Outstanding research paper awards of the Journal of the Chinese Medical Association in 2018

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In this December issue of the Journal, I am glad to introduce the winner of the 2018 Journal of the Chinese Medical Association Outstanding Research Paper Award. The award was selected from all original articles published in the 2018 print issues of the Journal of the Chinese Medical Association (JCMA).1–3 The winner is Dr. Ho’s work from the Taipei Veterans General Hospital and National Yang-Ming University,4 and this article is entitled “Mesenchymal stem cells and their conditioned medium can enhance the repair of uterine defects in a rat model”, which has been published in the March issue of the JCMA.4 The winner received the honor at the Annual Meeting of the Chinese Medical Association on June 22, 2019 held in Taipei, Taiwan.

Dr. Chi-Hong Ho and his colleagues performed an interesting in-vivo animal study to evaluate the potential and possibility of the using mesenchymal stem cell (MSC) transplantation in the repair of a large uterine defect,4 which is a still biggest challenge in the management of this because of its associated subfertility and infertility. The strategy of Dr. Ho’s group was the combination of the MSC and MSC-conditioned medium (the main key factor as interleukin 6 [IL-6]), which was applied in the large defect of the uterus and the large uterine defect was successfully repaired.4 Therefore, the authors concluded that transplantation of bone marrow-derived MSCs could facilitate the wound healing process in the uterine defects, and the repairing process can be further augmented by IL-6.4 This impressive finding is worthy of discussion.

Uterine diseases, regardless of benign or malignant states, are very common in women during the reproductive age. Because of need of fertility maintenance, conservative treatment, including medical treatment or conservative surgeries, has been widely used in the routine clinical practice. However, many conservative uterine surgeries, including cesarean section, curettage, hysteroscopic surgery, and/or minimally invasive surgery or exploratory laparotomy (myomectomy), might induce scar formation or defect of repair.8,16 To initiate different types of wound healing, such as hypertrophic scar or keloid scar formation or defect of repair.8,16 To initiate different or to restart the proliferation or growth of cells, many cytokines or GFs (secreted by certain type of cells, such as fibroblast, immune cells, and/or others) are needed. The following are the examples: platelet-derived GF, fibroblast GF, nerve GF, transformation GFβ, (TGF-β1, TGF-β2, and TGF-β3), connective tissue GF, cysteine-rich 61, IL-6, IL-8, IL-10, homeobox 13, the Wnt signaling pathway, osteopontin, early growth response protein 1, plasminogen activator inhibitor-1 (PAI-1), macrophage migration inhibitory factor (MIF), and so on.8,16 Since it is rational to suppose that condition medium after incubation of the MSC might also contain a lot of amount of various kinds of cytokines and/or GFs, Dr. Ho used MSC-conditioned medium as agents in the treatment of uterine defect, and found MSC-conditioned medium (Asherman syndrome), or final malfunction of the uterus, which is associated with worse outcome of pregnancy and infertility.4,5,7 Therefore, any strategy to accelerate the healing process or to avoid scar formation after this type of surgery is welcome.8,9 In Dr. Ho’s study,4 there are two highlights worthy of our attention. One is the introduction to use the potential natural homologous or heterologous material (MSCs) in the management of large defect of the organ and the other is the use of the identified factor, such as IL-6, which could augment the effect of stem cells in the repair process of uterine defect after the thorough evaluation of certain type of paracrine factors (cytokines and/or growth factors [GFs]) from the MSC-conditioned medium, as shown in the current study.4 In fact, with much more understandings of the characteristics of the relatively ceased cells (stem cells) in organisms, recent studies have extensively used stem cells in application of various kinds of clinical problems, and its role is not only for prediction of disease course but also for restoration of function of injured tissue or organs.10–13

Cytokines and/or GFs have been widely distributed within the human body, which is not only a maintenance of normal function of well-beings but also an initiator or end-product of many physiological and pathological processes.13–15 Homeostasis of cytokines and/or GFs are critical for health of human beings, and any imbalance of these factors will result in a catastrophic situation and even causes death. Wound healing is a very much complex process, which at least contains three stages: the first step is immediate hemostasis and a prompt initiation of the inflammatory process; the second step is the proliferation process involving profuse fibroblasts, keratinocytes, and endothelial cells as well as accumulation of extracellular matrix; and the final step is the remodeling process relying on a controlled balance between the synthesis and degradation of the extracellular matrix and replacement of the original type III collagens by type I collagen to avoid the formation of unwanted wound healing, such as hypertrophic scar or keloid scar formation or defect of repair.8,16 To initiate differentiation or to restart the proliferation or growth of cells, many cytokines or GFs (secreted by certain type of cells, such as fibroblast, immune cells, and/or others) are needed. The following are the examples: platelet-derived GF, fibroblast GF, nerve GF, transformation GFβ, (TGF-β1, TGF-β2, and TGF-β3), connective tissue GF, cysteine-rich 61, IL-6, IL-8, IL-10, homeobox 13, the Wnt signaling pathway, osteopontin, early growth response protein 1, plasminogen activator inhibitor-1 (PAI-1), macrophage migration inhibitory factor (MIF), and so on.8,16 Since it is rational to suppose that condition medium after incubation of the MSC might also contain a lot of amount of various kinds of cytokines and/or GFs, Dr. Ho used MSC-conditioned medium as agents in the treatment of uterine defect, and found MSC-conditioned medium

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can enhance MSC working on repair of the large uterine defect. To identify which factors contributed to this effect, the authors first evaluated the content and amounts of cytokines and/or GFs in the MSC-conditioned medium and found IL-6, PAI-1, and MIF ranked the highest in levels. To test which one is a target, Dr. Ho used the neutralizing antibody against IL-6 in the MSC-conditioned medium and resulted in disappearance of the enhancing effects on uterine defect repair; concluding that IL-6 was a key factor for the acceleration of wound repair process in uterine defect after MSC treatment. Although this finding is interesting, the role of IL-6 for acceleration of wound healing might make confusion. It is unclear why the positive role of IL-6 on MSC is found in Dr. Ho’s study.

In fact, IL-6, one of the proinflammatory cytokines, plays a relatively complicated role in the wound healing process. In the initial stage of wound healing, IL-6 enables activated M1 macrophages to phagocytose neutrophils that have undergone apoptosis and remove any pathogens or debris in the wound. Recently, proinflammatory cytokines, although they are important in the initial stage of wound healing, are often considered to play negative role in the wound healing process. Since excessive production of these proinflammatory cytokines cause purulent inflammation, with subsequently resultant much more damage of the tissue during the wound healing process, much more evidence supported dampening purulent inflammation, decreasing neutrophil numbers, promoting alternative macrophage polarization (promoting a shift from M1 to M2 subtypes), reducing the expression of proinflammatory cytokines, and decreasing elastases production may have the beneficial roles of aiding wound closure and collagen deposition. In the spinal cord injury (SCI) animal model, Cheng and colleagues found that neural cell transplantation could modulate SCI-induced inflammatory responses (downregulation of tumor necrotic factor-α, IL-1β, IL-6, and IL-12) and enhance neurological function after SCI via reducing M1 macrophage activation and infiltrating neutrophils, suggesting the negative role in neural cell transplantation in the SCI model. The negative role of IL-6 in the healing process of bone is also reported on the murine and human bone fracture healing models. Since the results of Dr. Ho’s study seemed to be different from the recent understanding of the role of IL-6 on the wound healing process, much more studies to explore this topic and to clarify the role of IL-6 on the stem cell involving the wound healing process is welcome. Finally, as a Deputy Editor-in-Chief, on behalf of editorial board of the Journal of the Chinese Medical Association, I am pleased to congratulate Dr. Ho on his winning of the Outstanding Research Article Award. We believe that the authors’ and readers’ continuing efforts and contribution can accelerate the advancing development of medicine and further provide a much more better health care of humans.

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