Anti-inflammatory and Matrix Restorative Mechanisms of Platelet-Rich Plasma in Osteoarthritis: Response to Andia and Maffulli

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Am J Sports Med 2014 42: NP32
DOI: 10.1177/0363546514537996

Anti-inflammatory and Matrix Restorative Mechanisms of Platelet-Rich Plasma in Osteoarthritis: Letter to the Editor

DOI: 10.1177/0363546514536690

Dear Editor:

We read with great interest the article entitled "The Anti-inflammatory and Matrix Restorative Mechanisms of Platelet-Rich Plasma in Osteoarthritis," by Sundman et al.[3] As suggested by the title, we expected that the article would have clarified some mechanism underlying the action of platelet-rich plasma (PRP) on the articular joint. It has been a struggle in PRP research to identify the main mechanisms involved in anti-inflammatory and antinociceptive mechanisms, but unfortunately these were not unveiled in this article.

The article by Sundman et al[3] is a descriptive study, in a co-culture model of synoviocytes and chondrocytes, comparing the secretion of selected proteins (tumor necrosis factor–α [TNF-α], interleukin-6 [IL-6], and IL-1β) after 4-day incubation of cells with media containing leukocyte-reduced PRP or hyaluronan (HA) (media supplemented with 62.5% of PRP or 62.5% HA, 20 mg/mL). Other interesting aspects such as differences in gene expression of selected molecules in both synoviocytes (hyaluronan synthase–2 [*HAS-2*], matrix metalloproteinase–1 [*MMP-1*], *MMP-13*, and *TNF-α*) and chondrocytes (collagen type I α1 [*COL1A1*], *COL2A1*, aggrecan [*ACAN*], and *MMP-13*) were also explored.

We would like to remark on 2 issues that warrant consideration.

First, the authors base the clinical relevance of their results on reduced TNF-α secretion and infer the antinociceptive properties of PRP. The discussion of the results obtained overlooks the role of the immune system in these conditions. In fact, the effect of PRP or HA on synoviocytes or chondrocytes, concerning TNF-α, IL-6, or Il-1β changes, may be negligible if the immune contribution (ie, macrophages) is considered. Although PRP plays an important role in osteoarthritic inflammation, as recently reviewed,[2] PRP is not unequivocally anti-inflammatory, and at least 3 plasma proteins (α-2-macroglobulin, α-1-microglobulin, and vitamin D–binding protein [also known as group-specific component globulin]) activate macrophages via the innate immune toll-like receptor (TLR) TLR4 and induce the expression of TNF-α, IL-1β, IL-6, and vascular endothelial growth factor (VEGF). Therefore, in vitro studies on this topic cannot be readily extrapolated to the human in vivo situation, given the well-described and somewhat unpredictable interactions between different systems that cannot be reproduced in vitro.[2,3] Indeed, in complex degenerate systems such as the joint organ, there are several ways to transmit the same message (eg, pain). Thus, given these considerations, we respectfully suggest that that the clinical relevance of this carefully conducted experimental work has been overemphasized.

Second, the PRP used in the present study comes from healthy donors. The authors did not consider this in their discussion. This issue may prompt them to refine their conclusions and may encourage research toward the use of allogeneic healthy PRP.

Research in PRP is challenging not only because of its intrinsic molecular complexity but also because of protein functional redundancy. The transmission of inter- and intracellular signals, either in parallel or in converging pathways,[2,3] renders research challenging and begs the necessity of using system biology approaches to identify the main players in specific mechanisms.

We would like to congratulate the authors for opening the door to research in HA+PRP combination therapies, which seems promising for early management of knee osteoarthritis.

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The authors declared that they have no conflicts of interest in the authorship and publication of this contribution.

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Dear Drs Andia and Maffulli:

Thank you for your insightful comments regarding our manuscript. In vitro modeling of the clinical situation is

indeed very difficult. In the culture system utilized in our study, we optimized the system to include naturally diseased osteoarthritic tissues, including articular cartilage and synovial membrane, to mirror the arthritic environment within the knee joint. As you point out in your review article,[1] there are many effects of platelet-rich plasma (PRP) that might account for its mechanism of action in addition to those that we measured in the present study, emphasizing the need for further basic science investigations into PRP alone or as a combination therapy. In a subsequent clinical study, we compared PRP to hyaluronic acid with 5 synovial fluid aspirates used to analyze several anabolic and catabolic cytokines. This study, when completed, should provide evidence for mechanisms of action of PRP in osteoarthritic joints.

By virtue of the timing of tissue retrieval for this study, allogeneic PRP from healthy individuals was used out of necessity as reported in the materials and methods. Allogeneic PRP was not the focus of this study, nor were the implications of its use discussed. The clinical use of allogeneic PRP is obviously fraught with processing and regulatory issues beyond the scope of our study, and the authors are not currently advocating its clinical use analogous to its implementation in our study.

Thank you again for taking the time to comment on our research.

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One or more of the authors has declared a potential conflict of interest or source of funding: L.A.F. and B.J.C. are consultants to Arthrex Inc.

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