Editorial

Mesenchymal stem cell secretome to control inflammation in allergic conjunctivitis

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Su and colleagues (1) propose the use of culture medium from TNF-α pre-conditioned bone marrow-derived mesenchymal stem cells (MSC) as a novel therapeutic strategy for treating allergic conjunctivitis. MSC were exposed to TNF-α and conditioned medium was topically applied in the conjunctiva of mice with short ragweed pollen-induced experimental allergic conjunctivitis. Interestingly, ocular administration of TNF-α-conditioned medium reduced clinical signs and symptoms of allergic conjunctivitis. The anti-allergic effect of TNF-α-conditioned medium appeared to be due to the reduction of inflammatory cells infiltration and accumulation in the conjunctiva, inhibition of B cells, mast cells and histamine functions, through a COX-2-dependent mechanism. In fact, pre-treating MSC with COX-2 siRNA, the anti-allergic effects were abrogated. It seems that factors produced by MSC treated with TNF-α exert anti-allergic properties targeting simultaneously several key mediators of allergic reaction like B cells, mast cells, histamine and T helper 2 (Th2) cells.

Multipotent MSC are a rare subpopulation of pluripotent stromal cells that can be derived from different adult tissues (2). MSC are progenitors, able to differentiate into several cell lineages; they display beneficial effects in tissue repair and regeneration, and possess immunoregulatory properties. For these reasons MSC are considered as a promising novel therapeutic strategies for treating several pathologies, like immune-related diseases, graft versus host disease, liver diseases, cardiac diseases and amyotrophic lateral sclerosis (3). Moreover, in *in vivo* models of allergic diseases, like allergic rhinitis (4) and asthma (5,6), MSC exerted promising anti-allergic effects.

The therapeutic potential of MSC seems to rely on several key mechanisms: (I) the modulation of immune response; (II) the production and secretion of soluble factors (named collectively as "secretome"); (III) the possibility to differentiate into several cell lineages; (IV) the ability to migrate from the bloodstream to the site in which they are required (such as for example the site of inflammation or the injured tissue) (3,7).

Accumulating evidences suggest that the paracrine/autocrine effect, exerted by bioactive molecules produced by MSC, the secretome, may mediate their principal therapeutic properties, instead of their ability to transdifferentiate in order to substitute injured cells. MSC secretome is composed by numerous bioactive molecules, comprising chemokines, cytokines, growth factors, hormones, angiogenic factors and proteases (8), that mediate several biological functions. The possibility to use MSC secretome for therapeutical purposes represents an intriguing cell-free strategy with several advantages over cell-based strategies. To this aim conditioned medium derived from opportunely treated MSC could be used instead of MSC themselves.

Nevertheless, it is important to identify the exact factors involved and their concentration; numerous efforts have been done to unravel candidate modulators of paracrine effects responsible of immunomodulatory and anti-allergic properties of MSC secretome. A proteomic analysis of TNF-α-induced secretome of MSC revealed an increased production of 118 proteins, among them several cytokines and chemokines [like IL-6, IL-8, chemokine (C-X-C motif) ligand 6 and monocyte chemotactic protein-1], cathepsin L, matrix metalloproteases, protease inhibitors

and long pentraxin 3, a key inflammatory mediator of innate immunity (9). Other anti-inflammatory factors produced by MSC pre-conditioned with TNF-α are hepatocyte growth factor (HGF) (10), vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1) (11). HGF is known to protect tissues from inflammatory injuries and may be an important contributor of MSC secretome effects. Moreover, it has been shown that TNF-α induced MSC to increase prostaglandin E2 (PGE2) production (12). PGE2 mediates immunosuppressive effects of MSC acting probably on macrophages to increment their IL-10 production and on T-helper (Th) cells regulating the balance between Th1 and Th2 response (13,14).

Among other bioactive factors resolvins may play a pivotal role in anti-inflammatory and anti-allergic effects of MSC at ocular level, although it is not yet known if they can produce these pro-resolution lipid mediators. In fact, in conjunctival globet cells, which physiologically secrete mucins to protect the eye, resolvins E1 and D1 reduced their augmented secretion induced by leukotrienes (15), while resolvin D1 was able to block histamine-stimulated response in conjunctival globet cells (16).

Probably, a mixture of listed factors and other mediators not yet identified may contribute synergistically to beneficial effects of MSC conditioned medium; it is reductive to consider that only one or two modulators can mediate the complex physiological and therapeutic properties of MSC. Rather, it is necessary to find out the proper combination of bioactive modulators that summarizes beneficial effects of MSC secretome. One of the challenges is the complete knowledge of MSC secretome composition in order to better understand which factors are responsible of beneficial effects of MSC and to determine the optimal mixture of bioactive factors to achieve the best therapeutic effect. This is important as secretome may also contain molecules that are not beneficial but learning how to modulate MSC secretion it could be possible to avoid potential side effects. Nevertheless, the use of MSC conditioned medium represents a novel strategy for treating several diseases. The great potential of MSC culture medium usage for therapeutic purposes is highlighted also by several advantages over stem cells use: easier delivery, possibility of modulate MSC secretome *in vitro*, no issue on immunocompatibility and reduced concerns on tumorigenic potential of MSC (7).

The prevalence of ocular allergy is increasing rapidly worldwide, and although it does not represent sight-threatening conditions, allergic conjunctivitis may have a significant impact on quality of life, morbidity and productivity (17). Several agents are available for the treatment of allergic conjunctivitis, but patients frequently lack good control of symptoms and some are tolerating undesired side effects. Compared to older drugs, newer antihistamines, dual action agents and glucocorticoids have improved pharmacological management of ocular allergy; a single agent often acts through multiple mechanisms of action blocking various inflammatory mediators (18,19). However, currently, no drugs are available to abolish completely clinical symptoms of ocular allergy.

Allergic conjunctivitis represents a complex condition whose complete mechanism of action is not yet entirely uncovered. Culture medium from MSC, with its multiple mechanism of action, could be considered as a novel and promising therapeutic strategy for allergic conjunctivitis.

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Footnote

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

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