Clinical Summary

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Souza PR, Marques RM, Gomez EA, et al. Enriched Marine Oil Supplements Increase Peripheral Blood Specialized Pro-Resolving Mediators Concentrations and Reprogram Host Immune Responses. Circ Res 2020;126:75-90.

Omega-3 Supplementation Reprograms the Immune Response

This double-blind, crossover, placebo-controlled study, led by respected lipid mediator researcher Jesmond Dalli, PhD, is among the first to examine genomic effects of omega-3 fats on nutritional regulation of the immune response. The investigation found that generous supplementation with omega-3 fatty acids and their metabolites significantly alters the function of white blood cells and platelets as well as endogenous production of specialized pro-resolving mediators (called SPMs or PRMs), and thereby regulating the activation and targeting of the immune response.

Advances in our understanding of immune-active fats confirm that insufficient intakes of omega-3 fatty acids and deficient endogenous production of their metabolites (including resolvins, protectins, maresins, and lipoxins) can result in dysregulated leukocyte and platelet activation and perpetuation of an imbalanced immune response. Such impairments in immune resolution have been linked to chronic inflammation and other immune-mediated conditions.

It was previously thought that omega-3 fatty acids like eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid (EPA, DHA, and DPA) modulate inflammatory processes primarily by interfering with the metabolism of arachidonic acid. More recent research has discovered that metabolites of omega-3 fats influence the course of an inflammatory response

in an even more dynamic fashion by directly adjusting genomic control of immune cell populations and their functional programming.

The metabolites of omega-3 fatty acids, specialized pro-resolving mediators (SPMs/PRMs), are classed into categories according to their parent omega-3s:

- D-series resolvins from DHA and DPA (RvD1, RvD2, etc.)
- E-series resolvins from EPA (RvE1, etc.)
- Protectins and maresins from DHA and DPA (PDs and MaRs)
- Lipoxins from arachidonic acid (AA)

Specialized pro-resolving mediators are so named because their activities are characterized by promoting resolution of an immune response after injury, infection, or inflammation by 1) moderating the recruitment of leukocytes to an affected area, 2) reconfiguring chemical messaging among immune cells during a response, and 3) promoting clearance of cell debris and dead cells. Certain SPMs/PRMs are also involved in tissue remodeling.

In this experiment, 22 healthy volunteers aged 18-45 were given a series of single doses of placebo or 1.5 g, 3.0 g, or 4.5 g of total omega-3 fatty acids, in a double-blinded crossover study design. Blood samples were taken before and 2, 4, 6, and 24 hours after supplementation. Omega-3 fatty acids including ~46% EPA, ~33% DHA, ~18% DPA, and ~3% AA, and supplemented SPMs/PRMs included 17-hydroxy-DHA, 7-hydroxy-DHA, and 18-hydroxy-EPA (17-HDHA, 7-HDHA, and 18-HEPE). In addition to routine blood chemistry and hematology, blood levels of EPA, DHA, DPA, AA and their SPM/PRM metabolites were assessed at each time point. The researchers also exposed samples of participants' blood to the proinflammatory mediator platelet-aggregating factor (PAF) to investigate how supplementation may affect platelet aggregation and associated changes in immune activation and vascular function, and blood samples were separately exposed to pathogenic bacteria to study the effects of supplementation on the antimicrobial immune response.

According to the authors, in relation to omega-3 supplementation:

"Recent studies demonstrate that omega-3 fatty acids are converted into bioactive mediators, termed specialized pro-resolving mediators (SPM), that actively reprogram the host immune response to limit inflammation."
"Together, these findings indicate that changes in peripheral blood SPM concentrations are linked with a reprogramming of peripheral blood cell responses towards a protective phenotype."

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Comparing baseline values and placebo against single-dose intakes of 1.5 g, 3.0 g, and 4.5 g of total omega-3 fatty acids, major findings from this series of clinical experiments include the following:

- Results from this and other recent studies suggest that SPMs/PRMs are instrumental in reprogramming the immune response by actively coordinating actions necessary for resolving inflammation.
- Omega-3 supplementation increased plasma levels of metabolites from EPA, DHA, DPA, and AA, with greatest increases in E-series resolvins and DPA-derived D-series resolvins. The 3.0 g and 4.5 g total omega-3 dosage levels were found to upregulate the metabolomes of DHA, DPA, and EPA, with notable increases in the rarer maresin and protectin lipid mediators.
- At the 4.5 g intake level, total plasma SPM/PRM levels were significantly increased at 2 and 4 hours after supplementation, while at the 3 g intake level, they were significantly increased at the 2-hour mark.
- The authors note with interest that omega-3 supplementation increased plasma levels of arachidonic acid-derived SPMs/PRMs (called lipoxins) without significant changes to levels of potentially proinflammatory derivatives of arachidonic acid.
- The 3.0 g and 4.5 g total omega-3 dosages were associated with altered expression of surface adhesion molecules on neutrophils, platelets, and monocytes, indicating that this may be one of the mechanisms by which SPMs/PRMs affect chemotaxis (immune cells' movement towards affected areas) during an immune response.
- Supplementation was associated with altered white blood cell and platelet responses to platelet-aggregating factor, with the most marked pro-resolving effects seen at the 4.5 g total omega-3 dosage. In analysis, higher blood levels of particular D-series resolvins (Rv1, Rv2, Rv4, Rv6, and DPA-derived Rv5) were linked to reduced expression of cell markers associated with platelet aggregation.
- Supplementation was associated with heightened phagocytosis (engulfment of damaged or harmful substances by immune cells) of Staphylococcus aureus and Escherichia coli bacteria by leukocytes, with variable results at different dosages and time points. The authors remarked that the greatest phagocytic activity was seen at the 24-hour time point.
- The 4.5 g supplementation level was linked to altered transcription (reading and copying) of 141 genes, including several involved in mitochondrial function, antigen recognition, interferon production, white blood cell recruitment, cellular energy generation, endothelial responsivity, and other immunometabolic processes.
- The authors emphasize that while leukocyte SPM/PRM levels appear to reach a maximum about 2-4 hours after consumption of omega-3 fatty acids, significant effects on peripheral white blood cell activity were still seen 24 hours after supplementation. These researchers feel that SPM/PRM-mediated reprogramming of circulating immune cells transcriptomes may account for their prolonged effects on the immune response.

CONCLUSION

Omega-3 fatty acids like EPA, DHA, and DPA have demonstrated many direct benefits to immune, cardiovascular, and neurocognitive health. Their nutritional influence extends further, however, through the actions of their specialized pro-resolving mediator (SPM/PRM) metabolites. SPMs/PRMs directly alter cell functions and cell-to-cell interactions, yet further regulate immunometabolic activity at the level of gene expression. SPMs/PRMs represent a high level of immune control that is largely dependent on sufficient dietary intakes of omega-3 fatty acids.