The Role of Prostaglandin E$_2$ Receptor in the Inflammatory Process of Rheumatoid Arthritis

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INTRODUCTION

Prostaglandins (PG) are lipid compounds derived from eicosanoids which are produced from both linoleic acid (n-6) and alpha linolenic acid (n-3). Among PG, there is PGE₂ produced from the three isoforms of PGE synthase (PGES). PGE₂ is linked to vascular diseases and inflammation (i.e. rheumatoid arthritis) (1). Rheumatoid arthritis (RA) is autoimmune disease defined by joint inflammation, swelling of the synovium and joint swelling, all of which can result in cartilage and bone eradication. An effective therapy for RA symptoms are the intake of non-steroidal anti-inflammatory drugs (NSAIDS) which stops the function of cyclooxygenase (COX), which inhibits the production of PGE₂. PGE₂ can be secreted by macrophage cells and synovial fibroblast in the pathogenesis of RA. This makes PGE₂ of special interest in the potential treatment of RA (2).

REVIEW OF LITERATURE

I. Prostaglandins E₂ and New Therapy Tactic in Rheumatoid Arthritis

Yan et al., hypothesized that a synthesized inhibitor of the peptide mimtope of PGE₂ receptor EP4 may act as a potential treatment of adjuvant induced arthritis (AA) (2). Yan et al., experimented on Wistar rats (n=30) over the course of twenty-one days. The rats were randomly assigned to one of three treatment groups being given various milligram amounts of receptor inhibitor, PBP (named by research team) or assigned to positive or negative control group. The study included analysis of inflammation in ankle steeps, isolation of synoviocytes apoptosis detection kit and synoviocytes proliferation assay. The statistical analysis data were evaluated via one-way ANOVA and unpaired two-tailed student’ test when comparing treatment groups (AA). All AA study groups experimented with PBP demonstrated a 70% decline in the swelling of paws correlated to controls (P<0.05). The results also showed that PBP experimental
synthesized inhibitor could stop the synovial fibroblast rapid cell growth up to 50% compared to the controls. This shows that PGE$_2$ could play a role in promotion of synovial fibroblast proliferation, which means that inhibition of PGE$_2$ to its receptor EP4 could prevent PGE$_2$ from carrying out its function. Yan et al., concluded that inhibition of PGE$_2$ EP4 receptor could be the key to decreasing inflammation in ankles and decrease promotion of synovial proliferation (2).

Sugita et al., similarly hypothesized that compound A (of their own design) could inhibit PGE$_2$ synthesis and would have similar or potentially better results compared to indomethacin, MFG3 and m-PGES-1 inhibitor in regards to pyrexia, inflammation, GI injury and inflammatory pain (3). The experiment was conducted on female Slc Hartley guinea pigs. The results showed that compound A decreased yeast-evoked PGE$_2$ synthesis, strengthened the synthesis of TXB$_2$ and 6-keto PGF$_{1\alpha}$ in vivo. Furthermore, compound A decreased paw swelling in adjuvant-introduced arthritis rats. This study assists in providing further evidence of PGE$_2$ interconnection in inflammatory processes (3).

II. Prostaglandins E2 and Inhibition of Th1 differentiation and Th17 Expansion in Arthritis Models

Chen et al., hypothesized that the introduction of PGE$_2$ EP4 receptor antagonist ER-819762 or an anti- PGE$_2$ antibody can suppress production of T helper (Th1) differentiation, interleukin-23 (IL-23) synthesis in dendritic cells (DC) and Th17 cell expansion (4)-associated with RA inflammation. Chen et al., experimented on rats and mice, which included radiological EP4 receptor binding assay, cell-based GPCR assays, IL-23-induced Th17 expansion, collagen-induced arthritis model, glucose-6- phosphate isomerase (GPI)-induced arthritis model and Complete Freund's Adjuvant (CFA)- induced hyperalgesia in their research strategy.
Furthermore, results showed that the addition of PGE\(_2\) decreased total T cell generation but also intensified IL-17 synthesis. It was found that these PGE\(_2\) expressive events could be reversed by 0.1 or 1.0 \(\mu\)mol-L\(^{-1}\). Furthermore, the PGE\(_2\) function raised the percentage of IL-17 production cells (5% increase) and this was diminished by ER-819762. Moreover, ER-819762 proved to able to diminish IL-23 induced Th17 expansion without the presence of extracellularly added PGE\(_2\). ER-819762 reduced bone erosion in collagen induced arthritis and effectively reduced inflammation in rat models. Moreover, it was shown that receptor EP4 activation can intensify IL-23 manufacturing by triggered DC and that this is stopped by a particular EP4 receptor competitor or anti- PGE\(_2\) antiserum. Chen et al., concluded that the ER-819762 competitor of EP4 receptors can reduce inflammation and prove useful in therapeutic treatment of RA (4).

Gheorghe et al., examined the functionality of PGE\(_2\) operating mechanism enzymes within RA B-cells and calculated the outcome of B cell diminishing theory on the function in RA tissue (5). The study conducted synovial biopsies on RA patients (n=24) before and after rituximab therapy. Furthermore, the study of B cells expressing MPGES 1 and COX-2 were extracted from the synovial fluid and exterior plasma of RA subjects. The results showed that rituximab therapy had little effect on synovial enzyme functionality cooperatively with the PGE\(_2\) operating methods. In addition, a recent study has reported that optimal antibody production by B cells requires COX-2 coming from PGE\(_2\) (6), meaning that inhibiting this mechanism could result in decreased antibody production in synovial tissue resulting in reduced arthralgia occurrence (5).

III. Negative Regulation of the Prostaglandin E2 of Hypoxia-Enhanced Rheumatoid Tissue
Mitomi et al., examined the mechanism of regulation of synovial cells compared to hypoxia in RA individuals (7). Mitomi et al., experimented using hypoxic conditions, testing the effect on vascularendothelial growth factor (VEGF) release (n=33) for four weeks, the effect of periodic hypoxia on tissue growth \textit{in vitro} (n=7) for twenty-four hours twice a week for four weeks and the effect of intermittent anaerobic conditions on the PGE$_2$ functionality via RA synovial tissues (n=13). Results of the study showed significant (P<0.0001) VEGF enhancement under hypoxia condition, synovial overgrowth in RA patients under intermittent hypoxia is a product of released PGE$_2$ based on the significant (P<0.01) enhancement of PGE$_2$ under hypoxia. Mitomi et al., established that periodic anaerobic conditions induced negative reaction coordination by PGE$_2$ synthesis, in combination with proinflammatory products including M-CSF, MMP-9 and TNF-$\alpha$. Mitomi et al., concluded that endogenous PGE$_2$ down-regulates the positive results of anaerobic conditions on synovial overgrowth from tissue inflamed cells (7).

Kawahara et al., reviewed various studies in regards to PGE$_2$-induced inflammation (8). Kawahara et al., explained that aspirin-like drugs work via inhibiting COXs actions which prevents biosynthesis of PGs, which are theorized to play a critical role in inflammation processes (9,10). Furthermore, PGs have been linked to bring about vasodilation and intensification of local blood flow, initiating red flares and localized heat. In addition, another study reviewed by Kawahara et al., looked into EP4 receptor deficient mice along with mice lacking in all four of the EPs, yielding results of significant reduction of disease progression (11). PGE$_2$-EP4 inflammation. These studies, like others present more evidence that PGE$_2$ is linked to inflammation in RA (8).
IV. Variants of Genes Show Association Between Prostaglandin E2 and Rheumatoid Arthritis Inflammation

Korotkova et al., researched whether prostaglandin E synthase (PTGES) gene polymorphisms and the risk and severity of RA (12). Moreover, Korotkova et al., studied if whether altered mPGES-1 expression is attributed to PTGES genetic variation. Considering that microsomal PGE synthase (m-PGES-1) is the closing enzyme in PGE₂ synthesis, this study is of benefit to RA patients in their therapy treatment. The PTGES genetic variation was examined in RA test subjects (total n=3081) and had two control groups (total n=1900). Furthermore, mPGES-1 function was examined in synovial tissue from RA test subjects. Data was collected from Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) and the Leiden Early Arthritis Clinic (Leiden EAC) from the Netherlands. A higher percentage of the patients were female (64-70.4% experiment group, 21.9-74.6% control groups) with ages 51.7 ± 12.7 (EIRA) and 56.4 ± 15.4 (Leiden EAC) (12).

The results of the Korotkova et al. investigation showed a significant (P<0.05) relationship between risk for RA and PTGES single nucleotide polymorphisms (SNPs) (12). The research findings were affirmed by a meta-analysis of from Leiden EAC and EIRA with total OR 1.31 (95% confidence interval (1.11-1.56)). In addition, patients with the genotype correlated with an increased baseline disease activity score showed significantly (P<0.05) higher synovial tissue mPGES1 function. Korotkova et al., concluded that due to PTGES polymorphisms that there is a greater expression of mPGES-1 leading to increased PGE₂ synthesis and in turn severe inflammation in RA patients (12).

Yan et al., hypothesized that mechanical stretch may control the rapid reproduction of RA fibroblast-like synoviocytes (FLS) (a major promoter of PGE₂) by intervening in the
relationship between COX-2 and PGE$_2$ (13). The study type compared in vitro- grown RA cells and typical FLS. The results demonstrated that physical level (6%, 1 Hz) of cyclic automated stretch significantly (P<0.05) lowered the generation of RA FLS. Moreover, the introduction of programmed cell death was not observed by stretch in either groups. Furthermore, IL-1$\beta$ (5ng/ml)-interjected COX-2/ PGE$_2$ levels are suppressed by stretch in RA FLS solely. In addition, the results showed that elevated intensification (100 and 500 ng/ ml) of PGE$_2$ significantly (P<0.05) induced cell generation in RA FLS, and this introduction was unsuccessfully suppressed by stretch (13).

V. Role of Prostaglandin E2 in Joint Pain in Individuals at Risk for Developing Rheumatoid Arthritis

De Hair et al., investigated arthralgia in the progression of synovial inflammation in autoantibody-positive test subjects in danger for acquiring RA in the future and how the PGE$_2$ pathway plays a role (14). De Hair et al., followed nineteen autoantibody-positive individuals with joint pain (n=15) and/or a genetic past of RA (n=8) for two years. In addition, early arthritis patients who after the two years follow up evaluation qualified for RA classification (n=63), inflammatory diseases, including joints and the entheses, (SpA; n=14), or had unclassifiable arthritis (UA; n=27). Pain assessments and synovial biopsies by executing baseline mini-arthroscopy in all subjects. To examine and calculate PGE$_2$ enzyme operating mechanisms (mPGES; COX-1 and -2; 15-PGDH) tissue components were taken and analyzed via immunochemistry (14).

The results of De Hair et al., showed that subjects (n=15) with arthralgia compared to those without (n=4) had a higher functionality of COX-1 (p=0.078), and also COX-2 (p=0.470)
and 15-PGDH (p=0.352) demonstrating no statistical significance/ difference (14). Next, in a comparison between subjects who developed arthritis (n=6) and those who did not develop arthritis (n=13) there were no differences in function levels of 15-PGDH, COX-1, COX-2 or mPGES-1. The results thus far demonstrate the synovial expression of PGE$_2$ pathway has no effect in either joint pain or the introduction of arthritis in autoantibody-positive subjects in danger for establishing RA. Furthermore, De Hair et al., compared baseline functionality of PGE$_2$ enzymes between two outcome groups. The evaluation was conducted after two years on RA individuals fostering aggressive non-erosive (n=30) or erosive (n=11) condition, to observe if they had increased standard expression than clients with self-liming condition (n=13). De Hair et al., concluded that there was no statistical significance and that disease persistence is not correlated to synovial expression of PGE$_2$ passageway enzymes (14).

**Conclusion**

RA is a long-lasting abnormal immune system disease that involves aggressive synovial inflammation, proliferation, attack of T lymphocytes, blood plasma cells and macrophages, joint destruction, and severe disability (5, 12). PGE$_2$ is a powerful lipid mediator produced from arachidonic acid (AA) through the function of cyclooxygenase (COX) enzymes (15). Several studies presented both here and in other publications have well established that PGE$_2$ expression has significant influence in the pathogenesis of RA and its effects, notably inflammation, some however have shown otherwise (14). Moreover, this review has presented evidence that experimental inhibitors (i.e. PBP & ER-819762) aid in the reduction of both joint inflammation and joint dissolving and aid in pain relief when blocking PGE$_2$ (2,3,4). In addition, it was demonstrated that genetically predisposed individuals with polymorphism of mPGES-1 (the
terminal enzyme of PGE\(_2\) synthesis), may have a part in the disease development of RA and disease seriousness to uptake of mPGES-1 at the site of pain but more research is warranted (12). Another study suggested that it is an alternative mechanism that regulates the pain in individuals at risk for developing RA (14). Based on pre-existing publications, recent decrements and general scientific apprehension, it is widely understood that the study of PGE\(_2\) synthesis and RA inflammation still needs more research.

References


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