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COMMENTARY

New Horizons of Knowledge in Intervertebral Disc Disease

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Intervertebral disc disease (IVDD) refers to degenerative processes of the spine resulting in reduced shock-absorbing ability, which may ultimately lead to disc herniation and spinal cord compression. Back pain is associated with this condition, representing the clinical feature mostly frequently referred by the patients. The etiology, as for many musculoskeletal diseases, should be sought in environmental and genetic factors. These latter involve genes which are responsible for Collagen type IX and I, Aggrecan, Vitamin D receptor, while non-hereditary factors include primarily mechanical injuries, excessive loads and uneven weight distribution, as well as aging, obesity, chronic inflammation, and work-related risk factors like long sitting sessions, e.g. while driving, or non-ergonomics office equipment [1]. It is estimated that more than 200 million cases of lumbar degenerative spine disease occur, each year, worldwide, significantly contributing as a major cause of disability and socio-economic burden [2].

Disc disease-associated pain is commonly treated by non-invasive approaches which involve nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids and physical rehabilitation. When conservative treatments fail, interventions could currently employ epidural injections, spinal fusion procedures, arthroplasty and, more recently, regenerative approaches like intradiscal injections of mesenchymal stem cells (MSCs) and platelet-rich plasma (PRP). As a matter of fact, both well-established and promising new treatments might show some clinical limitations/evidences and lack of full consensus or long-term efficacy. Continuous advancement in research and biotechnology are also focused in treating the problem and provide more targeted solution to restore tissue functionality.

Molecular investigations analyzed the involvement of several cytokines in disc degradation process [3]. Interleukin-1 (IL-1), for example, which increase sensitivity to pain by stimulating prostaglandins and serotonin synthesis, has been studied in relation to apoptosis and autophagy in human nucleus pulposus (NP) cells [4]. It is stated that Il-1β triggers mitochondrial apoptotic mechanisms during degeneration processes which, in turn, generate accumulation of damaged mitochondria, eventually activating autophagic pathways as a countermeasure against apoptosis. IL-1β apoptotic effect on mitochondria is expressed by increased expression ratio of Bax/Bcl-2, releasing of cytochrome c and activation of caspase-9 and -3. Unfortunately, autophagy, in degenerative NP cells, is not always able to balance apoptosis but it potentially qualifies as a potential strategy to take advantage of in IVDD treatment. In a recent research, published in the *Journal of Investigative Surgery*, authors studied, in the context of disc disease, the effect of resveratrol (RSV) combined with 17β-estradiol (ES), potentially gaining a better insight into clinical therapies based on anti-apoptotic strategies [5].

Resveratrol, a plant protective phytoalexin produced in response to stresses, is called into question because of its anti-inflammatory properties, which may delay disc degeneration. Several evidences link IL-1β-induced inflammation to NP cells apoptosis, which seems to be decreased by resveratrol supplementation via downregulation of Bax protein and caspase-3 expression, and upregulation of Bcl-2 [6]. Since PI3K/Akt pathway might be inhibited by cytokine-induced inflammation and, in the same way, activated by resveratrol, this latter could be imagined as apoptotic suppressant (and maybe autophagic activator) in the context of disc degeneration. Resveratrol showed other important effects, involved in NP cells senescence and, consequently, homeostasis and inflammation, which comprise: stimulation of cells proliferation, decreasing of senescence-associated β-Galactosidase activity and G0/G1 cell cycle arrest, increasing of telomerase activity, downregulation of senescence markers (p16 and p53) and catabolism enzymes (MMP-3, MMP-13 and ADAMTS-4) and upregulation of matrix macromolecules (aggrecan and collagen II) [7].

Association of resveratrol with 17β-estradiol [5] is justified by the fact that this compound was found to inhibit extracellular matrix degradation in NP cells by stimulating the expression of collagen II and aggrecan, whereas downregulating MMP-3, via PI3K/Akt/FOXO3 pathway [8]. It should be reminded that MMPs, especially MMP-1, 3, 9 and 13, play a key role in the process of pro-inflammatory cytokine-induced IVDD, since they mediate a global instability, encouraging the degradation of ECM constituents. However, the role of estrogen, in this particular disease, is progressively drawing attention, in recent times, acknowledging the crucial role it fits in several dysfunction of musculoskeletal system. A fortiori, it should be taken into account the

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correlation between absence of estrogen in postmenopausal women and the rate of incidence in this population, which is higher than that estimated in age-matched men [9]. In addition, degree of disc degradation can be observed in association with lower expression of estrogen receptor (ERα and ERβ) in NP cells [10]. Some concerns should arise when estrogens are investigated to be included in clinical practice, in terms of safety and complications (e.g. risk of cancer, thrombosis etc.). For this reason, selective estrogen receptor modulators (SERM) and phytoestrogen (like the aforementioned resveratrol) are, as well, studied in this field of research.

The authors of the cited original article, in the *Journal of Investigative Surgery,* [5] explored the mechanisms of actions triggered by the association between the phytomolecule and the hormone, in order to confine the apoptotic effect of the inflammatory environment in which human NP cells were exposed to. The hypothesis of this study was based on their previous researches which were conducted, following the same ratio, on animal cells, suggesting the combination of the two compounds rather than the administration of the single one. Molecular analysis found out that cells treatment, in presence of RSV and ES, improved cell viability, suppressed by the presence of IL-1β, whereas diminished cells apoptosis, induced by the same cytokine. The merit of this investigation lies in questioning about the proteins acting downstream the pathway PI3K/Akt, concluding that the response to appropriate blockers (rapamycin and SB216763) outlines PI3K/AKT/mTOR and PI3K/AKT/GSK-3β pathways as those employed by RSV and ES. Surely, as already mentioned by the authors, these data need to be obtained in vivo, in order to represent a starting point toward a potential therapeutic alternative to be translated into clinical treatment for intervertebral disc degeneration. Furthermore, side effects, synergy and other interactions between these two compounds should be further clarified, for which this study stands as stimulus.

Intervertebral disc degeneration is difficult to recognized and distinguished from physiological changes that characterized aging, also because underestimation and lack of symptoms are common. In addition, there are still a lot of shadows regarding this topic that should be further investigated, like the involvement of the annulus fibrosis and cartilage endplates cells, when considering a therapeutic approach, or the biomechanical forces to which the disc is subjected to. In conclusion, we are sure that each new little or big step in this field will be crucial to further enhances and reveals new findings.

Disclosure statement

The authors report no conflict of interest.

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