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SHORT COMMUNICATION

Regenerative assisted microsurgery (RAM) and regenerative assisted supermicrosurgery (RASM): the future of microsurgery?

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My very last professional trip before COVID SARS 2019 pandemic in mid February 2020 has been to Taiwan at the Reconstructive Microsurgery Center – Chang Gung Memorial Hospital, kingdom of Legendary Professor Fu-Chan Wei the undisputed father of modern microsurgery [1]. At that time, nothing suggested that our professional lives were close to radically change, deeply impacted by the first of too many lockdowns due to the pandemic spreading, as described by Mayer and Persichetti [2].

In that occasion, I had the unique and undeserved honor to share, as Visiting Professor, the results of our researches in advanced regenerative surgery applied to the most challenging clinical situations. During that stay, where I have learned way more than what I have been able to share, I realized, if there was still the need to, how synergistic the use of regenerative surgery applied to the field of microsurgery could be.

Flying back home, ideas and projects started to swirl in my mind and deeply digging through all possible scientific rationales and reviewing many evidence-based data I built up the certitude that one of the most promising and exciting applications of regenerative techniques is certainly microsurgery and supermicrosurgery. In recent years, we have witnessed an incredible proliferation of increasingly advanced and complex microsurgical technologies that allow the most complex problems to be treated safely and reliably.

What only 10 years ago seemed to be unattainable goals have now become consolidated realities, and a new specialty, supermicrosurgery, allows today, in the most expert hands, to plan and manage the most challenging reconstructive strategies for vascularized tissue transplantation and reconstruction of lymphatic flow. The expert supermicrosurgeon can now routinely treat lymphedema, which too often is a consequence of cancer treatment, by connecting extremely fine lymph vessels between 300 and 900 microns using 14/0 sutures with 0.3-mm needles [3–6]. However, it is my modest opinion that we are rapidly approaching the physical limits of human dexterity and skill and that probably other strategies will soon have to be considered in order to further extend the horizons of this exciting specialty. The use, for example, of nanotechnologies applied to micro-robotics assistance designed to aid in stabilizing movements of the microsurgeon by filtering tremors and scaling down motions probably help overcome these human limitations, thereby enabling a breakthrough in supermicrosurgery able to further push its limits [7]. However, beyond these potential and future technical evolutions, I am firmly convinced that the use of advanced and targeted regenerative strategies can be of great benefit to improve and standardize the outcomes of this type of surgery.

As a matter of fact at the same time of the extraordinary advances made in the field of microsurgery in recent years, regenerative medicine and surgery merged with exciting discoveries allowing to tackle in a safe and efficient way even the most complex clinical situation thanks to an exponential effort of scientists and researchers. The possibility to control and limit the host inflammatory and immune response through cytokine modulation, to support cell intake and differentiation, and to stimulate a strong action of neo vasculogenesis, angiogenesis, and lymphangiogenesis are a today reality.

As well known, lymphangiogenesis plays an important physiological role in homeostasis, metabolism, and

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immunity. Several pro-lymphangiogenesis inducers, such as VEGF-C, hyaluronic acid, and ephrin-B2, has been identified and described, and various mechanisms that can be induced and enhanced through advanced regenerative strategies have been proposed to explain VEGF-C patterning during lymphangiogenesis [8, 9].

All the abovementioned features can be extremely important and synergic if implementing delicate and complex surgical procedures such as in microsurgery. During the immediate post-operative period, they allow to control the inflammatory response, support and enhance metabolic exchanges, and increase oxygen supply at the level of the anatomical structures dependent on the blood flow supplied by the microsurgical anastomosis and to reduce venous and lymphatic stasis.

Another fundamental aspect related to the use of specific regenerative components is constituted by the possibility of controlling and limiting the inflammatory response resulting from the surgical trauma and the related physio-chemical metabolic stress of the surrounding tissue through a strong modulation of cytokines activity, in particular of IL 6 and IL 6A [10, 11]. Furthermore, allotransplantation procedures could strongly benefit from regenerative stimulus to regulate immune response and optimizing long-term postoperative results [12, 13].

Particularly enriched and tailor-made regenerative protocols called Bio Active Composite Grafts (BACG) have been recently developed to improve cell intake, differentiation, and proliferation inducing the host recipient site to act as real bioreactor, still remaining within the limits of the present legal frame for cells therapies [14].

BACG are composed by several bio components, such as freshly mechanically isolated adipose-derived stromal vascular fraction (SVF) containing a rich pool of nucleated cells (up to 20×10^6/ml) including a significant quantity of mesenchymal stem cell (MSC) precursors (up to $600–700 \times 10^3$ cells/ml); especially enriched blood derivate such as platelet-rich fibrin (PRF) containing slow releasing growth factor (GF) and cytokines; and bio catalyzers such as amino acids (AA), vitamins, morphogenic proteins. In fact, regenerative mixtures showed a consistent increased synergic regenerative capability if compared to the use of any other single or individual component [15].

This very promising strategy can be used in the field of microsurgery in three different phases:

1) Before the surgery: to prepare and condition the donor bed in all those cases of elective and programmed microsurgical interventions. This step should to be carried out between four and six weeks before surgery.
2) Intraoperatively: the use of BACG contributes to reduce and modulate the immediate inflammatory response linked to the activation of the cytokine pools through slow releasing of specific GF meanwhile ensuring a “healing activity” sustained by pericytes [16].
3) In the post-operative period between the 2nd and the 10th week: to support the cellular recruitment toward specific cellular lines, support cell intake, and stimulate the angiogenesis and lymphangiogenesis processes.

The preliminary evaluation of the results obtained following the grafting of dedicated BACG during the final phase of the microsurgical procedure, mostly at the level of the boundaries between flaps and the recipient areas, clearly stands for a better control of the inflammatory response and an increased neo-angiogenesis activity supporting the intake and the integration of the flap itself [17, 18].

It is now mandatory to confirm the solid rationale behind this intuition providing additional data and further elucidate the therapeutic value of using regenerative strategies to consolidate outcomes and results. A synergistic and coordinated cooperation between experts in microsurgery and regenerative strategies will be fundamental to establish precise therapeutic protocols, both for the composition of the regenerative grafts and for the modalities and timing in which these will be used in the context of all types of micro-surgical and super micro-surgical procedures.

Guidelines should be established to identify ideal typology and proportion of the different regenerative components adapted to the different clinical and anatomical situations, depending on whether the need to stimulate the processes of angiogenesis or to modulate the inflammatory response is prevalent.

It will also be very important to select precise methods for evaluating results of these new therapeutic strategies in the different phases of treatment using the most reliable technologies. Many techniques for flap monitoring following free tissue transfer have been described, and certainly new ones will arrive soon. Clinical monitoring, thermo scanner, microdialysis, implantable Doppler probe, surface markers, and, whenever possible, histological and cytological exams of the grafted areas are some of the available options [19].

The scientific rationale supporting all the above considerations is solid and sufficient to justify foreseeing the possibility of structuring in a short time an International Multi Center Task Force in very close collaboration with the World Leaders of microsurgery and Regenerative technologies.

This will be the ideal option that could pave the way for a standardization of targeted protocols to support reliable and safe synergistic methodologies in a new specialized sector identifiable with the terms Regenerative Assisted Microsurgery (RAM) and Regenerative Assisted Super Microsurgery (RASM).

Declarations

Ethical statement No ethical approval nor informed consent is needed for this article.

Conflict of interest Michele L. Zocchi declares no conflict of interest.

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