



Effects of environmental factors and omega-3 fatty acids on rheumatoid arthritis

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Introduction

With a prevalence that has been estimated to be 0.5%±0.2% and a female predominance, rheumatoid arthritis (RA) represents the most common chronic systemic autoimmune rheumatism. Typically, RA is characterized by polyarticular pain, morning stiffness, fatigue, joint and bone inflammation and destruction (1). A more severe evolution is encountered in RA patients with an age lower than 50 years at diagnosis, anti-cyclic citrullinated peptides (anti-CCP) autoantibody (Ab) positivity, IgM rheumatoid factor (RF) at elevated levels (>50 UI/mL), and bone erosions (2,3). RA appears to present geographical variations with an apparent reduction from north to the south, and from urban to rural areas (4).

The deregulated immunological mechanisms leading to RA are complex and include primarily an abnormal cross-talk between antigen-presenting cells (APCs), T cells, and B cells which in turn contributes to the expansion of autoreactive lymphocytes, and to the production of high amounts of pro-inflammatory cytokines (*Figure 1*). After several months or years (5), persistent inflammatory arthritis leads to synovial hyperplasia, cartilage destruction, bone erosion, and neutrophil recruitment. In those patients with anti-CCP Ab and RF, referred to as Ab seropositivity (60–80%), such association is associated with more severe symptoms and joint damage, indeed the formation of immune complexes containing citrullinated peptides/anti-CCP Ab/RF can lead to abundant complement activation.

Moreover, there is consistent information from the

literature linking RA development with accelerating factors such as smoking, alcohol consumption, obesity, exposure to air pollution, a low level of formal education, and infections (6,7). At the opposite end, long-chain omega-3 polyunsaturated fatty acids [omega-3 fatty acids (OA3FA)] have a protective effect for RA development (8), and it has been further reported that OA3FA protects children at risk for type 1 diabetes from the development of pre-clinical islet autoimmunity (9).

Control of the immune system in RA by genetic and epigenetic factors

The use of monozygotic (MZ) twins and the determination of the concordance rate (CR), which tests the proportion of affected pairs in a disease, highlight the importance of the environmental component in RA (CR 10–40%). In contrast, an elevated CR characterizes autoimmune diseases with higher genetic components such as celiac disease (CR 75–85%) and psoriasis (CR 40–65%) (10).

The development of serological tools in the 1970s and the molecular biology tools in the 1980s have permitted the revelation of associations between RA and the shared epitope (SE) driven by the human leukocyte antigen (HLA) antigen D related region (DR) B1 (11). Several arguments support the possibility that citrullinated peptides interact with the peptide-binding groove of the SE, trigger autoreactive T-cell clonal expansion, and contribute to

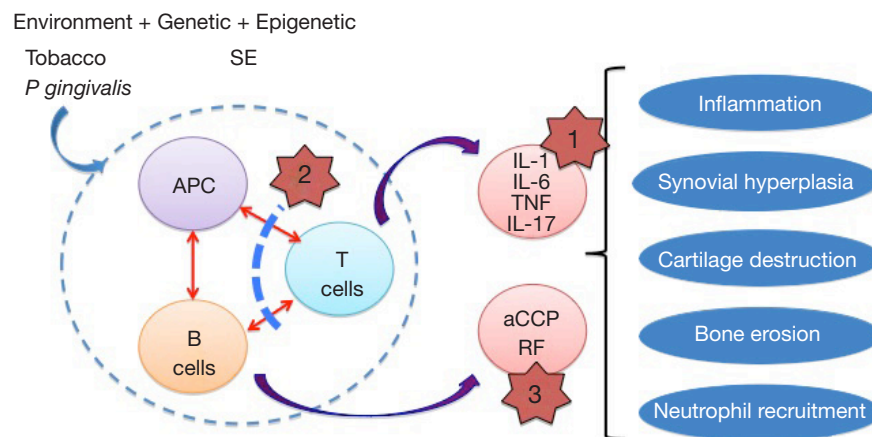


Figure 1 Antigen presenting cells (APC) present self (e.g., citrullinated peptides) to auto-reactive T cells, which induce macrophages to secrete pro-inflammatory cytokines and help B cells to produce auto-antibodies (e.g., anti-CCP Ab) and rheumatoid factor (RF) forming immune complexes. Cellular interaction, pro-inflammatory cytokines and auto-antibodies lead to the clinical manifestations of RA. Environmental factors (e.g., tobacco, infections), genetic factors [e.g., shared epitope (SE)], activate this process. In contrast, omega-3 fatty acids can inhibit this process (I) by inhibiting pro-inflammatory cytokine production; (II) by inhibiting the interaction between APCs and T cells through an interaction with the SE; and (III) by preventing anti-CCP and RF production.

the production of specific anti-CCP Ab. The association between SE and both anti-CCP Ab and RF is observed in 2/3 of patients with RA and an elegant HLA-DRB1 transgenic mouse model recapitulates the disease in the presence of citrullinated peptides (12). The association between anti-CCP Ab and RF negative RA patients and SE is poor. Furthermore, citrullinated peptide presentation of the SE can be influenced by common oral bacteria present within the dental plaque such as *Porphyromonas gingivalis* that promotes aberrant levels of citrullinated peptides by producing peptidylarginine deiminase enzymes which promotes arginine to citrulline conversion and then a local breach of tolerance, process amplified in smokers as tobacco promotes citrullinated peptide interaction with the SE (13). An elevated level of anti-CCP Ab is observed in SE-positive smokers.

Moreover, with the development of the genome-wide association study (GWAS) project, up to 100 genetic variations (SNPs) are associated with RA (14). From these genetic studies important pathways were highlighted to be crucial in the development of RA, including (i) antigen presentation (CMH/HLA); (ii) the citrullination process (e.g., PADI4); (iii) immune complex recognition and elimination (e.g., FCGR2A, FCRL3); (iv) cytokines (e.g., IL-2, IL-6R, IL-21, STAT4); (v) co-stimulatory pathways (e.g., CD28, CTLA4, CD40); and (vi) T and B cell activation (e.g., PTPN22, BLK). However, with

the exception of the SE HLA-DRB1 alleles genes that have a significant odds ratio (OR =2 to 5), non-HLA gene associations are usually not disease specific, geographically restricted, and with modest OR (1.1 to 1.8) suggesting, again, a modest contribution for genetic factors in RA. Last but not least, cross-talk exists between genetic and epigenetic factors as the distribution of the RA-associated genetic risk-factors overlap in effector memory CD4+ T cells with expression quantitative trait loci (eQTL, 50%) and/or long range epigenetic-regulatory sequences (80%) present outside promoter and gene coding areas (15-17). Epigenetic modifications include DNA methylation and histone modifications, and they are defined as changes affecting gene expression that do not involve change in the DNA sequence. Epigenetic mechanisms are intrinsically reversible, highly dynamic, and cell specific (18). Although incompletely understood, mechanisms affecting epigenetic pathways in RA are cell specific, controlled in part by pro-inflammatory cytokines, and reversible following treatment (19-21).

Omega-3 fatty acids (OA3FA)

Growing evidence suggests that particular diets containing fatty fish (e.g., salmon, lake trout, sardines and tuna) are beneficial for primary and secondary prevention of RA (22). Based on these observations, dietary regimens originating

from fish oils and containing the OA3FA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are available and assist in RA prevention and reduce the need for non-steroidal anti-inflammatory drugs (NSAIDs) (23). In support of these observations, the evaluation of OA3FA concentrations in tissues, especially in erythrocyte membranes, further supports that RA development is associated with lower levels of OA3FA (24), and this reduction was significantly increased when considering the anti-CCP Ab positive population at risk for future RA (25).

At least three mechanisms are described for OA3FA in RA:

- (I) In the first mechanism, OA3FA are suspected of preventing primarily and secondarily RA through their capacity to inhibit the production of pro-inflammatory eicosanoids such as prostaglandin E2 (PGE2) and leucotriene B4 (LTB4), which in turn inhibit the activation of the nuclear factor kappa B (NF- κ B), and thus the production and release of the pro-inflammatory interleukins (IL) [e.g., IL-1, IL-6, tumour necrosis factor (TNF)-alpha] that could ultimately result in the activation and maturation of autoreactive B cells and synoviocytes. OA3FA also prevents pro-inflammatory cytokine expression through the epigenetic pathway by restoring DNA methylation as demonstrated for the promoter of IL-6 (26);
- (II) In the second mechanism, *in vitro* experiments support an effect of OA3FA on cell surface receptors either directly by promoting their expression [e.g., vascular cell adhesion molecule (VCAM)-1 an adhesion molecule, and PPAR γ in monocytes] or repression (e.g., CCL5, HLA-DQ/DR), or indirectly through their action on the lipid rafts (e.g., IL-6 receptor, and CD28). Thereby, OA3FA reduce Th17 differentiation, enhance Foxp3+ CD4+ T cells regulatory functions, promote M2 polarization, and lower the number of NK cells (27);
- (III) In the third mechanism, an interaction between OA3FA and the SE is also suspected and this was recently demonstrated in an epidemiological study conducted in participants at risk for RA by Gan and colleagues (8). Indeed, an inverse association between OA3FA concentrations and SE + RF (OR =0.26; 95% CI: 0.09–0.77, P=0.02), or SE + anti-CCP Ab (OR =0.44; 95% CI: 0.21–0.93, P=0.03) was reported in two cohorts at risk for RA: one selected from first relatives of probands with RA

patients and another one with children possessing type 1 diabetes risk alleles, which includes SE. Furthermore, authors reported that increasing dietary OA3FA intake was protective for RF positivity in SE-positive participants (P=0.02). In contrast, no association was observed in participants who were SE-negative, or cases both positive for anti-CCP Ab and RF. The exact mechanism of this specificity and suspected cross-talk between OA3FA and SE is not completely understood and needs further exploration.

In conclusion, and according to the recently reported study by Gan and colleagues, the protective effects of OA3FA against the development of RA seems to be restricted to a subgroup of patients. As a consequence, such observations provide novel arguments for the utilization of fish oil supplementation as an adjunct therapy in selected patients with RA. However, better elucidation of the interplay between OA3FA, genetic and epigenetic factors is now required to characterize and select these patients.

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