



ESPS PEER REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 13411

Title: Mesenchymal stem cells and collagen patches for anterior cruciate ligament repair

Reviewer code: 01237968

Science editor: Xue-Mei Gong

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input checked="" type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

In this manuscript, the authors reported the effects of two different collagen scaffolds, Chondro-Gide (CG) and Novocart (NC) on anterior cruciate ligament (ACL)-derived tenocytes (TC) and bone marrow-derived mesenchymal stem cells (MSC). The results indicated that both TC and MSC adhered to CG and NC, and their mitochondrial activity increased after 7 days in culture. Meanwhile the number of TC was higher than that of MSC cultured on CG. Hydroxy-proline (OHP) and glycosaminoglycan (CAG) ratio of TC and MSC mixed culture was higher than that of TC or MSC alone. Quantitative RT-PCR analysis showed that the collagen scaffolds did not have significant effects on the expression of the ligament marker genes. The authors tried to characterize the effects of CG and NC on TC and MSC, but the data as well as discussion are unfortunately preliminary and/or not informative. Most of the data including those of DNA content (Fig.5), OHP and CAG amounts (Fig.7) and the expression of the ligament marker genes (Fig. 9), failed to show significant differences between the controls and the CG or NC-treated cells. In fig.4, the number of TC and MSC cultured on CG was less than that on NC, and the number of MSC was less than that of TC, but reasons of the differences such as differential cell attachment onto the substrate, cell proliferation or cell survival were not shown. In Fig.6, mitochondrial activity in TC and TC/MSC mixture cultured on CG significantly increased after 7 day in culture compared with that after 1 day. However, it is totally unclear how much CG was effective, because comparison of the activity in TC cultured on CG with that cultured in appropriate control condition was not shown. In addition, the



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authors claimed that ' patches promote adherence and proliferation of cells' in page 2, line 30, but the data only showed mitochondrial activity. In Fig. 8, OHP/CAG ratios in TC and MSC mixture significantly increased compared with those in TC or MSC alone, but meanings of the changes were not appropriately discussed. The authors claimed that 'the cells are modifying the underlying matrix' in page 3, line 4, but it is unclear what it means. In Fig.9, the expression of the tested genes was not significantly changed in TC and MSC among the tested cultured conditions, but the authors discussed the changes of the expression in page 3, line 5-6, and in page 15, lines 3-17, which is not appropriate. Additional points; 1. page 3, line 9-10: A meaning of this sentence is not clear. 2. Fig.5: Control samples without cells had significant amounts of DNA, indicating that NC and CG contain DNA. However why NC and CG with cultured cells did not have more of DNA? 3. Page 17, lines 27-30: It is unclear what the authors intend to mean, because MSC and TC were labeled with different fluorescent dyes and could be clearly distinguished.



ESPS PEER REVIEW REPORT

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<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

The authors suggest that collagen patches that have proven beneficial for repairing cartilage and meniscus may be suitable to repair the anterior cruciate ligament (ACL). Although the results are very preliminary, are very encouraging. Figure 9 shows as TC, when seeded on NC patch, overexpress collagen-2, unlike what is observed when they are grown on CG patch. How do you interpret this result? The combined use of MSC and TC provides some benefit to using only TC?. Although the results are preliminary, the authors could give their opinion. Minor comments: Page 5, line 19: Define DIS Some errors or confusion in the naming of the figures and tables in the text should be corrected: Page 16, lines 29 and 31: Results in the text refer to Figure 9, and not to Figure 6 Page 17, lines 18 and 19: Table 2 must be changed by Table 1 Page 18: Lines 3-4: Figure 5 must be replaced by Figure 7 Page 18: Lines 9 and 10-11: Figure 7 must be replaced by Figure 8 Figure 7: Given the order of appearance of the results in the text, it would be more convenient than the panel B of Figure 7 was actually the panel A. Data presented in Figure 8 (ratio of OHP/GAG) could be included as panel C in Figure 7



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ESPS PEER REVIEW REPORT

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
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<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

Since Dynamic Intraligamentary Stabilization (DIS) approach in anterior cruciate ligament (ACL) repair has shown promising clinical benefits. This study aimed to study insight as to whether the collagen patches that are currently approved and marketed for cartilage and meniscus repair are also suitable for ACL repair, and elucidate the extent to which they impact and interact with cells. They tested two commercially available collagen scaffolds with regards to cell viability, adherence and proliferation of seeded tenocytes (TC), the primary cell type in ACL tissue. Overall this is a beneficial study, however, some concerns need to be addressed. Methods section in Abstract is too long. The metabolic cell activity methods used in the manuscript is not clear and authors should use alternative methods to show metabolic activity of cells. To further support the expression of gene expression, the authors should also perform additional Western blot experiments to validate the findings. Writing part of this manuscript also needs improvement.



ESPS PEER REVIEW REPORT

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
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<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

This paper by horovitz et al. compared two different collagen patches seeding with either bone marrow mesenchymal stem cells or primary tenocytes for possible anterior cruciate ligament repair. Chongrogide is composed of porcine collagen I and III as a bilayer membrane. Novocart is a biphasic, three-dimensional collagen-based matrix from bovine. Both of collagen sponges have been used for cartilage repair. ACL injury is a common disease and the repair of ACL remains a challenge due to its limited self regenerative ability. Despite of the progression of reconstructive techniques for ACL repair, an ideal biological scaffold for ACL reconstruction is needed. Thus, this study is of importance. However, the following concerns should be addressed. 1. Overall, the written need to be improved. For example, in the abstract, the first two sentences of methods are background information. 2. Figure 4, in the chondrogide scaffold, the number of MSCs is low on both Day 1 and 7. Both TC and MSC decreased in the 1:1 premix. This should be described in the result section on page 12. Is the low number due to z scan level? Is the magnificent the same for the SEM of Novocart scaffold? 3. Figure 5 shows no difference in DNA content but figure 4 shows less MSCs on day 7. Is this discrepancy due to the large amount of DNA content in scaffold itself? 4. Figure 6 conflicts with figure 4 if the cell number of MSCs decreased on day 7 is true. In the method part, it states that the resorufine signal is proportional to the number of living cells and corresponds to the cell metabolic activity. If the number of MSCs on day 7 is decreased, would the fluorescence intensity be decreased? Please explain. 5. Figure 7, the GAG content of premix is lower than other groups on day



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7. Please explain. 6. A detailed description of gene change should be given in the result section. 7. Please discuss the advantages of the current strategy over the other tissue engineering techniques for ACL repair. 8. Biomechanical tests would add more value for the study.