The Price for Pain

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How much would you pay to play? Would you be willing to “play through the pain”? Currently, new treatment options have the potential to sealing the wound while innovating the field of molecular biology in developing further treatment for chronic knee pain and prolonging the quality of life.

As professional tennis player Rafael Nadal strides onto the tennis court, the viewers’ eyes are drawn to his bandaged knees, each knee wrapped in gauze like a birthday present. Indeed, Nadal doesn’t shy away from showing his chronic knee pain that robs him of a pain-free tennis match. The culprit: patellar tendinitis. The patella tendon, located below the patella (knee cap) and above the tibia (shin bone) is a tough fiber that connects the muscles and bones in the knee together and transfers the force of the quadriceps muscles when the knee strengthens. Commonly referred to as jumper’s knee, patellar tendinitis occurs when the patella tendon becomes repeatedly strained due to excessive jumping and landing and most commonly develops in athletes involved in high-impact sports such as gymnastics, and tennis. Despite the pain, athletes do whatever they can to prevent their knees from being yet another opponent to their success. Ice packs. Hot pads. Physical therapy. Knee braces. Gauze. Anything to shut the pain away. However, there’s only so much force the temporary treatments can handle before the pain breaks through the door. So was the story that unravelled for Nadal in 2009 when the pain was just too great to be sealed, forcing the star tennis player to pull out of Wimbledon. Nonetheless, the man himself sheds light on the dark plot of his tennis narrative, discussing his remarkable recovery after undergoing PRP. The nobleman shared his experience of undergoing platelet-rich plasma therapy (PRP) in 2010. However, Nadal isn’t the only one who stumbled upon the pot of gold. Vetrano et al. (2013) conducted two randomized clinical trials and treated athletes with either PRP or shock wave therapy. Not only did the athletes show improvement at the 6 and 12 month markings, but they also showed greater improvement than the athletes treated with shock wave therapy.

PRP is the plasma layer of blood that contains a higher concentration of platelets containing growth factors, a group of proteins that stimulate the regeneration of tissue. There are a variety of growth factors that target different tissues throughout the body, but, specifically, platelet-derived growth factors prompt the growth of connective tissue, such as the patella tendon. PRP illuminates the possibility of prolonging the quality of life for any individual suffering from chronic knee pain while extending careers and expanding opportunities. Although Nadal and other athletes continue to be plagued by chronic knee pain, current research has discovered how PRP works on the molecular level: PRP regulates the expression of genes involved in the inflammatory process, downregulating genes in tenocytes (tendon cells) that cause inflammation and pain while upregulating genes that secrete growth factors and anti-inflammatory proteins. New insight into the biological mechanisms of PRP and the inflammatory process could allow researchers to develop new treatments that can police the DNA highway and patrol the secretion of inflammatory and anti-inflammatory proteins. Perhaps athletes won’t always be subject to a painful passion?

In search of the hidden molecular footprint of PRP, Andia et al. (2015) examined gene expression and the modulation of interleukin (group of inflammatory proteins) secretion between healthy and inflamed tenocytes in hopes of enhancing current understanding of how PRP promotes the healing process. To uncover the secret workings of PRP, Andia et al. (2015) cultured healthy and tendinopathic cells from donors and let them grow. Subsequently, both tendinopathic and healthy cells were exposed to 3 different environments: no treatment, exposure to interleukin (IL)-1β and exposure to interleukin (IL)-1β with additional PRP treatment. PRP was obtained from the donors’ blood: by centrifuging the blood (separating the components of blood), the concentrated platelets and a portion of the plasma were drawn into a syringe and injected into the cell cultures. To track gene expression, Andia et al. (2015) converted the total RNA (codes for proteins) isolated from the cultured cells to DNA (genetic code) by reverse transcription. Now that the genes were lined up, the team was ready to investigate the markings left behind by PRP. After sleuthing the cell cultures, the detectives uncovered the anti-inflammatory characteristic of PRP: the answer to the mystery resided in changes in gene expression and changes in inflammatory protein secretion, the puzzle pieces were slowly starting to fit together.

The findings revealed that PRP lessens the inflammatory status of inflamed tenocytes by downregulating gene expression of interleukins. Tendinopathic cells treated with PRP showed downregulated gene expression of (IL)-1β, IL-6, IL-8, and MCP-1 (inflammatory signaling proteins, normally upregulated in tendinopathic cells) to a much greater extent than cells under no treatment or cells solely exposed to (IL)-1β (see Table 1). Moreover, tendinopathic cells experienced a greater secretion of HGF and VEGF, growth factors that boost tissue growth. However, healthy and tendinopathic cells experienced little differences in each of the 3 environments.

In summary, Andia et al. (2015) uncovered the immunomodulatory role of PRP, presenting the reduction of inflammatory proteins as a potential mechanism through which PRP can decrease pain and promote healing. The team of investigators closed the door on one mystery and opened several doors to other sleuth-worthy questions. How would results look in in-vivo models as opposed to cultured cells? Why was the secretion of some inflammatory proteins reduced (IL)-1β, IL-6, IL-8, MCP-1 while others were unaffected? There is no doubt that athletes suffering from chronic knee pain can benefit from PRP, but the study by Andia et al. presents possible ways to improve upon the current treatment. For example, since

<table>
<thead>
<tr>
<th>Experimental conditions</th>
<th>MCP-1/CCL2</th>
<th>VEGF</th>
<th>HGF</th>
<th>IL-6/ CXCL6</th>
<th>IL-8/ CXCL8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4 (0.8)</td>
<td>2.2 (0.5)</td>
<td>35 (5)</td>
<td>8.7 (0.8)</td>
<td>ND</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.5–6.5</td>
<td>0.8–3.7</td>
<td>18–52</td>
<td>6–11</td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td>475 (78)</td>
<td>6 (0.4)</td>
<td>8.7 (3.7)</td>
<td>1485 (302)</td>
<td>768 (175)</td>
</tr>
<tr>
<td>95% CI</td>
<td>227–722</td>
<td>5–7</td>
<td>–3.2 to 20.6</td>
<td>523–2448</td>
<td>209–1324</td>
</tr>
<tr>
<td>PRP</td>
<td>135 (22)</td>
<td>13 (0.7)</td>
<td>37 (10)</td>
<td>524 (64)</td>
<td>414 (34)</td>
</tr>
<tr>
<td>95% CI</td>
<td>87–183</td>
<td>11–14</td>
<td>15–59</td>
<td>383–664</td>
<td>340–488</td>
</tr>
</tbody>
</table>
Protein secretion by tendon cells at baseline, IL-1β exposure, and after platelet rich plasma treatment, table adapted from Andia et al (2015)

Cells treated with PRP experienced a lower secretion of the inflammatory proteins, MCP-1, II-6, IL-8, and IL-6 than the cells exposed to IL-1β.

Cells treated with PRP experienced a higher secretion of growth factors, VEGF and HGF than the cells exposed to IL-1β.

*CI stands for the Confidence Interval and describes the level of uncertainty associated with the measured data

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References


