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--Manuscript Summary--

Manuscript ID	ES-16-83
Title	Response Letter for "Mesenchymal stem cell secretome to control inflammation in allergic conjunctivitis"
Running Head	Mesenchymal stem cells secretome and ocular surface disorders
Keywords	Mesenchymal stem cells; secretome; allergic conjunctivitis;corneal transplantation;dry eye
Abstract	Mesenchymal stem cells (MSCs) possess a striking variety of biological functions, from tissue repair and regeneration to immunomodulatory and anti-inflammatory actions (2, 3). Thus, MSCs are considered as a promising novel therapeutic strategy for treating inflammation/immune-related diseases (2-5). However, for ocular surface inflammation/immune-related disorders, reported administration routes of MSCs are not ideal for treating patients in a clinical setting. Based on this weakness, we proposed and developed a novel approach where we have used culture medium from TNF-Î± pre-conditioned bone marrow-derived mesenchymal stem cells (MSC) (CMT) for treating ocular surface inflammation/immune-related disorders. As shown in our published paper, CMT markedly controlled allergic conjunctivitis (6). In our unpublished study, we further find that CMT treatment also leads to the beneficial effects on corneal transplantation, dry eye and ocular chemical burns in animal models (manuscript under preparation). These results have significantly supported the idea that local use of CMT may be considered as a promising novel therapeutic strategy for ocular surface inflammation/immune-related disorders. Currently, growing evidence supports that a mixture of mediators released by MSC, rather than one or two mediators alone, could be responsible for the beneficial effects of MSC conditioned medium (7,8). Consistently, we have identified that COX2/PGE2 signaling plays key roles in CMT-mediated anti-allergic effects, but PGE2 administration alone only resulted in partial effects of CMT in experimental allergic conjunctivitis. However, the bioactive mediators to contribute the beneficial effects of MSC secretome are not completely clear. Thus, it is desired to find out which factors may contribute together or synergistically to beneficial effects of MSC conditioned medium, and consequently to figure out the optimal mixture of these factors to gain the maximal therapeutic effect for clinical application. In an ongoing project, we have searched the bioactive factors of MSC secretome by whole gene scan and protein clip. Interestingly, we have observed that bioactive factors of MSC responsible for therapeutic effect of MSC are different in different pathological conditions. For example, PGE2 signaling of MSC did not work in corneal chemical burns and dry eye (unpublished data). This represents an additional challenge to rule out bioactive factors of MSC secretome and get ideal therapeutic effect of CMT. Nevertheless, the use of MSC conditioned medium represents a promising novel strategy for treating ocular surface diseases, including allergic conjunctivitis, ocular chemical burns, dry eye and corneal graft rejection. For clinical application, further studies should be warranted to better understand MSC secretome.
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Dear editors,

Dr. Spampinato gave an insightful comment on “Mesenchymal stem cell secretome to control inflammation in allergic conjunctivitis”(1). Dr. Spampinato proposed that it is key to get the complete knowledge of MSC secretome composition in order to better understand MSC secretome and to achieve the best therapeutic effect of MSC secretome for clinic setting. This comment is highly significant and important.

Mesenchymal stem cells (MSCs) possess a striking variety of biological functions, from tissue repair and regeneration to immunomodulatory and anti-inflammatory actions (2, 3). Thus, MSCs are considered as a promising novel therapeutic strategy for treating inflammation/immune-related diseases (2-5). However, for ocular surface inflammation/immune-related disorders, reported administration routes of MSCs are not ideal for treating patients in a clinical setting. Based on this weakness, we proposed and developed a novel approach where we have used culture medium from TNF-α pre-conditioned bone marrow-derived mesenchymal stem cells (MSC) (CMT) for treating ocular surface inflammation/immune-related disorders. As shown in our published paper, CMT markedly controlled allergic conjunctivitis (6). In our unpublished study, we further find that CMT treatment also leads to the beneficial effects on corneal transplantation, dry eye and ocular chemical burns in animal models (manuscript under preparation). These results have significantly supported the idea that local use of CMT may be considered as a promising novel therapeutic strategy for ocular surface inflammation/immune-related disorders.

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In an ongoing project, we have searched the bioactive factors of MSC secretome by whole gene scan and protein clip. Interestingly, we have observed that bioactive factors of MSC responsible for therapeutic effect of MSC are different in different pathological conditions. For example, PGE2 signaling of MSC did not work in corneal chemical burns and dry eye (unpublished data). This represents an additional challenge to rule out bioactive factors of MSC secretome and get ideal therapeutic effect of CMT.

Nevertheless, the use of MSC conditioned medium represents a promising novel strategy for treating ocular surface diseases, including allergic conjunctivitis, ocular chemical burns, dry eye and corneal graft rejection. For clinical application, further studies should be warranted to better understand MSC secretome.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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