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Opinion

CROSSTALK to Fight against Inflammation and Fibrosis: New Biological Medical Drugs Design for a New Age

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Opinion

Inflammation is the response of an organism's immune system to damage caused to its cells and vascularized tissues by any type of aggression, which may be of a biological, chemical, or physical nature. This inflammatory response must be self-limiting in time and intensity, since, if this is not the case and there is not perfect coordination between the innate and adaptive immune systems, at the very least a fibrotic process will be generated that will lead to a percentage loss of function in the affected tissue or tissues, and, in severe cases, could lead to a severe systemic inflammatory syndrome with positive feed-back systems, leading to a cytokine storm, which in turn could lead to multi-organ failure [1,2]. In the establishment, maintenance and termination of such a cytokine storm at the molecular level, soluble cytokine-like mediators (especially IL-1, IL-6, IL-18, etc...), growth factors (TNF-α, etc...), chemokines (MCP-1, MIP-1, etc...), molecules related to the cytokines (MCP-1, MIP-1, etc...) and cytokine-related molecules (MCP-1, MIP-1, etc...) are essential for the establishment, maintenance and termination of such a cytokine storm.), molecules related to the purinergic system (ATP, ADP), which will act on receptors such as Toll-like Receptors (TLRs), NOD-like Receptors (NLRs), RIG-type Helicase Receptors (RLRs) and purinergic receptors (P2X7).

Biopharmaceuticals [3], as their name suggests, are manufactured from biological sources, and can be formulated synthetically, semi-synthetically or even completely naturally. The definition of biological medicines encompasses a very heterogeneous range of medicines, such as whole or partial blood components, cell therapies, tissues, proteins, vaccines, and gene therapies.

Within this group, so-called biologics are becoming increasingly prominent, as they have clear competitive advantages over advanced cell therapy medicines or gene therapy medicines. With respect to advanced cell therapy drugs, biologics are cell-free and have several advantages that allow them to have fewer risks, fewer limitations, and greater efficacy than treatments based on the direct use of cells. For example, biological drugs are not influenced by aspects such as the age or sex of the donor, which is the case with advanced cell therapy drugs [4-8], and biological drugs also carry less risk when injected than drugs that contain cells in their formulation [9], This, together with aspects related to their manufacture and commercialization, such as wide scalability, storage capacity, fractionation, concentration, and the possibility of combining materials from different donors in their manufacture, make them much more interesting [10,11]. Finally, another aspect to highlight as an advantage of the new biologic drugs over advanced cell therapy is that the manufacturing method of these new biologic drugs can direct the response towards a specific cell type or tissue, achieving a tissue selectivity that is difficult to obtain in cell therapy. We must not forget that stem cells are organized in the organism in specific niches characteristic of each type of tissue and are clearly influenced by the cellular and extracellular microenvironment, so that all the secretome they produce, both

in soluble form (cytokines, etc.) and encapsulated in exosomes (miRNA, etc.), is tissue selective [12,13].

Among biological drugs, the most developed in recent years are monoclonal antibodies, specialized glycoproteins that are part of the immune system, produced by B-lymphocytes, with the ability to recognize specific molecules (antigens). Monoclonal antibodies have become essential clinical and biotechnological tools and have proven useful in the diagnosis and treatment of infectious, immunological and neoplastic diseases, but although these recombinant monoclonal antibodies are currently manufactured using phage library technology with genes encoding variable regions of immunoglobulins, These antibodies are not free from problems related mainly to immunogenicity reactions, which ultimately lead to variability in their efficacy, rendering them ineffective in a significant percentage of the patients to whom they are applied [14,15]. However, these losses in efficacy are not only due to the existence of immunogenicity reactions, including the generation of anti-drug antibodies, but also to the special mode of action that derives from their name, since monoclonal antibodies act against a single, specific target.

It is very difficult to explain the existence of a cytokine storm by the activation of a single receptor. If this were the case, treatment of the cytokine storm by a single monoclonal antibody, e.g., a monoclonal antibody against IL-1β or IL-6, would always be effective, and we know that this is almost never the case, as the SARS-COV-2 pandemic has recently demonstrated. Moreover, even if only one of the receptors is activated in the first instance, the simple start-up of its metabolic cascade will provoke the appearance of DAMPS (Self Damaging Molecular Patterns) that will stimulate other receptors. If we add to this the fact that in most cytokine storms, we do not see a single causative agent, but rather a group of them, we can understand that there is almost always a joint activation of several of these receptors, producing phenomena of agonism, synergy and antagonism between them [16]. Finally, if all this inflammatory tsunami is not controlled in time, the dreaded fibrosis with the consequent loss of function of the affected tissue, and even, in severe cases, autoimmune reactions, will appear as a minimum.

But in the cytokine storm we must also consider the involvement of the purinergic system [17-19]. Extracellular ATP or its enzymatic degradation products, such as ADP, AMP, and adenosine, can stimulate several membrane receptors [20]. Stimulation of the P2X7 receptor by ATP leads to activation of the NLRP3 inflammasome, and consequently of caspase 1, stimulating exaggerated secretion of IL-1β and IL-18 [21].

Based on the above, it is logical to think that to produce a global anti-inflammatory immunomodulatory effect that acts synergistically at all levels, avoiding feedback pathways that prolong inflammation over time with all its negative consequences, complex biological drugs are needed that act at multiple levels, in a synergistic and coordinated manner, avoiding the negative consequences of blocking, or stimulating a single pathway. For all these reasons, our research group at the R4T molecular and cellular biology research laboratory of the Hospital Universitario de Fuenlabrada, unlike the treatments tested to date to control cytokine storms based on the use of monoclonal antibodies used alone or in combination, proposes a biological therapy based on the use of allogeneic conditioned medium derived from M2-type macrophages and enriched with MSCs as a treatment.

Mesenchymal stem cells, placed in coculture with macrophages, not only respond to macrophages and adjust their secretome accordingly, but also macrophages respond to encounters with these cells, creating a feedback loop that contributes to immune regulation [22]. Our technological platform for the manufacture of complex biological drugs based on the establishment of an indirect cellular crosstalk allows us to generate various conditioned media, where all the growth factors, cytokines, chemokines, exosomes, miRNA, etc., that are naturally produced by these cells are present, respecting their composition and natural pleiotropic relationships, with an immunomodulatory cytokine profile that confers a powerful anti-inflammatory and antifibrotic action, in a totally tissue-selective manner.

For all these reasons, we are firmly convinced of the advantages of using complete conditioned media, manufactured through technological platforms that allow intercellular crosstalk between two or more specific cell types, as opposed to one of their purified components, given that their efficacy lies in the synergistic mechanism between their different components [23], the result of subjecting cell populations to a culture that, in vitro, attempts to emulate the anti-inflammatory, anti-fibrotic and regenerative immunomodulatory microenvironment that should occur under ideal in vivo conditions in diseased tissue.

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