**Format for ANSWERING REVIEWERS**

April 12th, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8396_review_manuscript).

**Title:** Inhibition of Rheumatoid Arthritis by Blocking Connective Tissue Growth Factor

**Author:** Kazuhisa Nozawa, Maki Fujishiro, Yoshinari Takasaki, and Iwao Sekigawa

**Name of Journal:** World Journal of Orthopedics

**ESPS Manuscript NO:**8396

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer as follows. The corrected parts in the manuscript are highlighted by yellow color.

(1) *In the Abstract, the statement in lines 7-8 "The binding of …. membrane bound TNFa" should be deleted.*

We deleted it.

(2) *In the Abstract, the phrase in lines 10-11 "We present the profile …. using infliximab; several proteins" should be deleted.*

We deleted it

(3) *The phrase "We have previously shown that several proteins, including CTGF" should be added just before "exhibited extensive changes …." in line 12.*

We added that sentence in the indicated part.

(4) *Pages should be numbered.*

We numbered our manuscript in bottom of pages.

(5) *In the third page of the paper, under the heading "Connective tissue growth factor", in line 7, the phrase "CTGF was discovered …. of a platelet" should read "CTGF was discovered after the detection of cross-reactivity between an antiserum to a platelet*".

We corrected the sentence according to the reviewer's suggestion.

(6) *In lines 13-14, the statement "Although a number … been defined" does not make any sense the way it is written. It should read as "Although a number of cell surface molecules, such as integrins,*

*have been currently proposed as candidate specific CTGF receptors, such receptors have not yet been definitely documented."*

We corrected the sentence according to the reviewer's suggestion.

(7) *In lines 16-18 of the same page "CTGF in the … autocrine system." should read as "In the articular tissue, consisting of different types of cells, CTGF is produced by chondrocytes and maintains cartilage tissue homeostasis via an autocrine process."*

We corrected the sentence according to the reviewer's suggestion.

(8) *In the following sentence, the word "null" does not seem the most appropriate and the word "complete" may fit better, whereas the "osteoclast-like formation" should read as "osteoclast formation" or "osteoclast-like cell formation".*

We corrected the sentence according to the reviewer's suggestion.

(9) *The word "system" following "autocrine" should better change to "process" in several points of the text.*

We replaced "system" into "process" in our manuscript according to the reviewer's suggestion.

(10) *In the Introduction, page 3, the word "using" in front of "infliximab" should be replaced by "with".*

We replaced "using" into "with" according to the reviewer's suggestion.

(11) *In page 6 line 8, the word "distraction" should change to "destruction".*

We corrected the sentence according to the reviewer's suggestion.

(12) *Figure 1 should be separated into two distinct figures: Fig. 1 and Fig. 2, instead of consisting of Fig. 1-1 and Fig. 1-2. Consequently, the following figures2, 3 and 4 should become 3, 4 and 5. Most importantly, all the figures should be given a title, besides the relatively extensive legend.*

We modified and renumbered the figures. In addition, we added a title in the figures according to the reviewer's suggestion.

(13) *The effect of TNFa on these two cells regarding CTGF is opposite to each other (according to the authors), they should make an appropriate comment.*

We commented the issue according to the reviewer's requirement. The comment is added in the ''Contribution of CTGF to the progression of RA" section and highlighted by yellow color. The comment is as follows;

''TNF receptors have shown to transduce and amplify receptor activation resulting different cellular fates such as NF-κB activation or apoptosis. Although precise intracellular mechanisms has not elucidated, previous studies have indicated that TNF-α increased or inhibited CTGF production depend on cell types. For example, TNF-α positively regulated CTGF production in mesangial cells (reference 17). On the other hand, TNF-α negatively regulated CTGF production in human lung endothelial cells (reference 18).''

*(14) The issue they should address is "Why the excess CTGF produced by the fibroblasts does not affect both osteoclasts and chondrocytes in a similar manner, i.e. with a positive effect on*

*chondrocytes as well?"*

We commented the issue according to the reviewer's requirement. The comment is added in the ''conclusion'' section and highlighted by yellow color. The comment is as follows;
''CTGF is a multiple functional cytokines and possess a several biological functions depend on the target cells. Although a number of cell surface molecules have been nominated as candidates currently for its specific receptors such as integrins, they have not been defined to date. Biological functions of CTGF may differ depend on its receptor as well as cell types.''

(15) *Is the direct inhibition by TNFa of the autocrine mechanism of CTGF production by chondrocytes able to overcome a direct stimulatory effect of the fibroblast produced CTGF on chondrocytes?? This issue should be definitely commented upon.*

We commented the issue according to the reviewer's requirement. The comment is added in ''Contribution of CTGF to the progression of '' section and highlighted by yellow color. The comment is as follows;
''Our data indicated that TNF-α was able to stimulate CTGF production in synovial fibroblasts. The excessive CTGF produced by synovial fibroblasts logically may function as protective factor for cartilage destruction in RA, because CTGF plays an important role for chondrogenesis. On the other hand, TNF-α has shown to induce catalytic enzymes production such as MMPs which cause cartilage destruction in synovial fibroblasts. Moreover, our data also indicated that TNF-α oppositely inhibited CTGF production in condrocytes. In RA, TNF-α possibly functions as positive regulator for cartilage destruction through catalytic enzymes production or the inhibition of CTGF production in condrocytes more efficiently rather than functions as negative regulator for cartilage destruction through increased CTGF production in synovial fibroblasts.''

(16) *In their Discussion and Conclusions, the authors should give information from their studies referenced #3 and #10, providing any available data on a possible in vivo evidence of CTGF involvement in RA pathogenesis.*

We created a new figure (Figure 4 in the revised manuscript) from our previous publications for providing possible in vivo evidence of CTGF involvement in RA pathogenesis according to the reviewer's suggestion.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Orthopedics.*

Sincerely yours

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