

# Editorial Commentary: Discovery: Progenitor Cells and Endothelial Cells Are Found in the White-White Zone of the Meniscus, But This Does Not Mean That These Tears Heal or Should Be Repaired



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**Abstract:** More than 35 years ago, the concept of vascular zones of the meniscus was introduced. It has been shown that blood supply is limited to the peripheral 25% of the lateral and 30% of the medial meniscus. This obviously has repercussions with regard to the healing potential of meniscus tears, whether repaired or not. In general, tears that extend into the white-white zone, such as flaps, cleavage tears, and radial tears, are deemed irreparable. However, several recent reports have suggested that radial tears in the white-white zone, when repaired, heal and have good clinical outcomes. Now progenitor mesenchymal cells have been identified in the white-white zones, confirming the potential of the meniscus to heal. However, blood supply was demonstrated only by indirect signs such as the presence of endothelial cells and the presence of endothelial surface markers.

See related article on page 252

Thirty-five years ago, Arnoczky and Warren taught us that vascularization of the meniscus is limited to the peripheral 25% of the lateral and 30% of the medial meniscus.<sup>1</sup> Endoligamentous vessels from the anterior and posterior horns travel only a short distance into the substance of the menisci and form terminal loops, providing a direct route for nourishment.<sup>2,3</sup> For the remaining 75% of the meniscus, nourishment is received from the synovial fluid via diffusion or mechanical pumping.<sup>3,4</sup> The concept of the red-red, red-white, and white-white zones was born. Blood supply, or lack thereof, has important implications for meniscal tears, their ability to heal, and our ability to repair them. Tears that extend into the white-white zone, such as flaps, cleavage tears, and radial tears, are deemed irreparable and better treated with meniscectomy or at least resection of the avascular component.<sup>5</sup> These recommendations are directly related to vascularity.<sup>3</sup>

However, we as surgeons constantly push the envelope, and several studies have reported good clinical outcomes with repair of radial meniscus tears, challenging this old paradigm.<sup>6-9</sup> Maybe there finally is potential for healing in the white-white zone? Obviously this would require blood supply and cells that can replicate.

And this is exactly what Chahla, Papalamprou, Chan, Arabi, Salehi, Nelson, Limpisvasti, Mandelbaum, and Steyn have proposed in their study titled, "Assessing the Resident Progenitor Cell Population and Vascularity of the Adult Human Meniscus."<sup>10</sup> They have investigated the presence of progenitor cells using cell surface markers and assessed "vascularity" by demonstrating endothelial "vascular" cells. The authors reported that the white-white zone is in fact vascularized.<sup>10</sup> If this does not blow you away, what else will? Finally we have proof that the entire meniscus has a blood supply, and now we can go ahead and also repair tears in the white-white zone.

But hold on. Is this really proof of vascularity and the potential of healing? A deep dive into basic science is necessary to understand the results of this study better. The authors have identified mesenchymal stromal cells or progenitor cells from the meniscus. Strictly speaking, these cells are not pluripotent undifferentiated stem cells. While they remain undifferentiated they are not

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true stem cells.<sup>11</sup> Their differentiation potential is different, and they can differentiate only into mesenchymal (osteogenic, chondrogenic, adipogenic) cell lines.<sup>11</sup> Surface markers are used to identify these cells, and the CD90, CD105, and CD73 markers are used as confirmation, but CD14, CD34, and CD45 should also be used as negative markers.<sup>11</sup> The authors have used CD90 and CD105 but not the other markers. The significance if this “omission” is not clear to a layperson like me. Could this have introduced selection bias? The authors have also used CD44 for identification. CD44 is widely expressed in almost all body cell types, and again the significance of this is not clear to me.<sup>12,13</sup> However, the authors were successful in inducing the 3 mesenchymal cell lines (osteogenic, chondrogenic, adipogenic), demonstrating that the cultured meniscal cells were able to differentiate. So theoretically, these meniscal cells can differentiate irrespective of the zone in the meniscus.

Great, now we only need adequate blood supply in the white-white zone for cell replication and healing of meniscus tears. And this is where the vascularity assessment comes in. As previously shown by Arnoczky and Warren<sup>1</sup> and many others, Chahla et al.<sup>10</sup> observed larger vessels in the red-red and red-white zone.<sup>10</sup> For the white-white zone, they concluded that the presence of endothelial cells by immunofluorescence analysis is sufficient proof of blood vessels.<sup>10</sup> Yes, the vascular endothelium is the inner layer of arteries, veins, and capillaries, but the luminal endothelial cell surface also contains glycocalyx, a multilayer of glycoproteins and proteoglycans.<sup>14</sup> In addition to the endothelial cells and basal lamina that form these capillaries and sinusoids, a few scattered pericytes should also be present.<sup>15</sup> Again, I am no expert, but if the the authors had been able to show that these factors were also present, then their case would be stronger. Simply using triple immunostaining with  $\alpha$ -smooth muscle actin and demonstrating the presence of the endothelial marker CD31 may not be enough to convince the skeptic. So is the presence of endothelial cells enough to call the white-white zone supplied with blood vessels? To me, the evidence seems pretty poor, and a healthy amount of doubt seems justified.

Let's call it what it is: great basic science research and well above our heads. But irrespective of whether we are academic surgeons, I believe we do need to expose ourselves to these difficult-to-understand basic science studies and concepts. Or we may end up like our much older generations, not knowing how to use a modern

cellular phone or log on to the internet. On the other hand, do we need to understand the space shuttle to repair a meniscus tear? Probably not.

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