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Inflammaging in the intervertebral disc

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Abstract

Degeneration of the intervertebral disc – triggered by ageing, mechanical stress, traumatic injury, infection, inflammation and other factors – has a significant role in the development of low back pain. Back pain not only has a high prevalence, but also a major socio-economic impact. With the ageing population, its occurrence and costs are expected to grow even more in the future. Disc degeneration is characterized by matrix breakdown, loss in proteoglycans and thus water content, disc height loss and an increase in inflammatory molecules. The accumulation of cytokines, such as interleukin (IL)-1 β , IL-8 or tumor necrosis factor (TNF)- α , together with age-related immune deficiency, leads to the so-called inflammaging – low-grade, chronic inflammation with a crucial role in pain development. Despite the relevance of these molecular processes, current therapies target symptoms, but not underlying causes. This review describes the biological and biomechanical changes that occur in a degenerated disc, discusses the connection between disc degeneration and inflammaging, highlights factors that enhance the inflammatory processes in disc pathologies and suggests future research avenues.

Keywords

Intervertebral disc, chronic inflammation, inflammaging, senescence, mechanical loading, matrix fragmentation, obesity, *Propionibacterium acnes*

The concept of inflammaging

During the course of life, humans are exposed to numerous internal and external damaging agents, including products of metabolic stress, UV light or pathogens. The body can counterbalance the detrimental effects that these stressors exert by various mechanisms (DNA repair, cell apoptosis/autophagy, etc.), at least to a certain degree.¹ Induction of immune and inflammatory processes are also a part of the body's toolbox to shield itself from these types of dangers, but to ensure healthy ageing, later neutralization of these inflammatory processes is required. However, there are cumulative data indicating a decrease in the counteraction capacity with increasing age.¹ Consequently, pathology-associated ageing that is linked to an imbalance between inflammatory and anti-inflammatory networks occurs. This imbalance is further promoted by age-related immune deficiency termed immunosenescence, which entails a reduced capability of the body to effectively combat stressors.²

The resulting low-grade, chronic inflammation was termed inflammaging by Franceschi et al.³ Since then, inflammaging (also known as inflamm-ageing⁴) was found

to induce endocrine, metabolic and nutritional changes that likewise promote pro-inflammatory conditions.⁵ Importantly, recent research highlighted that inflammaging is based on a complex relationship between pro- and anti-inflammatory markers, including the activation of counter-regulatory mechanism.⁶ Inflammaging has been described as an important contributor to numerous age-related diseases, including osteoarthritis, Alzheimer's disease, atherosclerosis, heart disease or type II diabetes.⁴ In

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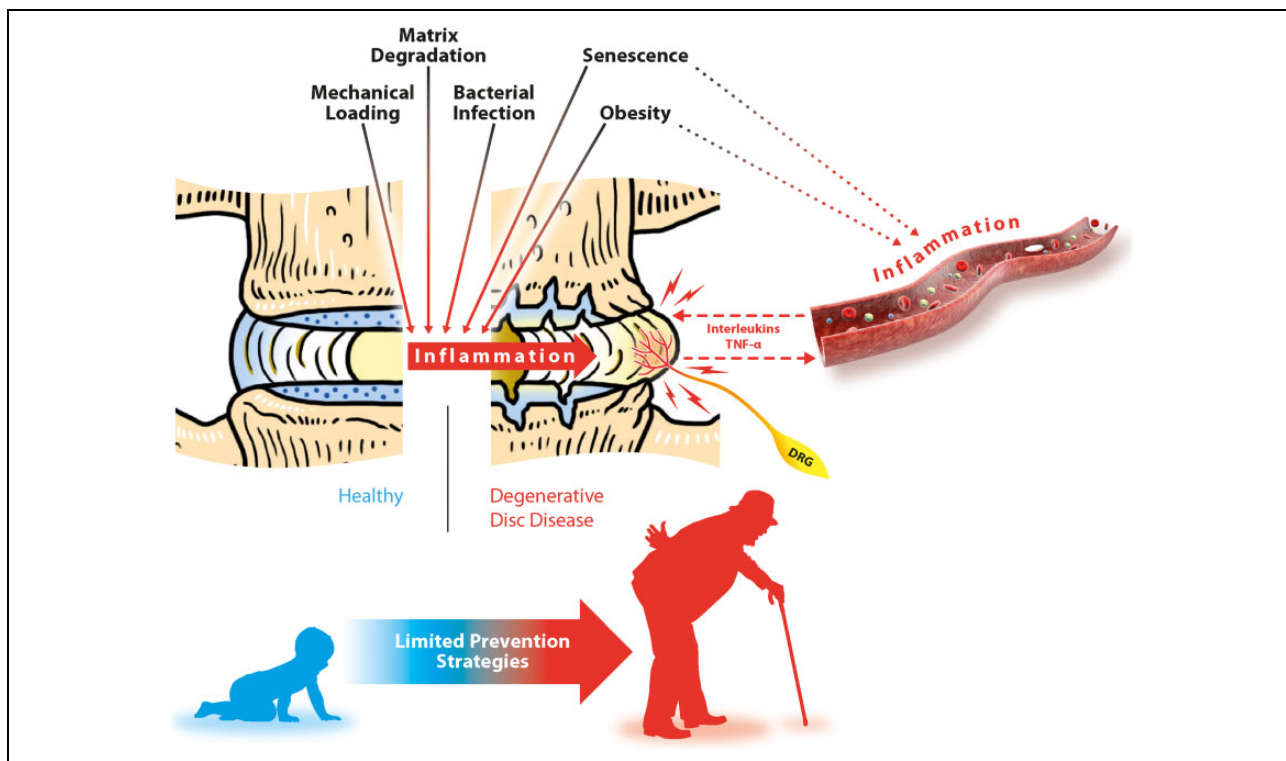


Figure 1. Concept of inflammaging in the IVD.

the musculoskeletal system, age-related changes include loss of bone mass, as well as degradation of cartilage and intervertebral disc (IVD) tissues.⁷ As the term inflammaging has recently also emerged in the context of disc pathologies,⁸ the subsequent chapters will provide an overview of the current state of the art.

Ageing and degeneration of the IVD

Degeneration of the IVD is a major contributor to low back pain (LBP).⁹ Due to the lifetime prevalence of 84%,¹⁰ LBP – and thus also disc degeneration – has a major socio-economic impact. In fact, the financial burden related to LBP is approximately 2% of the national gross domestic product in various countries.^{11,12}

IVD degeneration is an age-related process, with an early onset.^{8,13} Ageing IVDs are characterized by a shift from anabolism towards catabolism, with a consequent matrix breakdown, loss of hydration in the nucleus pulposus (NP) and reduction in disc height. These changes not only result in altered biomechanics but also in neovascularization and neoinnervation, at least in the annulus fibrosus (AF).¹⁴ With ageing and the loss of tissue homeostasis, cells are exposed to damaging factors (such as damaged matrix products, toxins or oxidative stress), leading to increased cell death and senescence.^{15,16}

The prevalence of IVD degeneration is vast. A recent cross-sectional population study with 1043 volunteers showed that 40% of individuals under 30 years of age had

IVD degeneration, with an increase to over 90% in the 50- to 55-year-old group.¹⁷ Due to ongoing ageing of the population, the number of those with IVD degeneration – and thus the associated socio-economic impact – will even further increase in the future. However, it has to be noted that only a subpopulation develops painful disc degeneration, whereas it is asymptomatic in approximately two-thirds of the population.^{18,19} As described in more detail in the later sections, inflammation and inflammaging contribute to disc-related LBP.

Inflammation and degenerative disc disease

Inflammation has been described as the major pathological contributor to the development of painful disc degeneration, also termed degenerative disc disease (DDD; Figure 1). While local inflammation arising within the IVD tissue has been extensively studied over the past decade, first evidence also points to the role of systemic inflammation in DDD. Table 1 summarizes the pro-inflammatory molecules that are involved in the development of DDD.

Systemic inflammation

With technical advancements in the cost-effective analysis of proteins, clinicians and researchers have become increasingly interested in the identification of biomarkers in the biological fluids of patients, predominantly blood.

Table 1. Pro-inflammatory cytokines involved in DDD. For more information, please refer to the cited literature.

	IL-1 α	IL-1 β	IL-2	IL-4	IL-6	IL-8	IL-10	IL-12	IL-15	IL-17	TNF- α	PGE2	IFN- γ
Systemically increased					20,21,23,25	25				21			
Locally increased	27,31	27,28,31,39,41	27,28	27,28,32	8,27,28,32,36	8,27,28,33,36,38	27,28,38	32	8	27,28,32	8,27-30,33-36,41	27,28	27,28,32,37

DDD: degenerative disc disease; IL: interleukin; TNF: tumor necrosis factor; PGE: prostaglandin; IFN: interferon.

Biomarkers can be of tremendous value not only in early detection of diseases and prognosis, but also in management and monitoring.

Studies investigating serum samples demonstrated an age-dependent increase in numerous inflammatory cytokines, including interleukin (IL)-6 and tumor necrosis factor- α (TNF- α), supporting the notion of age-associated chronic, low-grade inflammation and hence inflammaging.^{20,21} Interestingly, a meta-analysis of eight studies, including 263 subjects with IVD degeneration (bulging, protrusion or sequestration) and 129 healthy controls, demonstrated an association between IL-6 serum levels and the occurrence of IVD degeneration, with higher levels in those affected.²² Recent work by Weber et al. not only confirmed that serum IL-6 correlated with age but also highlighted that levels were significantly higher in subjects with LBP arising from disc herniation (DH), DDD or spinal stenosis, compared with non-affected controls.²³ As participants were controlled for age during recruitment, these findings point towards a general presence of inflammaging, but with disease-specific alterations in the cytokine expression patterns. Furthermore, higher IL-6 serum levels were reported as an indicator of inferior recovery in patients with lumbar radicular pain due to lumbar DH over the course of 1 year, as demonstrated by the Oswestry Disability Index and visual analogue scale.²⁴ Aside from IL-6, IL-8 has also been suggested as a potential biomarker in DH and the level of associated pain, but possibly also in DDD without the occurrence of IVD protrusion.^{25,26}

In summary, these results indicate that systemic inflammation not only represents a link between ageing and IVD pathology, but also disc-related LBP.

Local inflammation

Past research has provided ample evidence for the expression of inflammatory mediators in the IVD, including IL-1 α , IL-1 β , IL-2, IL-4, IL-6, IL-8, IL-10, IL-17, TNF- α , prostaglandin E2 (PGE2) and interferon- γ (IFN- γ),^{27,28} partially with an age- and degeneration-dependent expression profile.²⁹⁻³¹ Importantly, invading cells of the immune system, for example, in case of herniation, can produce pro-inflammatory cytokines. IVD cells themselves are also a source of pro-inflammatory cytokines, with some differences between NP and AF cells, for example, with regard to IL-1 α , IL-1 β , IL-6, IL-17 and TNF- α .^{8,31,32}

Several of these inflammatory mediators are major pathological markers, with higher levels in “diseased” IVDs. Higher levels of TNF- α and IL-8 were measured in DDD samples compared to DH samples and this likely contributes to more severe back pain commonly observed in DDD patients.³³ On the other hand, DH samples – which are characterized by enhanced macrophage infiltration and rare lymphocyte infiltration – possess higher levels of IL-4, IL-6, IL-12 and IFN- γ than DDD samples.³²

The presence of these inflammatory mediators not only aggravates IVD degeneration, for example, by inducing the

expression of matrix degrading enzymes, by enhancing cellular senescence, as well as by inhibiting extracellular matrix (ECM) synthesis,^{28,30,34,35} but also plays a crucial role in pain development. In fact, there is clear evidence that a variety of pro-inflammatory cytokines are upregulated in patients with higher pain sensation (such as IL-1 β , IL-6, IL-8, IL-10, TNF- α , IFN- γ ^{36–39}) – albeit with differences between studies likely associated with patient selection and consequent dissimilarities in pathology inclusion criteria.

The mechanisms of cytokine-induced pain sensation are complex.^{27,40,41} During DH, pain sensation can be due to mechanochemical irritation of spinal nerves caused by the inflammatory nature of the extruded NP material (radiculopathy) and/or nerve infiltration into the compromised disc (nociception). In cases of DDD, LBP develops through newly invading nociceptive nerve fibers, either via nociceptive or neuropathic mechanisms. Pro-inflammatory cytokines and chemokines also induce immune cell infiltration into degenerated IVDs and these cells further aggravate the inflammatory status. Additionally, resident and infiltrating cells release neurogenic factors that not only facilitate nerve ingrowth into the IVD, but also induce the expression of pain-associated cation channels in the dorsal root ganglion (e.g. ASIC3, TRPV1).

Ageing-related inducers of inflammation in the IVD

It is likely that several biological processes ranging from senescence, mechanical loading, matrix degradation, bacterial infection to obesity contribute to inflammaging in the IVD (Figure 1). Some examples of these processes are explained below.

Senescence

Senescence is the biological ageing of cells that is associated with a cessation in cell division, yet continuous metabolic activity. Numerous methods and markers are used to identify senescent cells, ranging from senescence-associated β -galactosidase (SA- β -gal) staining over telomeres shortening to induction in the expression of cyclin-dependent kinase inhibitors p16INK4a or p21(Waf1/Cip1). Using these techniques, senescent cells were shown to accumulate during IVD ageing and specifically in degenerated and herniated IVDs.^{42–45}

Two general forms of senescence exist, typically termed as (telomere-dependent) replicative senescence and stress-induced premature senescence, and both can be present in the IVD cells.^{46,47} Both types of senescence share similar phenotypic features, including a shift towards an immunogenic phenotype. This phenotype is generally known as senescence-associated secretory phenotype (SASP) and is characterized by a pro-inflammatory secretome (the collection of proteins secreted by a cell), with enhanced expression of IL-6, IL-8 and IFN- γ in IVD cells.⁴⁸ Furthermore, senescent cells are responsible for enhanced catabolism and ECM degradation through stimulation of matrix

metalloproteinases (MMP) -1, -2, -3, -9, and -13.^{44,48} Therefore, senescence is likely an important contributor to premature disc ageing and inflammaging (Figure 1).^{44,49}

Mechanical loading

The IVD is a mechanically complex tissue, in which hydrostatic pressure/compression and osmotic stresses predominate in the NP and tensile and shear stresses preside in AF. IVD cells have been shown to respond to mechanical stresses in a dose-, frequency-, duration- and zone-specific manner.^{15,50,51} Moderate physiological levels of stress produce anabolic responses, whereas hyper-physiological stresses not only bias towards catabolism and reduced viability, but also induce inflammation.^{52–58}

Importantly, ageing and consequent degeneration alter the load distribution in IVDs and result in higher compressive axial and tensile radial strains.⁵⁹ Areas of peak stresses hence exist within degenerated IVDs. Cells located in these regions will experience disproportionately high loads during normal physiological activities, hence responding with catabolism and inflammation rather than anabolism (Figure 1). In fact, previous research has demonstrated that cellular responses to physical stress are graded by the degree of tissue degeneration.⁵⁵ Transient receptor potential (TRP) channels, a family of multimodal cation channels, may represent a molecular link between mechanical loading and inflammation in the IVD. TRP channels, which have been described to play a crucial role not only in mechanosensing, but also in transmission of inflammation and pain, have recently been detected in the IVD.^{8,60,61} The mechanism of locally altered load distribution, together with potentially altered mechanotransduction mechanisms (e.g. vial-altered TRP channel expression with ageing and degeneration),⁸ helps to rationalize why mechanical loading originating from normal daily activities may result in low-grade inflammation in ageing IVDs.

Matrix degradation

Age-associated degeneration of the IVD is characterized by degradation of the ECM, leading to a decrease not only in total proteoglycan and collagen content, but also in altered expression and synthesis of other matrix components.^{62,63} Specific enzymes, for example, reactive oxygen species, can induce fragmentation of these ECM proteins. A number of these fragments have been described to be biologically active and some possess inflammatory properties (Figure 1). In fact, fragments of hyaluronic acid were already shown to induce catabolic and inflammatory responses in IVD cells.⁶⁴

Aside from hyaluronic acid fragments, additional matrix cleavage products occurring during ageing and degeneration of the IVD may contribute to IVD inflammaging, albeit likely in a size-specific manner. Fragmentation of the small, leucine-rich proteoglycan biglycan takes place in pathological human IVDs⁶⁵ and these

fragments were shown to induce pro-inflammatory processes in, for example, macrophages.^{66,67} Our own unpublished data indicate that fibronectin fragments – which are present in degenerating IVDs^{68,69} – also induce inflammation in IVD cells, similar to numerous other cell types.⁷⁰ Other possible fragmentation products that may play a role in mediating IVD inflammaging include those of versican, decorin, elastin or laminin.^{67,71,72}

Bacterial infection

Propionibacterium acnes (*P. acnes*) infection is one of the hypothesized causes of the development of chronic, low-grade IVD infection and Modic changes.⁷³ Due to IVD ageing and altered IVD biomechanics, clefts and tears occurring in the outer layer of the AF promote neovascularization and allow for easier bacterial invasion. Importantly, this new microenvironment can enhance the growth of anaerobic bacteria.⁷⁴

Previously, bacterial infection with, for example, *P. acnes* was believed to arise from epidural injections and contaminations during surgeries or tissue collection.⁷⁵ However, recent studies were able to demonstrate that an infection with *P. acnes* is likely independent of these factors.^{76–79}

Although *P. acnes* infection is associated with chronic inflammation in IVDs (Figure 1), with stimulation of various pro-inflammatory cytokines (e.g. IL-8, macrophage inflammatory protein (MIP)-1 α , TNF- α),⁸⁰ the exact mechanism of inflammation induction remains unknown. However, recent evidences point towards activation of Toll-like receptors (TLR) 2 and 4, and subsequent induction of the NF- κ B pathway.^{80,81}

Obesity

Obesity is linked not only to a large number of comorbidities, including a significant association with the incidence of type II diabetes, various types of cancer, cardiovascular diseases, asthma or osteoarthritis,^{82,83} but also with the development of disc degeneration and chronic back pain.^{84,85} A recent meta-analysis calculated that the risk of LBP increased by approximately two fold in obese patients, but with a relatively weak statistical association (odds ratio 1.8).⁸⁶ Interestingly, when patient selection criteria were tightened, focusing solely on morbidly obese people (body mass index >40), the prevalence of LBP was significantly higher in the obese group compared to a control group with normal weight,⁸⁷ demonstrating that relevant weight thresholds may exist. The underlying pathophysiological mechanism leading to disc degeneration, DDD and LBP in obese patients is believed to be three fold.

Firstly, increased mechanical loading originating from the excessive body weight in obese patients is thought to contribute to reduced disc height (i.e. disc space narrowing), increased severity of disc degeneration and a higher number of degenerated levels in the lumbar spine.^{88–90} As described

above, alterations in the loading patterns, especially in case of coexisting degeneration of the IVD, can lead to inflammatory responses and may play a part in the observed inter-relationship between obesity, disc height and recent pain.⁸⁸

Secondly, overweight or obese patients may have a higher prevalence of LBP due to enhanced systemic expression of fat-derived inflammatory mediators. Adipocytes can produce cytokines, especially with ageing, when they undergo a phenotypic shift towards a SASP, resulting in enhanced expression of pro-inflammatory cytokines and adipokines, including leptin.^{91–93} Leptin is a noteworthy adipokine as its expression levels are not only associated with body fat content,⁹⁴ but also with pain levels or pain sensitivity⁹⁵ such as osteoarthritic pain or neuropathic pain.^{96–98} Systemic leptin is hence discussed as a biomarker for pain prediction in various pathologies^{95,99,100} and a first study published recently highlighted its potential application in predicting the duration of LBP.¹⁰¹

Thirdly, atherosclerosis or high serum lipid levels may have a negative impact on IVD nutrition by impairing the diffusion of nutrients through the adjacent vertebrae into the IVD.¹⁰² Interestingly, high cholesterol not only leads to an accumulation of fat in endplates and vertebral bodies as recently described by Sasani et al., but also results in a higher prevalence of disc degeneration¹⁰³ – likely due to nutritional deficits.¹⁰⁴

In summary, the biomechanical and biological consequences of obesity seem to contribute to IVD inflammaging (Figure 1). When taking into account that the prevalence of obesity has almost doubled over the past 30 years, this mechanism is likely to gain increasing importance in the years and decades to come.¹⁰⁵

A clinician's perspective

Until today, clinicians are predominantly guided by the patient history, as well as by signs and symptoms in combination with neuroradiological imaging, especially magnetic resonance imaging (MRI). Neurosurgeons and orthopedic spine surgeons are trained with a mechanistic understanding of the prevalent pathologies. Therefore, mechanical approaches are usually offered to patients suffering from disc pathologies. This may include selective microsurgical removal of space occupying disc material, decompression of the spinal canal or in some cases fusion of the degenerated segment.

This review article shall help to increase the awareness that – aside from mechanical factors – local inflammation and specifically inflammaging play a crucial role in disc pathologies, including DDD. The pathological mechanisms may differ depending on the pro-inflammatory profile, likely reflected in the degree of pain experienced by patients.¹⁰⁶ This has indeed a strong potential to change clinical practice from diagnosis to treatment.

Current efforts aim at combining technological developments with advancements in biology (including inflammation),

thereby building the foundation for improved diagnosis. This will not only be limited to improved MRI analysis,¹⁰⁷ but may also entail tracing¹⁰⁸ and assessment of biomarkers.^{109,110} Furthermore, a precise diagnosis will allow for more personalized treatments, for example through neutralization of specific cytokines.¹¹¹ In the future, combination therapies that not only modulate inflammation, but also restore the ECM can be envisioned possibly by combining pharmaceuticals with, for example, stem cell application.¹¹² Stem cells may not only counteract the degeneration-associated loss in ECM due to their anabolic function, but may also furthermore contribute to modulating inflammation via their anti-inflammatory and immune-modulatory capacity.¹¹³ Gene therapy or genome editing (such as CRISPR/Cas) could be used to mobilize the host cells and potentially provide long-lasting results.^{114,115}

This review clearly demonstrates that the mechanism of inflammaging is highly complex. Despite recent speculations on the role of *P. acnes* infection in inflammation and pain development in the IVD, biology-driven treatments cannot solely rely on the use of antibiotics to combat low-grade infection with *P. acnes* bacterium. Future research will be needed to better understand the interaction, crosstalk and association between the numerous cytokines involved in inflammaging and their role in the development of DDD and other disc pathologies. Increased knowledge will be crucial for the development of effective – and potentially personalized – molecular treatments targeting inflammaging.



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