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Editor's Spotlight/Take 5

Editor's Spotlight/Take 5: Mesenchymal Stem Cells in Synovial Fluid Increase After Meniscus Injury

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We tend to underestimate the harm caused by meniscus tears. Their frequency, and the ease with which they are treated today, can lull us into the belief that they are minor injuries. They are not.

Even leaving aside the fallout from treatments prior to the era of arthroscopy, which often resulted in progression to end-stage arthritis with cruel efficiency, these injuries are bad actors. "Routine" meniscus tears can be game-changers [10]. Whether treated without surgery or with contemporary arthroscopic approaches, patients with meniscus tears need to make good exercise choices, as the injury [4] and the surgery commonly used to treat it (partial meniscectomy) [2] increase a patient's risk of developing arthritis later in life.

Repair would be vastly preferable, but because of poor vascular supply to the inner, less-well vascularized (and more commonly torn) portions of the meniscus, it rarely is an option. For this reason, the foundational work of Ichiro Sekiya MD, PhD et al. in this issue of *Clinical Orthopaedics and Related Research®* (*CORR®*) is very exciting.

In a well-controlled observational study, Professor Sekiya (Fig. 1) and his group at the Center for Stem Cell and Regenerative Medicine in Tokyo determined that cells with key characteristics of mesenchymal stem cells — including multipotentiality and the expected surface epitopes — are present to a vastly larger degree in injuries with meniscus tears than in uninjured knees. In prior animal work, they demonstrated that synovium-derived mesenchymal stem cells injected into knees adhered to the lesion, differentiated into meniscal cells, and promoted healing of meniscal tears [6, 7]. The fact that these cells appear to promote healing, and that their number can be increased in response to a stimulus, (such as injury, as they showed in this *CORR®* article) raise both interesting questions and potential therapeutic avenues: Do meniscal tears in the avascular regions fail to heal spontaneously because insufficient numbers of stem cells are available? Might increasing their number or their activity boost the likelihood that these tears would heal? Only time will tell.

However, the current and earlier work of Professor Sekiya's group suggests that we may be much closer to those kinds of answers than is commonly thought. If so, what a breakthrough that would be. I urge you to have a look at "Mesenchymal Stem Cells in Synovial Fluid Increase After Meniscus Injury" in this month's *CORR®*. It may be a glimpse into the future.

Note from the Editor-In-Chief: In ''Editor's Spotlight,'' *one of our editors provides brief commentary on a paper we believe is especially important and worthy of general interest. Following the explanation of our choice, we present* ''Take Five,'' *in which the editor goes behind the discovery with a one-on-one interview with an author of the article featured in* ''Editor's Spotlight.''

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Take Five Interview with Ichiro Sekiya MD, PhD, senior author of "Mesenchymal Stem Cells in Synovial Fluid Increase After Meniscus Injury"

Seth S. Leopold MD: *Congratulations on an important, well-designed, and well-executed study. I would like to ask you to do something we do not do in scientific papers, but I think readers would appreciate your perspective: Given the progress that you and others in this field are making, where do you think we might be in 5 years in terms of using synovium-derived mesenchymal stem cells for the healing of meniscal injuries?*

Ichiro Sekiya MD, PhD: Thank you for highlighting our study. I believe that the synovium is a very useful source of mesenchymal stem cells, particularly because it is easy to harvest synovium and synovium-derived mesenchymal stem cells. These cells also have been shown to have a higher proliferative capacity and cartilage differentiation potential than cells from other mesenchymal tissues. I think that mesenchymal stem cells have advantages in simplicity and safety compared with induced pluripotent stem cells or embryonic stem cells. As such, mesenchymal stem cells are currently closer to clinical application. We hope synovium-derived mesenchymal stem cells will be placed into general clinical use to help compliment the ever growing repertoire of treatment modalities available to orthopaedic surgeons within the next 5 years.

Dr. Leopold: *Would you walk us through the kinds of experiments that might get us from today to that point?*

Dr. Sekiya: We already have begun performing transplantations of synovium-derived mesenchymal stem cells to cartilage defects in clinical practice. In many patients, cartilage defects, and their associated symptoms, have been improved without adverse events. We currently have a plan to use synovium-derived mesenchymal stem cells to enhance meniscus healing after meniscal suture in cases with hard-to-treat meniscus injuries, such as complex or degenerative tears. We have already obtained promising results in rat [9] and rabbit [6, 8] models. Our pig models are currently in the process of review.

Dr. Leopold: *What analogous lines of inquiry are underway — in your lab or elsewhere — in other joints?*

Dr. Sekiya: Synovium may be a reservoir for mesenchymal stem cells to contribute to intraarticular tissue repair. After intraarticular tissues are injured, mesenchymal stem cells may be mobilized from synovium to synovial fluid, adhere to the injured site, and contribute to repair [6, 8, 9]. We are currently investigating how mesenchymal stem cells are mobilized from synovium to synovial fluid in a simple in vitro model. Another interest of ours also relates to the mechanism behind this natural repair process. As synovium-derived mesenchymal stem cells have two roles to enhance meniscus healing (to differentiate into meniscal cells directly, and to produce trophic factors), we currently are examining trophic factors of synovium-derived mesenchymal stem cells in the knee joint following meniscus injury. We also are interested in mesenchymal stem cells in other joints, such as the shoulder and ankle.

Fig. 1 Prof. Sekiya and his group determined that cells with key characteristics of mesenchymal stem cells — including multipotentiality and the expected surface epitopes — are present to a larger degree in knees with meniscus tears than in uninjured knees.

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Dr. Leopold: *I would like to ask you two questions about the different "languages" that clinicians, clinician-scientists, and scientists "speak." Many clinicians find reading this kind of research somewhat intimidating; so much so, that some will entirely avoid these papers. First, what do you recommend that the curious clinician do (or read, in preparation) before approaching these kinds of papers, which may be very unfamiliar initially?*

Dr. Sekiya: As an introduction to the topic, I would recommend three review articles. De Bari et al. [3] outlined stem cell-mediated strategies for the repair of joint tissues. Caplan [1] summarized the biological basis for the in vivo function of mesenchymal stem cells through development and aging. Fox et al. [5] introduced synovial stem cells as a cell source for cartilage and meniscus regeneration.

More generally, in order to engage a general readership of this sort, I believe that studies regarding clinical-oriented basic research should be selected for publication in *CORR®*, but to a lesser degree if at all, studies of purely basic research. To draw readers in, the title of a paper should be attractive enough to get the attention of curious clinicians. I also believe that graphical illustrations help convey the information meant for the *Methods*, *Results*, and *Conclusions* sections. These illustrations should be used as much as possible to help readers quickly and accurately gauge the scope and clinical implications of a body of research. I find that this is beneficial both for scientists and clinicians.

Dr. Leopold: *The second part of my question: What can scientists like yourself, editors like me, and perhaps others (specialty societies, perhaps), do to help break the "language barrier" between basic scientists and clinicians?*

Dr. Sekiya: Technical words that may be unfamiliar to clinicians should be explained clearly. Selected papers should be introduced in a broad but brief manner in other sections of the same journal such as your "CORR Insights®" commentaries or "Editor's Spotlight/Take 5" features like this one, placing special emphasis on future applications and impact on the field. Providing readers with some of the peer reviewers' comments along with responses from authors, as some journals do, also can help audiences better understand the study.

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