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Correspondence

Reply to J. Magalon et al.

Nicoletta Del Papa,* Gabriele Di Luca,† Domenico Sambataro,* Eleonora Zaccara,* Wanda Maglione,* Armando Gabrielli,‡ Paolo Fraticelli,‡ Gianluca Moroncini,‡ Lorenzo Beretta,§ Alessandro Santaniello,§ Gianluca Sambataro,¶ Roberto Ferraresi,# and Claudio Vitali**

*U.O.C. Day Hospital Reumatologia, Ospedale G. Pini, Milano, Italy
†U.O.S. Chirurgia Vascolare, Ospedale G. Pini, Milano, Italy
‡U.O. Clinica Medica, Dipartimento di Medicina Interna, Ospedali Riuniti, Ancona, Italy
§Centro di Riferimento per le Malattie Autoimmuni Sistemiche, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milano, Italy
¶Dipartimento Medicina Interna e Reumatologia, Campus Biomedico, Roma, Italy
#Laboratorio Emodinamica Periferica Interventistica, Humanitas Gavazzeni, Bergamo, Italy
**Servizio di Reumatologia, Istituto San Giuseppe, Anzano del Parco, Como, Italy

Dear Editor,

We read with great interest the Letter to the Editor by Magalon et al. (this issue), commenting on our previously published article, "Regional implantation of autologous adipose tissue-derived cells induces a prompt healing of long-lasting indolent digital ulcers in patients with systemic sclerosis" (3).

In their letter, a number of interesting questions are raised. First of all, Magalon et al. wonder why we did not use the terminology proposed by the International Federation of Adipose Therapeutics and Science (IFATS) and the International Society of Cellular Therapy (ISCT) to define two phenotypically well-characterized populations of cells, that is, the heterogeneous group of cells composing the stromal vascular fraction (SVF) and the adipose-derived stromal/stem cells (ASCs) (5).

The rationale for using a partially different terminology is very simple. As detailed in the article, we applied the Coleman fat grafting technique (1), without any digestion of fat tissue or phenotypic characterization of its different cellular components.

In a previous study, we demonstrated that autologous fat tissue grafting in the sclerotic lip of patients with systemic sclerosis (SSc) was capable of inducing an increased elasticity of perioral skin with an improved mouth opening (2). We also clearly showed that this procedure was able to induce a local neoangiogenesis. Starting from this experience, we decided to perform a second open therapeutic trial aimed at investigating whether regional autologous fat grafting could also favor the healing of longstanding indolent digital ulcers, a real problem, clinically important and often intractable, in patients with SSc.

The statistically significant effectiveness and the absolute safety of this procedure is extensively reported and discussed in our article (3). So we purposely used a different terminology to point out that we locally transplanted all of the fat cellular components, inclusive of ACSs and SVF, as well as mature adipocytes. The different terminology did not create misinterpretation of our results, as demonstrated by the very pertinent comments in the letter by Magalon et al.

Which cellular or soluble components of adipose tissue are responsible for ulcer healing in SSc is a very intriguing question. Granel et al. recently demonstrated that local injection of separated SVF in the fingers of patients with SSc was a safe procedure and induced a significant improvement of hand disability and pain, Raynaud phenomenon, finger edema, and quality of life (4). A reduction of the ulcer number was also noticed, though not included among the primary and secondary study end points. That is why the details of this marginal finding were not mentioned in the main paper but reported only in the appendix (4).

In contrast with the results of our article, Granel et al. did not observe any variation of the number of capillaries

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Address correspondence to Nicoletta Del Papa, U.O.C Day Hospital Reumatologia, Ospedale G. Pini, Via Pini, 9–20122, Milano, Italy.
Tel: +39-0258296663; Fax: +39-0258296495; E-mail: delpapa@gpini.it

in the nailfold videocapillaroscopy at any follow-up time after the SVF grafting procedure (4).

Consequently, we can argue that Granel et al.'s and our studies are not comparable at all, since different therapeutic procedures were adopted to reach completely different end points.

In conclusion, the present state of the art does not allow for an answer to the key question raised by Magalon et al. as to which component(s) of fat tissue may more consistently favor digital ulcer healing in our patients and whether mature adipocytes may play a role in the complex intercellular, autocrine, and paracrine mechanisms that act as inducers of the observed regenerative and angiogenetic effects.

We totally agree with the final comment by Magalon et al., pointing out that controlled and comparative studies are certainly needed to confirm the promising results obtained by both autologous fat grafting and SVF injection procedures in open studies. We are also convinced that more advanced technologies, adopted in future studies, may greatly contribute to a better understanding of the mechanisms underlying the effectiveness of these cell-based therapies.

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