



# New strategies accelerate the path to overcome refractory interstitial cystitis

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Female pelvic floor disorders, a chronic, complex and inflammatory disease, including overactive bladder, stress urinary incontinence, pelvic organ prolapse, and interstitial cystitis (IC), are increasing prevalent on a global scale, which significantly affect quality of life, such as increased health care visits, disturbance of sleep, higher rates of depression and anxiety, increased risk of fall-related injuries, increased risk of urinary tract infection, and reduced work productivity, leading to significant social and economic burdens.<sup>1-7</sup> Among these female pelvic floor disorders, IC (also called as bladder pain syndrome) may be one of the most troublesome disorder, because etiology is still uncertain, and diagnosis remains by exclusion as well as the diagnosis is often delayed in the patient's journey, contributing to a profound impact on the emotional, psychological, and social well-being of the patient.<sup>5-8</sup> Due to aforementioned reasons, the management of women with IC is still a biggest challenge for both physicians and patients. Although hyaluronic acid (HA, hyaluronan), a hydrophilic glycosaminoglycan (GAG) macromolecules with -COOH and -OH functional groups, as a member of the polysaccharides family, plays a critical role in the extracellular matrix (ECM) and provides evidence showing the accumulation of HA may trigger the regeneration process of injuries endothelium or epithelium of urinary bladder (IC) to reach the restoration of normal urinary bladder function,<sup>5-7,9-11</sup> there is no doubt that some patients with IC (30%-40%) will not respond to intravesical HA and/or treatment provided by other conventional strategies, and this clinical situation is called as refractory IC.<sup>5,6</sup> In the current issue of the *Journal of the Chinese Medical Association*, we are happy to learn the research addressing this-type problem (refractory IC). Hung et al<sup>12</sup> tried to investigate whether the use of the combination of an autologous emulsified fat (nanofat) and platelet-rich plasma (PRP) could provide a new vision or strategy in the management of the women with refractory IC or not.

The authors enrolled six women with refractory IC who were treated with intravesical therapy of nanofat and PRP combination and found that all patients had marked improvement of the overall bladder conditions on Pain Visual Analog Scale, Interstitial Cystitis Symptom and Problem Index, and a scaled Global Response Assessment.<sup>12</sup> The current study is exciting and worthy of our attention.

Regenerative medicine, a wide range of natural approaches which include the use medicine (agents, reagents, drugs), biologics, stem cell therapy, tissue engineering (using biodegradable porous three-dimensional scaffolds for mimicking the structure and functions of the natural ECM), cellular reprogramming, and gene therapy, curbs various diseases, mediated by repairment of the damaged tissue or organ and maintenance of essential function or restoration of the normal anatomy or function.<sup>13-15</sup> In the current article,<sup>12</sup> the authors explored the effect of biocellular regenerative medicine in the management of women with refractory IC by intravesical therapy with an autologous emulsification and filtration of the lipoaspirates and PRP. The aforementioned strategy took the following advantages. First, nanofat, an injectable product of adipose tissues contains at least two compact pockets of essential components, and both of which provide a key factor for the path to the success during the regenerative process. One is the adipose tissue-derived stem cells (ASCs, mainly as CD34+-rich ASCs): a subtype of mesenchymal stem (stroma) cells (MSCs), which possess differentiation ability, in vitro expansion, release of trophic materials, as well as angiogenic, antiapoptotic, and immune-modulatory properties.<sup>14</sup> In fact, nanofat is one of the richest sources of ASCs and other progenitor cells, and all are the critical component for the success of repair, healing and regeneration.<sup>15</sup> The other is to establish vascular and naive cellular matrix (a potential back-bone structure as ECM, microvascular fragments [MCFs, containing fragments of arterioles, venules, and capillaries identified by cluster of differentiation 31 [CD31 or platelet endothelial cell adhesion molecule-1] and  $\alpha$ -smooth muscle actin, vascular endothelial growth factor [GF], platelet-derived GF, hepatocyte GF, hepatocyte GF, transforming GF- $\beta$ , basic fibroblast GF, insulin-like GF 1, and granulocyte-macrophage colony-stimulating factor] and possible various pockets of GFs, cytokines, adipokines, and transcriptional factors [lipoxin, resolvins, protectins, neurotrophic factors, angiogenin, matrix metalloproteinase 9, leukemia inhibitory factor, macrophage migration factor, bone marrow protein 2, 4, and interleukin 1RA, 4, 8, 10, 11, and 13] which altogether from secretomes).<sup>12,15</sup> The use of adipose tissue as a resource takes advantages, which not only can be obtained by

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easy and reproducible manner (accessibility, harvesting, potential, extraction by a non-terminal procedure) but also is absence of ethical concerns.<sup>14,15</sup> Additionally, besides nanofat, ASCs, and secretomes, the products of adipose tissue including macrofat, microfat, MCFs, the stromal vascular fraction (SVF), and exosomes, contributing to various needs for generative medicine, based on minimal or more manipulation procedure of the adipose tissue.<sup>15</sup>

PRP, an autologous blood-derived product containing high platelet concentrations and other factors, influences various cellular processes, including homing of stem cells, cellular migration, proliferation, and differentiation, angiogenesis, macrophage activation, and collagen and matrix synthesis, to finish the enhancement of healing processes, immunomodulatory and paracrine properties of damaged tissue or organs.<sup>16</sup> In fact, PRP offers a dramatically powerful augment of the natural healing response and the promising results seem to be found in a shorter time period for the treatment of different musculoskeletal tissue injuries, chronic wound, nonhealing ulcers, as well as various kinds of genitourinary organ injuries, contributing to the successful tissue expansion, proliferation, and rejuvenation.<sup>16</sup> Similar to the advantages of nanofat, PRP also has a low cost, easy and fast isolation without major side effects or ethical considerations.<sup>16</sup> Therefore, it is not surprising to find the exciting results when the combination of both promising products is applied to the patients with refractory IC in Hung et al's<sup>12</sup> study.

The development of regenerative medicine is attractive and may change our living, since aging process is continuous. All we can do welcome more and more studies attempting to evaluate the underlying mechanisms of these "exciting products" to validate the clinical benefits of the patients who suffer from disease- or ageing-related bothering in the future.

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