PERIPHERAL BLOOD NEUTROPHIL LEUKOTRIENE B₄ RELEASE AND MIGRATION IN RHEUMATOID ARTHRITIS

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Abstract—The present study was designed to compare peripheral blood neutrophil migration and leukotriene (LT) release between patients with rheumatoid arthritis (RA) and healthy controls and to correlate the neutrophil functions with clinical disease activity. Nineteen patients with moderately active RA and 19 age and sex matched healthy volunteers participated in this study. Isolated peripheral blood neutrophils from RA patients released equal amounts of LTB₄ but their random migration was enhanced as compared with neutrophils from healthy controls. LTB₄ release in whole blood was significantly lower in samples from RA patients than in those from the healthy volunteers (13.5 ± 1.4 and 19.1 ± 1.4 ng/10⁶ neutrophils respectively; P < 0.001). LTB₄ release from isolated RA neutrophils correlated with the levels of C-reactive protein, duration of morning stiffness and Ritchie articular swelling index. Concentrations of hyaluronate, cyclic AMP and 13,14-dihydro-15-keto-prostaglandin were not different between patients with RA and healthy volunteers. Neither was there any difference in TXB₂ production by platelets during blood clotting. In conclusion, peripheral blood neutrophils of RA patients seem to be primed and/or activated as their random migration is enhanced as compared with those of healthy volunteers. In RA, LTB₄ release from peripheral blood neutrophils seems to reflect the clinical activity of the disease. However, RA neutrophils released smaller (in whole blood) or equal (isolated cells) amounts of LTB₄ as compared with the respective controls. These contradictory findings suggest that LTB₄ release from peripheral blood neutrophils has no major role in the regulation of disease activity in rheumatoid arthritis.
INTRODUCTION

Rheumatoid arthritis (RA) is characterized by synovial fluid rich of neutrophils and their proinflammatory products. Neutrophils have been proposed to be activated or primed in peripheral blood in RA (1–3). Activated neutrophils migrate into the affected joint, release soluble lipid class inflammatory mediators, proteolytic enzymes and toxic oxygen radicals and thus amplify the ongoing inflammatory process (4). In addition, neutrophils seem to be involved in the pathogenesis of cartilage destruction in RA (1, 2). Recently, the increased migration and respiratory burst capacity of neutrophils was shown to predict the appearance of radiologic erosions at the joints of RA patients (5).

Neutrophils produce LTB$_4$, which has been found in increased amounts in rheumatoid synovial fluid (6). LTB$_4$ is able to activate neutrophils to adhere, aggregate, degranulate, migrate and produce reactive oxygen species (6, 7). LTB$_4$ production by synovial fluid neutrophils has been found to be altered in comparison with peripheral blood neutrophils (8–11). In addition, peripheral blood neutrophils from RA patients have been reported to possess altered activity in some ex vivo tests as compared with neutrophils from healthy controls (12–18).

If blood neutrophils, in addition to synovial fluid neutrophils, are activated in RA, one would suggest that their activation state is controlled by the disease activity or vice-versa. If this is the case, neutrophil functions should reflect the disease activity of RA. To test this hypothesis, LTB$_4$ release and migration of isolated blood neutrophils from RA patients were compared with those of healthy controls and correlated with known clinical and laboratory parameters measuring disease activity.

PATIENTS AND METHODS

Patients. Nineteen patients (5 males and 14 females; mean age 50 years, ranging from 17 to 65) with mild or moderate RA fulfilling the criteria of the American Rheumatism Association (19) and age and sex matched healthy volunteers participated in the study. The duration of rheumatoid arthritis was on average 12 years (range 0.6–37 years). Healthy controls abstained from any drugs for at least one week before sampling. RA patients were allowed to take acetaminophen but not any other non-steroidal anti-inflammatory drugs as analgesics. Drug treatment with disease-modifying antirheumatic drugs (DMARDs) was continued. Seven patients had gold therapy, seven sulfasalazine, two chloroquine, one D-penicillamine, one azathioprine and one patient had no DMARD treatment. A written informed consent was obtained and the study was approved by the ethical committee of Tampere University Hospital. Eight RA patients were classified into Steinbrocker (20) stage III, six into stage II and one patient for each stages 0, I and IV. The Steinbrocker