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Journal of Experimental Pathology Commentary

News About the Extracellular Vesicles from Mesenchymal Stem Cells: Functions, Therapy and Protection from COVID-19

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Abstract

This is a Commentary of a review about extracellular vesicles of immune cells published two years ago in Clinical and Experimental Immunology, a prestigious journal of the field. The aim is to establish whether, and to what extent, results in scientific area of the review have been extended and strengthened by innovative findings of considerable interest. The analysis of the recently published results has revealed that in various areas of the review developments have occurred. However, innovative findings have been only about the extracellular vesicles secreted by mesenchymal stem cells, usually indicated as MSC-EVs. Based on these findings, the Commentary has been focused on recent MSC-EVs findings presented in three Sections dealing with 1. recently appeared, relevant functions of the latter vesicles; 2. therapeutic processes developed according well known criteria, however innovative in many respects; and 3. protection of COVID-19 disease patients from organ lesions induced by the specific virus, SARS-CoV-2, during the disease. As everybody knows, the COVID-19 pandemic started at the end of 2019, thus after the publication of the aforementioned review. Data of Section 3 are therefore innovative, of great potential interest also at the clinical level, applied by translational medicine to various organs, from lung to brain, heart, kidney, immune and other cells. In view of its relevance, the author expects that research and medical use of MSC-EV, active at present, will be further developed, acquiring additional relevance in the near future.

The present Commentary is a critical follow-up of a previous review about "Extracellular vesicles, news about their role in immune cells: physiology, pathology and diseases", appeared in Clinical and Experimental Immunology last June 2019 [1]. During the last 5 years several reviews about the immune role of exosomes and extracellular vesicles (EVs, combinations of exosomes and ectosomes [2]) had already been published. Most such reviews, however, were specialized, reporting basic and/or applicative effects induced in specific immune cells, operative alone or in cooperation with non-immune cells, including cells of cancer and cancer microenvironment. At variance with the specialized reviews, the aforementioned review had been planned in general terms, focused on the main effects induced by immune EVs on healthy, pathological, and diseased cells. In all reported studies the observed effects of EVs were variable, dependent on their heterogeneity and on the environment where their interaction with target cells was taking place. All together, these results had been conceived as tools, useful to increase knowledge about various diseases, dealing especially with their diagnosis and with the development of innovative therapies.

The immune studies about pathology and diseases, governed by various EVs, have been intensely pursued during the last two years, i.e. after the publication of author's review [1]. The conditions most often investigated have been those already mentioned, dealing with the interaction of two immune cells [3] and the co-operation of single immune cell with non-immune cells of cancer [4,5] or cancer microenvironment [6,7]. In many such recent studies, interest was mostly due to new cell types and/or new techniques employed. However, the general framework remained similar to the previous reviews. Therefore, these studies did not appear appropriate for a Commentary.

Another issue that, in contrast, appeared appropriate to author for the Commentary is related to mesenchymal stem cells (MSC), a family of multipotent cells discovered several decades ago. MSC cells, resident in the stroma of all body tissues, are competent for self-replication and multidirectional differentiation, favorable for culturing, manipulation and attenuation of inflammatory processes. Such properties of MSC do not depend only on their direct intercellular communication. In addition to the release of soluble and bioactive factors, such as cytokines and growth factors, MSCs undergo secretion of specific EVs, referred to as MSC-EVs. Investigated from 2015, such EVs have grown progressively to a maximum in 2020. In most cases the MSC-EVs have been found to induce effects analogous, but simpler and clinically more convenient, with respect to those of their parental cells. Among their functions, MSC-EVs modulate immune responses. Recruitment in their proximity of needed cells may result in boosting immune response, associated in many cases to protective roles in infectious diseases. Examples concerning MSCs and diseases had been already included in author's previous review [8-10]. At the time, however, relevant properties, concerning MSC-EV production and function had not been established.

At this point, the introduction of the Commentary on MSC-EVs and their role in immunities, is complete. The presentation of their recent developments is organized in three Sections dealing with the innovative role of MSC-EVs, their therapeutic perspectives, and their promising role in the protection of severe lesions induced during the COVID-19 disease. In view of the recent appearance of the latter disease such a protective role of MSC-EVs was unexpected.

Innovative Role of MSC-EV

The general effects of MSC-EVs, in particular their suppression of inflammation, promotion of regeneration, and immunomodulation, remained as reported previously. However, the parallel investigation of EVs secreted by MSCs of different origin emphasized the heterogeneity of their effects. For example, EV regulation can make prominent both the innate and adaptive immune reactions; the EV-induced altered effects can appear in several immune cells, not only various lymphocytes but also natural killer cells, dendritic cells and especially macrophages; MSC-EVs can govern immune-modulatory effectors or transmit active signal molecules, thus participating in various distinct processes such as differentiation, activation, proliferation and also suppression of immune cells [11-14]. Moreover, MSC-EVs from different tissues (bone marrow, adipose tissue, and umbilical cord) exhibit different cargo proteins [15]. This difference is relevant also because proteins and microRNAs (miRNAs) of such cargos induce different therapeutic effects. In addition, they operate as biomarkers, relevant for the diagnosis and the treatment of autoimmunity–related diseases [16,17].

Innovative results have been reported about MSC-EVs of specific origin. The immune cells of adipose origin, mostly stimulated by the above vesicles, are specific macrophages that induce regulations of immunomodulatory and inflammatory-mediated responses. For these effects macrophages are considered for therapy of immune-mediated diseases [18]. Analogously, the vesicles have been shown to ameliorate the conditions of a mouse model with immune mediated aplastic anemia [19] and to mitigate trained immunity in the brain [20]. Moreover, the intranasal administration of MSC-EV meliorates the experimental autoimmune encephalomyelitis [21]. The concomitant study of two diseases, multiple sclerosis and amyotrophic lateral sclerosis, demonstrated the expression in the MSC-EVs cargo of six miRNAs, two of which were found to dampen the pro-inflammatory phenotype of microglia, with ensuing decrease of its neuroinflammation [22]. Moreover, the well-known, anti-apoptotic neutrophil effect of MSC is due to its MSC-EVs, reinforced if isolated from the Wharton's jelly. With this action the EVs appear to induce protection on neutrophil function and lifespan [23].

Therapeutic Role

An advanced therapeutic role of MSC-EVs, developed during the last few years, is based on their well-known immune-modulatory potential of vesicles processed by various treatments including their drug accumulation followed by intracellular target release. Exciting vesicles operate by their cargo components, with concomitant crossing of biological barriers and without immune rejections and lung entrapments, where anti-inflammatory and/or regenerative actions are needed. MSC-EVs, administered both locally and systemically, induce multiple effects [24,25]. Together with reduction of inflammation and fibrosis associated with diseases they suppress the detrimental immune response of inflamed tissues and promote survival and regeneration of injured parenchymal cells [26]. Moreover, the MSC-EV modulation of immune responses is able to attack diseases by activation of autophagy and/or inhibition of apoptosis, necrosis, oxidative stress and other processes [27,28]. At clinical stage, the effect of many MSC-EVs closely resembles the responses to MSC, and the number of protected diseases is considerable. In some cases, the similarity between MSC and their EVs, initially limited, becomes stronger a few days later. Moreover, since the use of MSC-EVs have appeared safe in humans, with low risk of immune- and carcinogenicity, their use for therapy in translational medicine is expected to become more

common in the near future [16,24,25,29-31].

Protection of the COVID-19 Disease

COVID-19 is a disease rapidly evolving into a pandemic, an unprecedented global health emergency, aggravated at present by the lack of effective therapies. In view of the time of its identification (in Italy the end of February 2020), presentation about the MSC-EV effects on the disease, absent from the author's review [1], is presented here as a completely innovative area of MSC-EV function. The severe lesions of the lung, the brain and other organs, induced by the COVID-19 virus SARS-CoV-2, are well known [32,33]. The presentation of possible anti-COVID-19 tools attracts therefore great interest. During the last two decades MSCs have been tested for treatment of various pathologic conditions, including acute and chronic lung diseases. The MSC-EV protective results against COVID-19, obtained recently, are solid as documented by several clinical trials, recently initiated or planned in several Countries [34,35].

The severity of COVID-19 seems to be mostly dependent on the patient responses. Over-activation of the immune system, developed by the system of the patients in the attempt to kill the SARS-CoV-2 virus, can cause a "cytokine storm" which in turn can induce an acute respiratory distress syndrome (ARDS), a well as multi-organ damage ultimately leading to death. It is known that, in COVID-19 patients, the immunomodulatory properties of MSCs ameliorate the cytokine-storm by providing a treatment through inhibiting or modulating the pathological events, especially those of severe cases [36,37]. Protection by MSCs is due to the release of their EVs, working through immunomodulatory effects, striking the COVID-19 balance in the immune cells of patients, with added advantages of increased safety and tissue penetration [38-39]. Interestingly, the MSC-EVs of mice were found stronger in their protection against ARDS if released from original cells pre-stimulated to release neurotrophic and immunomodulatory factors [40]. The result obtained by MSC-EVs could regulate, in infected patients the inflammatory responses, promoting tissue-repair and regeneration of damaged organs [34,37-39]. Moreover, the MSC-EVs, active by molecules of their cargo, could also operate against weak antiviral antibodies, which contribute to dysfunctional responses [31].

Ongoing studies have been focused on the mechanisms by which MSC-EV, as a therapeutic option, induces alleviations of inflammatory responses and thus promote the restoring of injured tissues. Among the molecules of the vesicle cargos are miRNAs known to exacerbate cytokines and chemokines with stimulate cell death and coagulation cascade genes. Some miRNAs were found to modulate above processes, and thus to prevent tissue damage. Therefore, the heterogeneous cargo molecules of MSC-EVs are relevant for the survival of CAVID-19 patients [41]. In other studies, SARS-CoV-2 was shown affected by MSC-EVs in the brain hippocampus. Such EVs have a cell-free action by which viruses are degraded apparently by an adaptive antiviral function, possibly active against the genes of various factors. The antiviral immunity of brain MSC-EVs appears promising to fight not only SARS-CoV-2, but also other viruses [42].

Conclusion

The present Commentary has demonstrated, on the one hand, that the review on EVs of immune cells that the author published in 2019 [1] covered ample biomedical issues, at the time highly interesting, which has been further developed in the two subsequent years; on the other hand, innovative findings in the same field, focused however on MSC-EVs, i.e. vesicles from a specific family of original cells, have been developed very intensely, reaching highest levels during the last two years. The areas of the latter research have been particularly interesting, emphasizing 1. the innovative role covered by MSC-EVs, different in many respects from those of other EVs, and 2. the therapeutic perspectives which, based on criteria and mechanisms typical of exosomes, offer various, much more innovative aspects, characterized by significant potentials. In the author's presentation, however, the highest perspectives deal with an aspect, totally unexpected during the last two years, concerning the possible role of specific MSC-EVs to participate in the defense of COVID-19 patients from the severe lesions induced by the SARS-CoV-2 virus. Such lesions are present in many organs, beginning with the lung and then with the brain, kidney and others. The extraordinary effects induced by MSC-EVs suggest, on the one hand, an impact much greater than those recently reported by other types of EVs; on the other hand, the possibility that MSC-EV protection is effective also after its direct administration in the tissues, starting with the brain, active not only against SARS-CoV-2 but also against other viruses.

A final aspect of the author's presentation, until now left out from this Commentary, deals with the clinical aspects of MSC-EVs action, concerning in particular translational medicine. The MSC-EV therapy is produced by small structures, different from whole cells [42]. Vesicles modulate immune responses as effectively as MSCs themselves, however with various advantages, including increased safety and faster tissue penetration. Knowledge about the numerous proteins involved in the complex interplay of MSC-EVs with immune cells, and about their function, promoted a good understanding of their functions [25,43]. MSC-EVs participate in intercellular communication events. In addition to the diseases, they

contribute to the healing of injured tissues and organs. Therefore, they can be manipulated and applied to establish novel cell-free therapeutic approaches for treatment of a variety of pathological conditions, distinct from those induced by viruses mentioned previously. In comparison with their donor cells, MSC-EVs offer more stable events, with diminished safety risks of microvasculature occlusion [44,45]. The author conclude that MSC-EVs possesses most of the functional and therapeutic activities recognized to their original cells during the decades of their employment. In view of their relevance during the intense research, the author expect these activities to be further developed in the near future.

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