OSTEOBLASTS SECRET A HIGH LEVEL OF BROMODOMAIN INHIBITOR, I-BET762 INHIBITS OSTEOCLAST GENESIS BY INHIBITING SOLUBLE RANKL – IMPLICATIONS FOR THE PATHOGENESIS OF RHEUMATOID ARTHRITIS


Acknowledgement: I confirm that there is no conflict of interest

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Background: Osteoblasts (OBs) are known to respond to human M-CSF and RANKL, and differentiate into OCs in the presence of vitamin D3 and PGE2. In this case, but OPG and M-CSF were detectable at a level comparable to mouse BMCs, OBs do not differentiate into OCs unless both M-CSF and RANKL were added to the culture. RANKL was not detected in the culture supernatant of synoviocyte culture. We propose that this is the system by which ectopic differentiation of OCs is prevented.

Methods: Human synoviocytes were prepared from synovium obtained in the course of joint replacement surgical operations performed at Saitama Medical University Hospital. Written informed consent, approved by the ethics committee of the hospital, was obtained from each patient prior to the experiment. Mouse OBs were obtained from the calvaria of newborn C57BL/6 mice. Mouse BMCs of the hospital, was obtained from each patient prior to the experiment. Mouse synoviocytes and BMCs might be developed. Through this analysis, we attempted to clarify the characteristics of synoviocytes in the pathogenesis of bone destruction observed in RA.

Results: When synoviocytes and BMCs were cultured with 1,25(OH)2D3 and PGE2, OCs were not induced. OC precursor cells did not seem to even survive. Too, BMCs did not survive unless exogenous M-CSF was added, and they did not differentiate into OCs in the presence of both cytokines.

Objectives: Our aim was to examine whether a co-culture system of human synoviocytes and mouse BMCs might be developed. Through this analysis, we attempted to clarify the characteristics of synoviocytes in the pathogenesis of bone destruction observed in RA.

Conclusion: We found that ATO prevented activated naïve CD4+ T-cell differentiate into Th17 cell and reduced cytokine production by activated Th17 cells by downregulating their signature transcription factors, STAT3 and orphan nuclear receptor (ORR). Notably, ATO reduced Th17 cells frequency while increased Treg cells frequency under specific polarizing conditions from treatment-naïve RA patients by transfecting siRNA STAT3 and lentivirus STAT3 to verity the mechanism of ATO on Th17/Treg balance in vitro. Collagen-induced arthritis (CIA) model was constructed to detect the clinical score, histopathological change, bone destruction, Th17/Treg proportion and joint tissues immunohistochimistry. Single cell sequencing and other methods have been applied too.

Results: We found that ATO prevented activated naïve CD4+ T-cell differentiate into Th17 cell and reduced cytokine production by activated Th17 cells by downregulating their signature transcription factors, STAT3 and orphan nuclear receptor (ORR). Notably, ATO reduced Th17 cells frequency while increased Treg cells frequency under specific polarizing conditions from treatment-naïve RA patients by transfecting siRNA STAT3 and lentivirus STAT3. Furthermore, we have noticed that intervention of ATO in CIA model attenuated joint inflammatory infiltration and bone destruction, significantly improved the imbalanced Treg/Th17 ratio. In detail single cell sequencing and other methods have been applied too.

Conclusion: ATO may be a immune modulator candidate for treatment-naïve RA patients via balancing well Treg/Th17 cell ratio through STAT3 regulation.

REFERENCES


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ARSENIC TRIOXIDE IMPROVES TREG AND TH17 BALANCE VIA MODULATING STAT3 IN TREATMENT-NAÏVE RA PATIENTS

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Background: We have a long-term interest in novel arsenic trioxide As2O3 (ATO) medical application since some acute promyelocytic leukemia (APL) patients have been cured by first using ATO and survived for more than 45 years successfully treated by Prof. Zhang Tingtong in our institute. Moreover, our previous studies have shown that ATO significantly suppress angiogenesis and induced fibroblast-like synoviocytes (FLS) apoptosis in collagen induced arthritis (CIA) model [1]. However, the extract mechanism by which ATO anti-rheumatic and whether this occurs via modulation of immune system are still unclear.

Objectives: To investigated the immunologic mechanism by which ATO may inhibit T helper 17 cells (Th17) differentiation while promote regulatory T cells (Treg) generation via modulating signal transducer and activator transcription 3 (STAT3) in treatment-naïve RA patients.

Methods: Naïve CD4+T cells sorted by fluorescence-activated cell sorting (FACS) from treatment-naïve RA patients and healthy controls were used to investigated the effect of ATO on its polarization process and related cytokines. Knockdown or enforced expression of STAT3 transfection experiments were conducted by small interfering RNA (siRNA) and lentivirus STAT3 to verity the mechanism of ATO on Th17/Treg balance in vitro. Collagen-induced arthritis (CIA) model was constructed to detect the clinical score, histopathological change, bone destruction, Th17/Treg proportion and joint tissues immunohistochimistry. Single cell sequencing and other methods have been applied too.

Results: We found that ATO prevented activated naïve CD4+ T-cell differentiate into Th17 cell and reduced cytokine production by activated Th17 cells by downregulating their signature transcription factors, STAT3 and orphan nuclear receptor (ORR). Notably, ATO reduced Th17 cells frequency while increased Treg cells frequency under specific polarizing conditions from treatment-naïve RA patients by transfecting siRNA STAT3 and lentivirus STAT3. Furthermore, we have noticed that intervention of ATO in CIA model attenuated joint inflammatory infiltration and bone destruction, significantly improved the imbalanced Treg/Th17 ratio. In detail single cell sequencing and other methods have been applied too.

Conclusion: ATO may be a immune modulator candidate for treatment-naïve RA patients via balancing well Treg/Th17 cell ratio through STAT3 regulation.

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BROMODOMAIN INHIBITOR, 1-BET762 INHIBITS PRODUCTION OF PRO-INFLAMMATORY MEDIATORS BY DOWN-REGULATING BROMODOMAIN AS AN EPGENIC READER IN RHEUMATOID ARTHRITIS MODEL

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Background: Rheumatoid arthritis (RA) is a chronic autoimmune disorder, characterized by joint inflammation and bone destruction. The fibroblast-like synoviocyte contributes to the pathogenesis of RA through proliferation and production of cytokines. Recently, blockade of the bromodomain and extra-terminal domain