular FAs were extracted, derivatized to FA methyl esters (FAME), and analyzed using gas chromatography. Total protein content was also measured and used to normalize fatty acid content. Global proteomic analysis was performed using LC/MS to measure relative expression levels of proteins between treatment groups. Significant ($p < 0.05$) changes in expression between treatment groups (>1-fold) were analyzed using differential enrichment analysis of proteomics data (DEP). Biological pathways were analyzed using proteins that survived the cutoff criteria via gene set enrichment analysis (GSEA). EPA treatment significantly modulated proteins in the "neutrophil degranulation" pathway (GO:0043312) with pathway adjusted-p values of $3.68 \times 10\text{-}13$. EPA significantly altered expression of 66 proteins in this pathway, including increasing peroxiredoxin-6 and heat shock protein 90, relative to IL-6. These changes in protein expression in BECs correlated with large, significant increases in the EPA/AA ratio from 0.025 ± 0.002 to 1.72 ± 0.20 (>67-fold increase, $p < 0.001$).

CONCLUSION: EPA favorably modulated proteins in brain ECs related to neutrophil degranulation in a manner that correlated with increases in the EPA/AA ratio. The anti-inflammatory benefits may contribute to reduced stroke risk with IPE as demonstrated in outcome trials.

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P013
INTESTINAL ADAPTATION TO SHORT-TERM, EXTREME FAT CONSUMPTION ALTERS TRIGLCYERIDE-RICH LIPOPROTEIN SECRETION AND INTESTINAL LIPID HANDLING IN MALE AND FEMALE MICE

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BACKGROUND: Dysregulated postprandial metabolism including elevated chylomicron remnants, contributes to atherogenesis. The ketogenic diet is a patient-accessible metabolic health intervention whereby nutritional ketosis is achieved by consuming predominantly fat (>70% of kcal) with restricted carbohydrates and protein. It has been established that intestinal enterocytes package dietary triglycerides (TG) into chylomicrons for transport into circulation and store excess TGs as cytosolic lipid droplets (CLDs) such that nutrient absorption is maximized.

METHODS AND RESULTS: The current study aimed to characterize the impact of diet composition on postprandial intestinal lipid handling in male and female wild-type mice. We evaluated intestinal cytosolic lipid droplets, TG secretion rates, and intestinal morphology with short-term, high-fat Western diet (WD) and an extreme fat, low protein, carbohydrate-restricted ketogenic diet (KD) before developing obesity. For three weeks, mice previously fed a grain-based standard laboratory diet (GBD) were switched to a WD or KD. Both male and female KD-fed mice displayed significantly higher plasma TG levels in response to an olive oil gavage than WD- and GBD-fed mice. At fasting, intestinal TG mass was significantly higher in both male and female