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Letter to the editor

Nuts and bolts of Exosomes in Aesthetic Medicine

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Abstract. Over the past decade, the body of knowledge about the behavior and properties of exosomes has grown exponentially, resulting in an overwhelming number of published scientific articles. Exosomes are constitutively synthesized and released by many human cells, plants, animal cells, and even bacteria. Exosomes can be derived from the patient's tissues (autologous exosomes), from other human tissues (allogenic exosomes), and plants, animals, or bacteria (xenogenic exosomes). Exosomes offer innovative treatment options in medical aesthetics, such as repairing, regenerating, and rejuvenating skin tissue, preventing and reducing scarring, regulating pigmentation, promoting hair growth, and increasing the survival of fat grafts in aesthetic treatments. However, the significant cost of production is a clear indication of the industry's first steps in its development. Furthermore, performing these therapies in a private medical office is expensive, and the technical requirements need an in-depth analysis. The key points identified as corrupting, misleading, or confusing concepts (source, cargo, process of origin, and quantity) should be clarified. For all the above, more clinical trials need to be conducted for regulatory approval because, to our knowledge, no exosome-based products or therapies have been approved by any regulatory agency. Nonetheless, exosome treatments undoubtedly represent a breakthrough for aesthetic regenerative medicine.

Key words: exosomes, transport vesicles, cosmeceuticals, regenerative medicine, wound healing, skin rejuvenation

Introduction

Exosomes are cell-derived nanovesicles that transport proteins, all sorts of nucleic acids and lipids, and play a significant role in almost every physiological process that takes place in the human body. Cells and platelets release exosomes constitutively, and their function, based on what is known so far, is to communicate with neighboring or distant cells[1] facilitating a coordinated tissular response to virtually any stimulus. Exosomes possess unique physicochemical properties, such as a low degree of antigenicity and a great capability to cross tissue barriers or escape from mononuclear phagocytic cell systems[2].

In the last decade, evidence on exosome behavior and characteristics grew exponentially and led to an overwhelming number of published scientific articles. Similarly, to what happened with cell therapies, exosomes were initially regarded as just another promising tool within the regenerative medicine armamentarium. However, because of their easier manipulation requirements and a better safety profile when compared to cells, they are now skyrocketing the medical community's interest. Exosome therapies have added advantages that cannot be overlooked, such as: i) high long-term stability, ii) high targeting capacity that will surely be able to improve drug efficacy and delivery, and iii) cargo capabilities, among others. Today, they can be procured from bone marrow, placenta, adipose tissue, blood, umbilical cord, and they have been found in every tissue and body fluid. Exosomes offer innovative treatment options for repairing, regenerating, and rejuvenating skin tissues, preventing and reducing scarring, regulating pigmentation, promoting

hair growth, and increasing fat graft survival in aesthetic treatments[1,2].

Some clinical trials (CTs) have probed the efficacy of exosomes in all sorts of strategies and diseases: COVID-19[3], colorectal cancer[4], antitumor immunity[5], chronic kidney diseases[6], or wound healing[7]. There are few CTs on aesthetic medicine, and many of them are still recruiting (i.e. NCT05658094, NCT02565264, NCT05969717), unknown status (i.e. NCT02565264, NCT02737267), or have been completed without published results (i.e. NCT05523011, NCT05475418, NCT03459703).

Regenerative medical procedures are usually manual-based and require highly skilled operators[8], determining very limited yield and high production costs. Since biological materials must be procured from and readministered to a human being, medical facilities and specialized personnel requirements are drawn major attention. The significant initial expenses of implementing any of these therapies in a private medical consultation had to be evaluated thoroughly. Understandably, the overall costs of shifting from conventional to regenerative therapies resulted in a delayed implementation of aesthetic regenerative treatments. Finally, the lack of a thorough understanding of the action mechanism and the absence of legal regulations constituted two more barriers that restricted the implementation of aesthetic regenerative therapies and stood between the patient's interest and physician's treatment eligibility.

Additional considerations must be taken into account when facing the utilization of exosomes in aesthetic regenerative medicine, since processing procedures and techniques (grafting, isolation, purification, optimization, administration) are not fully agreed upon. The standardization of future procedures and clinical guidelines should overcome this otherwise huge obstacle for proper clinical implementation. The development of standardized quality control procedures and a more comprehensive understanding of the molecular communication between exosomes and their target cells would be beneficial[9]. To date, numerous researchers and health centers have already developed their own manufacturing processes. However, the effective transference of these achievements to the clinical field remains elusive. Further clinical trials are required for regulatory clearance since no exosome-based products or therapies are, to our knowledge, currently approved by any regulatory agency[10]. The need for precise guidelines, recommendations, and regulations for their use in the aesthetic field is urgent. The aim of this manuscript is to deal with the so far identified and pinpointed issues that currently pervert the medical communication and impair the commercialization and proper usage of exosome-based products in the European aesthetic medicine market. We do not intend to compare commercial products, but aim to assess the problems that determine whether they are truly or legally accepted as such.

Exosomes in the aesthetic medical field

Undoubtedly, exosome treatments represent a breakthrough for aesthetic regenerative medicine. However, the line between reality and science fiction has been blurred, and some things should be clarified without further delay. Four major key points have been identified as corrupting, misleading, or confusion-spreading concepts: a) source, b) cargo, c) process of origin, and d) quantity.

a) Source

As previously mentioned, exosomes are constitutively synthesized and released by all sorts of cells, and even by sub-cellular structures, such as platelets[11]. This occurs in every living organism and on a regular basis. Exosomes can be grafted from the patient´s own tissues or from other human tissues. The first are autologous exosomes, the latter, allogenic. Exosomes can also be obtained from plants or animal cells, and even from bacteria. All these can be considered xenogeneic exosomes. Technically, lexical inconsistencies and some minor terminological discrepancies can be found in the literature, but, for the sake of clarity, we will categorize exosomes as they were described.

Legislation voids are currently being exploited by commercial companies that are making a profit from the eagerness in the market towards exosome products[12]. However, having less regulations than desired does not mean a total lack of them[13–15]. In Spain and

great part of Europe, to the current knowledge of the author, there is not a single certified injectable exosome product. Allogenic exosome high-end products are dealing with regulatory entities, trying to certify their isolation and concentration procedures. Their alleged little antigenicity will require a paradigm shift and consume time and efforts to produce a great amount of high-quality evidence. Allogenic injectable exosomes will become a reality and the gold standard in the future. In the present moment, however, they are left only for top research players and their clinical implementation in standard medical consultations is not legal and stands closer to science fiction than reality.

On the other hand, autologous exosomes are currently the only possible injectable option, which is quite a meaningful observation. Some commercial efforts have developed new techniques to improve orthobiologic materials and were able to achieve secretomes with higher regenerative power that contain huge amounts of autologous exosomes. They are subjected to the same regulations as any other autologous treatment, such as PRP. This is the case of Photothermal Biomodulation (Meta Cell Technology, Spain) or artisanal filtration-ultracentrifugation.

Finally, there are cosmetic exosome-based products. The European legislation currently forbids human-origin molecules in cosmetic products, thus leaving the door open solely for non-human exosome cosmetic-based products. Of course, INCI and public health report requirements must be met, but it is fair to say that some allogenic non-human exosome-based cosmetic products are currently being commercialized (e.g.: Xoglo™, Purasomes™, Exo-Skin™)[16].

b) Cargo

Another issue that should be a concern for the medical community is the rationale behind exosome-based treatment indications. That is to say: does the indication make any sense? Exosomes are nanovesicles with a membrane and a cargo. The bi-lipidic layer membrane expresses tetraspanins and many other surface proteins. The cargo varies among each exosome, but in general, they can be loaded with proteins, nucleic acids, and all sorts of molecules, such as: RAB, ANNEXINS, mRNAs, CD63/81/9, HSP 60/70/90, miRNAs, lncRNAs, ESCRT, SNARE, DNA, or OPNs, among many others.

Exosomes may differ in functionality, being involved in diagnostic and/or therapeutic procedures. The detection of any surface protein can lead to the identification of certain exosomes, which in turn could account for a certain physio-pathological status. This is closely related to the exosome´s wonderful diagnostic possibilities. On the other hand, the therapeutic capabilities of exosomes will be almost solely related to their content. Exosomes can exert an epigenetic action, determining, for example, major down regulations of specific protein synthesis on target cells, among other actions[17].

Cosmetic exosome-based products can have a physical as well a chemical action, but always limited to certain superficial layers of the skin. On the contrary, the effects of any injected product should be more ambitious, targeting broader regions, deeper tissues, or even a systemic action. Regardless of their cosmetic benefits, an unavoidable question stands out. Besides the regulation that explicitly forbids the injection of cosmetic products, and leaving aside the temerity of attempting a parenteral administration of something that was not meant to be injected: what would the epigenetic benefits that patients would obtain from an animal, vegetal or bacterial exosome be? Avoiding the answer to this question shows a lack of understanding the way exosomes act and their aim or physiological reason-to-be.

c) Process of origin

Naïve exosomes are naturally synthesized by our own bodies[17], as opposed to bioengineered exosomes that are the result of laboratory manipulations. The stimulation and favoring of naïve exosomes' release and collection is gaining adepts worldwide for its resembling innocuity, while being able to deliver higher regenerative power. Therapies like photothermal biostimulation help release exosomes from PRP platelets and play a major role in freeing the tethered ones.

For now, naïve exosomes allow physicians to comply with regulations, since they do not require standardized isolation and processing methods. These are extemporaneous products that remain under the same

regulation of the ortho-biologics that gave origin to exosomes (eg.: PRP, SVF). On the other hand, bioengineered exosomes must be very clear on the yield and purity, which will vary depending on the method used. The isolation and purification of exosomes at a large scale is not a great problem for naïve exosomes but can be one of the most important obstacles for bioengineered exosomes[18,19]. The same applies to storage.

d) Quantity

In aesthetic medicine, every time something attracts rocket-high-level interest, we witness a commercial race. It has happened before many times, and it is happening right now with exosomes. The most relevant echoes of this race are found in the quantity of exosomes per vials being advertised: 1 billion, 10 billion, 50 billion… infinity. As goes, the questions that physicians avoid asking are always the ones underlying the importance of the number of exosomes per vial.

First, what do you want to achieve with this treatment? Unless the answer to this question is related to the skin benefits of a cosmeceutical product, the number of exosomes in the vial is irrelevant and does not make any sense because they cannot be injected. Second, what are the active ingredients of the product? Unless the answer to this question is related to animal, vegetal or bacterial components, the number of exosomes in the vial is irrelevant and does not make any sense because cosmeceuticals with human derivates cannot be commercialized. Lastly, where do you get this product from? Unless the answer to this question is related to certified medical devices or legally commercialized cosmetics, the number of exosomes in the vial is irrelevant and does not make any sense because manual preparations cannot currently be commercialized.

Conclusions

Exosomes have an incredible potential for aesthetic medicine and general health issues. The future seems bright when we consider the endless possibilities of a bioengineered low antigenic target-electable therapy. But this is the future. Currently, aesthetic physicians can benefit from this therapy in very limited ways: i) allogenic exosomes from approved non-human cosmeceuticals, and ii) naïve autologous exosomes derived from processes that improve PRP-like products, such as photothermal biomodulation.

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