Dietary ω-3, ω-6, and ω-9 Unsaturated Fatty Acids and Growth Factor and Cytokine Gene Expression in Unstimulated and Stimulated Monocytes

A Randomized Volunteer Study

Klaus H. Baumann, Franz Hessel, Iris Larass, Thomas Müller, Peter Angerer, Rosemarie Kiefl, Clemens von Schacky

Abstract—Dietary ω-3 fatty acids retard coronary atherosclerosis. Previously, we demonstrated that dietary ω-3 fatty acids reduce platelet-derived growth factor (PDGF)-A and PDGF-B mRNA levels in unstimulated, human mononuclear cells (MNCs). In a randomized, investigator-blinded intervention trial, we have now compared the effect of ingestion of 7 g/d ω-3, ω-6, or ω-9 fatty acids for 4 weeks versus no dietary intervention on PDGF-A, PDGF-B, heparin-bound epidermal growth factor (HB-EGF), monocyte chemoattractant protein-1 (MCP-1), and interleukin-10 gene expression in unstimulated MNCs and in monocytes that were adherence-activated ex vivo in a total of 28 volunteers. In unstimulated MNCs, mRNA steady-state levels of PDGF-A, PDGF-B, and MCP-1 were reduced by 25±10%, 31±13%, and 40±14%, respectively, after ω-3 fatty acid ingestion, as assessed by quantitative polymerase chain reaction (all P<0.05). In monocytes that were adherence-activated ex vivo for 4 and 20 hours, mRNA steady-state levels of PDGF-A, PDGF-B, and MCP-1 were reduced by 25±13%, 20±15%, and 30±8%, respectively (all P<0.05). Interleukin-10 and HB-EGF mRNA steady-state levels were not influenced by ω-3 fatty acid ingestion. Expression of all respective mRNAs in control volunteers or in those ingesting ω-6 or ω-9 fatty acids were not altered. We conclude that human gene expression for PDGF-A, PDGF-B, and MCP-1, factors thought relevant to atherosclerosis, is constitutive, is constant, and can be reduced only by dietary ω-3 fatty acids in unstimulated and adherence-activated monocytes. (Arterioscler Thromb Vasc Biol. 1999;19:59-66.)

Key Words: mRNA ■ platelet-derived growth factor ■ monocyte chemoattractant protein-1 ■ interleukin-10 ■ heparin-bound epidermal growth factor

Ingestion of fish or fish oil rich in the 2 ω-3 fatty acids eicosapentaenoic and docosahexaenoic acids lowers mortality in patients after a myocardial infarction.1 Although this may partly be due to reductions in fatal arrhythmias,2 we recently demonstrated that dietary ω-3 fatty acids have a beneficial effect on the course of coronary atherosclerosis, as assessed by the coronary angiogram.3 Various mechanisms of action have been described for dietary ω-3 fatty acids.4-6 One of them, reduced platelet-derived growth factor (PDGF)-A and PDGF-B mRNA steady-state levels in unstimulated, human mononuclear cells (MNCs) after ingestion of dietary ω-3 fatty acids,7 demonstrated that human gene expression can be influenced by dietary components.

Monocytes/macrophages play a pivotal role in atherosclerotic plaque formation.8-10 Monocytes and macrophages have been shown to synthesize and secrete a series of cytokines and growth factors influencing the atherosclerotic process at the site of a vascular lesion.11-13 Among the factors induced and secreted by monocytes/macrophages by a stimulus, like adherence, are PDGF-A, PDGF-B, heparin-bound epidermal growth factor (HB-EGF), monocyte chemoattractant protein (MCP)-1, and interleukin-10.14-15 IL-10 is a cytokine synthesis inhibitor.16 PDGF and HB-EGF are potent mitogens for smooth muscle cell proliferation.17 MCP-1 is an attractor and activator of monocytes.18 Both MCP-1 and PDGF are currently thought to be intimately involved in the pathogenesis of atherosclerosis.8,10,18 It is currently unknown whether human gene expression for PDGF-A and PDGF-B can be reduced by other dietary unsaturated fatty acids, such as ω-6 or ω-9 fatty acids, or is reduced solely and specifically by ω-3 fatty acids. It is also unknown whether this reduction persists after mild monocyte stimulation by adherence ex vivo. Therefore, we conducted a randomized, investigator-blinded volunteer trial to evaluate the effects of dietary ω-3, ω-6, and ω-9 fatty acids on PDGF-A, PDGF-B, MCP-1, HB-EGF, and IL-10 gene expression in human MNCs.

Methods

Volunteer Study

Male volunteers (n=28, 20 to 38 years of age) who were judged healthy by medical history, routine clinical examination, and

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normal laboratory screening values were recruited for this study. Written, informed consent was obtained, and volunteers were randomized to supplement their usual diet with seven 1-g capsules per day containing either omega-3 fatty acids (fish oil based; eicosapentaenoic acid 41.4%, docosahexaenoic acid 23.6%, total saturated fatty acids 0%, omega-9 fatty acids, and total omega-6 fatty acids 3.9%), omega-6 fatty acids (corn oil based; linoleic acid 50.1%, total saturated fatty acids 12.9%, and total omega-3 fatty acids 0.6%), or omega-9 fatty acids (olive oil based; oleic acid 60.5%, total saturated fatty acids 13.7%, and total omega-3 fatty acids 0.6%), all in the form of ethyl esters for 4 weeks. All formulations were kindly provided by the Biomedical Test Materials Program of the US Department of Commerce, National Oceanic and Atmospheric Administration/National Marine Fisheries Services, Charleston, SC. Thus, 7 volunteers supplemented their diet with omega-3, 7 with omega-6, and 7 with omega-9 fatty acids, while 7 volunteers served as controls. Blood samples were taken at the onset of the study and on the day after the 4-week intervention ended. Serum parameters were measured in an automated Hitachi 917 or 717 serum analyzer. Investigators involved in the analyses of the study were blinded with respect to randomization of the volunteers. The study was approved by the Ethics Committee of the Faculty of Medicine of the Ludwig Maximilians-Universität, Munich, Germany.

Preparation of Human MNCs
Platelet-free human peripheral MNCs were isolated from healthy, male volunteers after an overnight fast as described earlier. In brief, peripheral venous blood was obtained by a free-flow technique and anticoagulated with acid-citrate-dextrose. After dextran sedimentation, MNCs were enriched by density centrifugation through Ficoll-Hypaque (Sigma). Our cell preparation results in unstimulated MNCs, as evidenced by very low levels of IL-1β measured by radioimmunoassay. The cell composition of MNCs was determined by light-microscopic analysis of May–Grünewald/Giemsa–stained smears. Typically, the mononuclear fraction contained, on average, 60% monocytes, 35% lymphocytes, <5% granulocytes, and no platelets. Eight cell preparations for the current study contained, on average, 61.8% monocytes, 33.2% lymphocytes, <5% granulocytes, and no platelets. The absence of platelets was further verified by checks for EGF mRNA, a specific platelet marker. MNCs (2 × 10⁶) were taken for analyses of unstimulated MNCs.

Cell Culture
Freshly isolated MNCs (2 × 10⁶) were resuspended in “autologous medium,” which consisted of phenol red-free Dulbecco’s modified Eagle’s medium (Gibco-BRL) supplemented with 5% serum prepared from coagulated venous blood (1 hour, 37°C) of the respective donor at the respective time point, 1% glutamine (Gibco-BRL), 100 U/mL penicillin, and 100 mg/mL streptomycin (Gibco-BRL). Cells were cultured at 37°C in a humidified atmosphere with 5% CO₂.

Preparation of Total RNA
Total RNA of MNCs was prepared by using Trizol (Gibco-BRL) and following the manufacturer’s protocol.

cDNA Synthesis
RNA aliquots of samples being compared with each other were simultaneously reverse-transcribed into cDNA by using M-MLV reverse transcriptase (Gibco-BRL) and oligo(dT)₁₅ (Boehringer Mannheim).

Quantification of mRNA by Polymerase Chain Reaction (PCR) Analysis
A PCR-based technique was used to quantify mRNA steady-state levels in MNCs, as detailed earlier. The position and references for oligonucleotide primer (Mikrogen) selection are shown in Table 1. Typically, nested amplification of cDNA templates was performed in a 50-μL total reaction volume containing 10 μmol/L dNTP, 1.00 U DNA Taq polymerase (Boehringer Mannheim), and oligonucleotide primers (0.04 to 1.5 μmol/L). A standard PCR cycle profile for quantitative analysis was as follows: 94°C, 30 seconds; 54°C, 25 seconds; and 72°C, 30 seconds. Cycle numbers were chosen to ensure log-linear amplification. Amplified products were separated on a ethidium bromide–stained agarose gel (1.4%) and photographed under UV light (Polaroid 665 film), and the negatives were analyzed and quantified with an UltraScan laser densitometer (Pharmacia). cDNA amplification products were quantified relative to the respective β-actin signals.

Cloning and Nucleotide Sequencing
Amplified PCR fragments were ligated into pGEM-T vector (Promega). Cloned PCR segments were sequenced using the Sequenase 2.0 kit (Amersham) to confirm the presence of correct amplification products.

ELISA
Cytokines and growth factors that accumulated in conditioned medium of cultured monocytes were quantified using commercial ELISAs for MCP-1 (R&D Systems) and IL-10 (Boehringer Mannheim). PDGF-AA and PDGF-BB were determined using a sandwich ELISA. The anti–PDGF A-chain monoclonal antibody (127.2.2.2.2) was kindly provided by Zymogenetics and used for capture of PDGF-AA, and a rabbit anti–PDGF-A polyclonal antibody (Santa Cruz Biotechnology) was used for detection. For measurement of PDGF-BB, a monoclonal antibody (PGF-007) was kindly provided by Mochida Pharmaceutical Co (Tokyo, Japan) and used for capture, and a rabbit polyclonal antibody (Santa Cruz Biotechnology) was used for detection.

Statistics
The data are expressed as mean±SD. Student’s 2-tailed t test was applied, and P≤0.05 was regarded as statistically significant.

Results
Volunteer Study
Dietary interventions for 4 weeks with all study capsules were well tolerated by all 28 volunteers, and no side effects were reported. The numbers of capsules returned indicated complete compliance by the volunteers, which was con-
firmed by analysis of plasma phospholipid fatty acid compositions (Table 2). Cholesterol, LDL, HDL, triglycerides, or any of the other safety or routine parameters were in the normal range in all groups of healthy volunteers initially and at the end of the study.

**Gene Expression in Unstimulated, Human MNCs**

IL-10 mRNA steady-state levels in unstimulated MNCs were low: in 21 of 56 samples they were below the level of detection. PDGF-A, PDGF-B, MCP-1, and HB-EGF mRNA levels were detectable in all 56 preparations of unstimulated, freshly isolated MNCs (Figure 1). mRNA steady-state levels of these genes in MNCs of volunteers without dietary intervention revealed no significant alterations (Figures 1 and 5 through 7). Similarly, neither dietary \( \omega-6 \) nor \( \omega-9 \) fatty acids altered the mRNA steady-state levels of PDGF-A, MCP-1, HB-EGF, and IL-10 in unstimulated MNCs (Figures 2, 3, and 5 through 7). In unstimulated MNCs of volunteers with \( \omega-3 \) dietary supplementation, the mRNA steady-state levels of IL-10 and HB-EGF were unchanged (Figure 4). However, MCP-1, PDGF-A, and PDGF-B mRNA steady-state levels were reduced by 25\% 6 10\%, 31\% 6 13\%, and 40\% 6 14\%, respectively \((P<0.05)\), after dietary \( \omega-3 \) fatty acid ingestion (Figures 4 through 7).

Taken together, these data show that in unstimulated, human MNCs, only dietary intervention with \( \omega-3 \) fatty acids reduced MCP-1, PDGF-A, and PDGF-B mRNA steady-state levels.

**Gene Expression in Adherence-Stimulated Monocytes**

Monocytes stimulated by adherence obtained from control volunteers and from volunteers ingesting \( \omega-6 \) or \( \omega-9 \) fatty acids for 4 weeks showed no significant change in mRNA steady-state levels of PDGF-A, PDGF-B, MCP-1, HB-EGF, and IL-10 (Figures 1 through 3 and 5 through 7). Dietary supplementation with \( \omega-3 \) fatty acids left HB-EGF and IL-10 mRNA steady-state levels in monocytes stimulated by adherence unaltered (Figure 4). However, MCP-1, PDGF-A, and PDGF-B mRNA steady-state levels were reduced in adherence-stimulated monocytes of volunteers ingesting \( \omega-3 \) fatty acids (Figures 4 through 7). Taken together, these data show that in unstimulated, human MNCs, only dietary intervention with \( \omega-3 \) fatty acids reduced MCP-1, PDGF-A, and PDGF-B mRNA steady-state levels.

**TABLE 2. Plasma Phospholipid Fatty Acid Composition Before and After the Respective Dietary Intervention**

<table>
<thead>
<tr>
<th>Plasma Fatty Acid</th>
<th>No Dietary Intervention (Control)</th>
<th>( \omega-3 ) Fatty Acids</th>
<th>( \omega-6 ) Fatty Acids</th>
<th>( \omega-9 ) Fatty Acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>C18:1( \omega-9 ) Before</td>
<td>10.4±0.6</td>
<td>11.1±1.5</td>
<td>10.7±0.7</td>
<td>11.5±1.6</td>
</tr>
<tr>
<td>After</td>
<td>10.6±0.8</td>
<td>9.4±1.5*</td>
<td>11.3±2.1</td>
<td>14.0±1.9*</td>
</tr>
<tr>
<td>C18:2( \omega-6 ) Before</td>
<td>26.2±0.6</td>
<td>23.4±4.0</td>
<td>25.3±2.6</td>
<td>22.2±8.5</td>
</tr>
<tr>
<td>After</td>
<td>25.7±2.2</td>
<td>18.4±1.7*</td>
<td>26.3±5.0</td>
<td>25.1±7.6*</td>
</tr>
<tr>
<td>C20:4( \omega-6 ) Before</td>
<td>8.7±1.3</td>
<td>9.6±1.5</td>
<td>8.2±2.3</td>
<td>9.8±2.4</td>
</tr>
<tr>
<td>After</td>
<td>9.2±1.0</td>
<td>8.1±1.0</td>
<td>8.3±1.6</td>
<td>9.1±1.5</td>
</tr>
<tr>
<td>C20:5( \omega-3 ) Before</td>
<td>1.0±0.4</td>
<td>1.5±0.4</td>
<td>1.1±0.5</td>
<td>1.5±0.9</td>
</tr>
<tr>
<td>After</td>
<td>1.5±0.5</td>
<td>7.2±1.9*</td>
<td>1.0±0.3</td>
<td>1.9±1.2</td>
</tr>
<tr>
<td>C22:5( \omega-3 ) Before</td>
<td>1.0±0.1</td>
<td>0.9±0.1</td>
<td>0.8±0.2</td>
<td>0.9±0.3</td>
</tr>
<tr>
<td>After</td>
<td>1.0±0.2</td>
<td>1.4±0.3*</td>
<td>0.8±0.2</td>
<td>0.9±0.1</td>
</tr>
<tr>
<td>C22:6( \omega-3 ) Before</td>
<td>3.3±0.4</td>
<td>3.1±0.4</td>
<td>2.7±1.3</td>
<td>2.6±1.3</td>
</tr>
<tr>
<td>After</td>
<td>3.3±0.9</td>
<td>5.6±1.5*</td>
<td>2.5±1.1</td>
<td>2.9±1.3*</td>
</tr>
</tbody>
</table>

Fatty acid methyl esters were formed and analyzed as described in Methods. Fatty acids are given as relative % of total fatty acids, mean±SD. Each group comprised 7 volunteers.

* \( P<0.05 \), compared with before the study.

**Figure 1.** From a control volunteer without dietary intervention: expression of \( \beta \)-actin, PDGF-A, MCP-1, HB-EGF, IL-10, and PDGF-B assessed as mRNA steady-state levels in freshly isolated, unstimulated, human MNCs (0 hours, top) and monocytes/macrophages activated by adherence for 4 hours (middle) or 20 hours (bottom) before (lanes 1, 3, 5, 7, 9, and 11) and after (lanes 2, 4, 6, 8, 10, and 12) 4 weeks. M indicates molecular size markers. Samples were analyzed as detailed in Methods.
reduced in monocytes stimulated by adherence for 4 hours, by 35±6%, 25±6%, and 20±15%, respectively (Figures 4 through 7, all P, 0.05). In monocytes stimulated by adherence for 20 hours, MCP-1, PDGF-A, and PDGF-B mRNA steady-state levels were reduced by 30±8%, 25±13%, and 20±15%, respectively, after ω-3 fatty acid dietary intervention for 4 weeks (Figures 4 through 7, all P<0.05). Taken together, these data indicate that in monocytes stimulated by adherence ex vivo, mRNA steady-state levels of PDGF-A, PDGF-B, and MCP-1 were reduced only by dietary ω-3 fatty acids.

Accumulation of Cytokines and Growth Factors in Conditioned Medium

PDGF-A, PDGF-B, MCP-1, and IL-10 were detectable in conditioned media of all samples of monocytes stimulated by adherence for 20 hours. Accumulated amounts were close to the respective assay’s detection limits and revealed no significant differences in any group on the respective dietary interventions.

Discussion

In the current study, we demonstrate that supplementing the diet of volunteers with ω-3, but not with ω-6 or ω-9, fatty acids reduces PDGF-A, PDGF-B, and MCP-1 mRNA steady-state levels in unstimulated MNCs and that this reduction persists after stimulating human monocytes by adherence ex vivo. Thus, we have extended our earlier observations on decreased PDGF-A and PDGF-B mRNA steady-state levels in unstimulated human MNCs after dietary ω-3 fatty acid supplementation.7

As yet, interactions of dietary fatty acids and gene expression have hardly been investigated in humans.29–31 This is probably due to methodological problems. Our cell preparation procedure results in platelet-free MNCs.7,11,19,20,28 For monocyte activation and differentiation, we decided to use an established model ex vivo, ie, their adherence to polystyrene.14,15,32,33 Activating monocytes ex vivo by adherence requires the presence of serum factors.34 Therefore, we left the monocytes to adhere for 4 or 20 hours in the presence of 5% serum from the respective donor at the respective time point. Nested PCR is capable of detecting and quantifying minute amounts of mRNA.7,11,19,20 On adherence, few monocyte mRNA levels respond in a predictable and reproducible manner.11 However, PDGF-A, PDGF-B, and MCP-1 mRNA steady-state levels in unstimulated MNCs were reproducible and...
constant\textsuperscript{[11]} (not shown) and responded to adherence predictably and reproducibly under constant dietary conditions\textsuperscript{[11]} (data not shown; Figures 1, 5, 6, and 7). Thus, by using an established model and our methods,\textsuperscript{7,11,19,20,28} we have demonstrated that the genes for PDGF-A, PDGF-B, and MCP-1 are expressed reproducibly and are quantitatively constant in unstimulated human MNCs and that human MNC stimulation by adherence ex vivo elicits reproducible and predictable responses in mRNA levels.

Previously, we demonstrated reduced PDGF-A and PDGF-B, but not insulin-like growth factor, platelet-derived endothelial cell growth factor, and transforming growth factor\textbeta, mRNA levels in unstimulated MNCs and that human MNC stimulation by adherence ex vivo elicits reproducible and predictable responses in mRNA levels.

PDGF-A and PDGF-B, though to a quantitatively somewhat lesser degree, probably owing to interindividual differences. We extend our observations to MCP-1, another growth factor implicated in the pathogenesis of atherosclerosis\textsuperscript{[15,18,35,36]}: mRNA levels of MCP-1 were also markedly reduced after supplementation of the volunteers’ diets with \( \omega-3 \) fatty acids. (Figures 4 and 7). To our knowledge, no modality has previously been demonstrated to affect MCP-1 mRNA steady-state levels. Moreover, we have now demonstrated the reduction in mRNA levels to be induced solely by \( \omega-3 \), and not by \( \omega-6 \) or \( \omega-9 \), fatty acids. This result suggests that dietary \( \omega-3 \) fatty acids, but no other class of unsaturated fatty acids, specifically regulate gene expression of PDGF-A, PDGF-B, and MCP-1. From our data, we cannot delineate the underlying
mechanisms. We can, however, exclude a nonspecific effect on gene expression exerted by dietary unsaturated fatty acids. The effect we observed appears to be a consequence of distinct regulatory pathways responsive to \( \omega-3 \) fatty acids. In vitro, in human monocytic cells, \( \omega-3 \), but not \( \omega-6 \), fatty acids significantly reduced the mRNA and protein expression of CD36, also known as the scavenger receptor for oxidized LDL.\(^{37}\) As in the current investigation, a mechanism of action of \( \omega-3 \) fatty acids was not delineated. Future investigations will be needed to elucidate regulatory pathways responsible for our findings.

Reduced PDGF-A, PDGF-B, and MCP-1 mRNA steady-state levels in unstimulated MNCs translate into lower respective mRNA steady-state levels in monocytes stimulated by adherence in cells from donors supplementing their diets with \( \omega-3 \) fatty acids only (Figures 4 through 7). IL-10 and HB-EGF mRNA steady-state levels were not affected by ingestion of \( \omega-3 \) fatty acids after cell adherence. In control volunteers, as in the volunteers ingesting \( \omega-6 \) or \( \omega-9 \) fatty acids, all mRNA steady-state levels investigated were unaffected in monocytes stimulated by adherence (Figures 1 through 3 and 5 through 7). Reduced gene expression in unstimulated MNCs translated into quantitatively comparable reduced gene expression in monocytes stimulated by adherence (Figures 4 through 7). Thus, \( \omega-3 \) fatty acids seem to affect less the increase in response to adherence than conserve reduced PDGF-A, PDGF-B, and MCP-1 mRNA steady-state levels of the unstimulated MNCs.

In vitro, putative mechanisms of action have been described relating dietary components and gene expression; transcription factors related to the carbohydrate-response region may be involved in mediating unsaturated fatty acid signaling.\(^{38}\) Nuclear factor peroxisome proliferator–activated receptor might be involved.\(^{31,39}\) In experimental animals, dietary \( \omega-3 \) fatty acids regulated apoA-I, apoA-II, and acyl-coenzyme A oxidase gene expression.\(^{40}\) Antioxidant vitamins may play a role in regulation of gene expression of immune cells.\(^{41}\) However, because it is unclear whether the mechanisms described in vitro can be applied to the human in vivo/ex vivo situation, future investigations will focus on the mechanisms of action responsible for the effects of dietary \( \omega-3 \) fatty acids on human monocyte gene expression.

The effect of supplementing a human diet with \( \omega-6 \) or \( \omega-9 \) fatty acids with respect to MNC or monocyte gene expression ex vivo has not yet been studied to our knowledge. In vitro, e.g., in hepatocytes, a number of different unsaturated fatty acids reduced mRNA levels for pyruvate kinase, fatty acid synthase, and the S14 protein indiscriminately.\(^{42}\) Epidemiologically, a high intake of \( \omega-6 \) polyunsaturated fatty acids is correlated with a high rather than a low incidence of cardiovascular disease,\(^{43}\) whereas a high intake of \( \omega-9 \) fatty acids, as in the Mediterranean diet, is correlated with a low incidence of cardiovascular disease.\(^{44}\) Clearly, the effects of dietary \( \omega-6 \) or \( \omega-9 \) fatty acids on human gene expression as close as possible to the in vivo situation merit further study.

The current investigation was primarily aimed at alterations in human MNC and monocyte gene expression after ingestion of different classes of unsaturated fatty acids. Only limited amounts of blood can be obtained from a volunteer, resulting in small sample sizes. Therefore, we were unable to demonstrate whether alterations in gene expression were translated into alterations in the respective product levels. In other studies, after dietary intervention with \( \omega-3 \) fatty acids, alterations on the human monocyte/macrophage product level have been observed, like reductions in IL-1\(\beta\), IL-6, and tumor necrosis factor formation after stimulation with strong agents like lipopolysaccharide.\(^{45–47}\) Thus, a stronger stimulus on a larger sample will be used in our future investigations to clarify the effect of
dietary ω-3 fatty acids on PDGF and MCP-1 on the product level.

In conclusion, we demonstrate that PDGF-A, PDGF-B, and MCP-1 mRNA steady-state levels in unstimulated MNCs and in adherence-activated MNCs were decreased after supplementing the volunteers’ diets with ω-3 fatty acids. This decrease was specifically induced by dietary ω-3 fatty acids, since neither dietary ω-6 nor ω-9 fatty acids altered the mRNA steady-state levels investigated. Thus, ingestion of ω-3 fatty acids by volunteers specifically reduces gene expression of PDGF-A, PDGF-B, and MCP-1, factors that are currently thought to play an important role in the pathogenesis of human atherosclerosis.

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References


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