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REVIEW ARTICLE

Mechanical loading of the intervertebral disc: from the macroscopic to the cellular level

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Abstract
Purpose Mechanical loading represents an integral part of intervertebral disc (IVD) homeostasis. This review aims to summarise recent knowledge on the effects of mechanical loads on the IVD and the disc cells, taking into consideration the changes that IVDs undergo during ageing and degeneration, from the macroscopic to the cellular and subcellular level.
Methods Non-systematic literature review.
Results Several scientific papers investigated the external loads that act on the spine and the resulting stresses inside the IVD, which contribute to estimate the mechanical stimuli that influence the cells that are embedded within the disc matrix. As disc cell responses are also influenced by their biochemical environment, recent papers addressed the role that degradation pathways play in the regulation of (1) cell viability, proliferation and differentiation and (2) matrix production and turnover. Special emphasis was put on the intracellular-signalling pathways, as mechanotransduction pathways play an important role in the maintenance of normal disc metabolism and in disc degenerative pathways.
Conclusions Disc cells are exposed to a wide range of mechanical loads, and the biochemical environment influences their responses. Degeneration-associated alterations of the disc matrix change the biochemical environment of disc cells and also the mechanical properties of the disc matrix. Recent studies indicate that these factors interact and regulate disc matrix turnover.

Keywords Intervertebral disc mechanobiology · Spinal loads · Intradiscal pressure · Degenerative environment · Mechanotransduction

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Introduction

To maintain erect posture and to allow motion of the upper body, high loads are developed by the musculature of the back and exerted on the lumbar spine. The IVD is, therefore, a loaded environment, in which the cells are subjected to mechanical stimuli, such as tensile, compressive and shear stresses and strains. These stimuli influence the metabolism and activity of the cells in the disc matrix.

Intervertebral discs act as the joints between the bony vertebrae and provide the spinal column with mobility and flexibility. Their complex structure is an optimal adaptation to the main mechanical functions of the disc, such as transmission of compressive loads through the spine, bending and twisting.

These complex mechanical functions can be explained by both the morphological structure and the biochemical composition of the disc matrix, which are adapted to these functions. IVDs have a central gellous tissue zone, the nucleus pulposus (NP) that is surrounded by the fibrous lamellae of the annulus fibrosus (AF). At the upper and lower border to the adjacent bony vertebrae of each disc are

the cartilage endplates (CEP) with the adjacent subchondral bone. Each of these tissue regions, which are different with regard to structure and cellular composition, play an important role in the physiological and biomechanical function of the motion segments.

This article defines the external and internal loads on the IVD by summarising recent knowledge of the literature and own studies supported by EU-FP7 project Genodisc. Firstly, this article reviews scientific literature investigating the external loads that act on the spine and the resulting stresses inside the IVD, with special emphasis on the comparison between healthy and degenerated discs. All these data contribute to estimate the mechanical stimuli that influence the cells that are embedded within the disc matrix.

The second part of this article summarises recent knowledge of disc cell responses to mechanical loading. A special focus is to summarise previous and recent findings on disc cell responses to mechanical loads in an altered biochemical environment due to degeneration and ageing. In addition, recent literature on the type and intensity of signalling pathways that play a role in the regulation of viability, proliferation, differentiation and matrix production by IVD cells is summarised with special consideration of the role of the biochemical environment.

There are several recent reviews in the literature that give a very comprehensive overview on disc mechanobiology and served also as a reference material for the present article [28, 29, 46, 92]. It is not our intention to summarise and repeat concepts that are already mentioned there. However, the purpose of the present article is to review how age-related and degenerative changes of the disc environment influence and alter disc responses to loading on the disc organ and cellular level to understand how disc mechanobiology is altered in the pathogenic pathway of degeneration.

External and internal loads on the macroscopic level

External loads on the spine

The type and magnitude of the spinal loads are peculiar to the human species, due to the profound evolutionary changes in the human spine anatomy and musculature in comparison with quadruped mammalians after acquisition of the erect posture. Despite some similarities even great apes have an unbalanced upright position which can be sustained only with significant muscular effort and for short periods of time, in marked contrast with the ergonomic and balanced upright posture of the human spine. The profound evolutionary changes in human spine anatomy and musculature that have enabled erect posture are believed to be related to the higher incidence of spinal pathologies in humans [39].

External loads acting on the spine are related to body weight, including inertial effects and the muscular forces necessary to maintain equilibrium and allow for motion. In the standing position, the centre of gravity of the upper body lies in front of the spine, while the vertical plumb line passing through C7 is more posterior (Fig. 1) and generally intercepts the endplate of the sacrum in a well-balanced spine [39]. To balance the flexion moment due to body weight, thereby avoiding anterior collapse of the rib cage, the posterior spinal muscles exert a force [24]. This muscular action sums up to the body weight, resulting in high compressive loads acting on the spine. Keeping and changing different postures [87], carrying weights and body motion further increase the spinal loads [13] and introduce more complex stress components in addition to pure compression.

Spinal loads cannot be measured directly in vivo and should, therefore, be estimated by indirect methods, e.g. calibrated strain gauges mounted on spinal fixation devices. To date, instrumented posterior rods [83, 86, 102] and

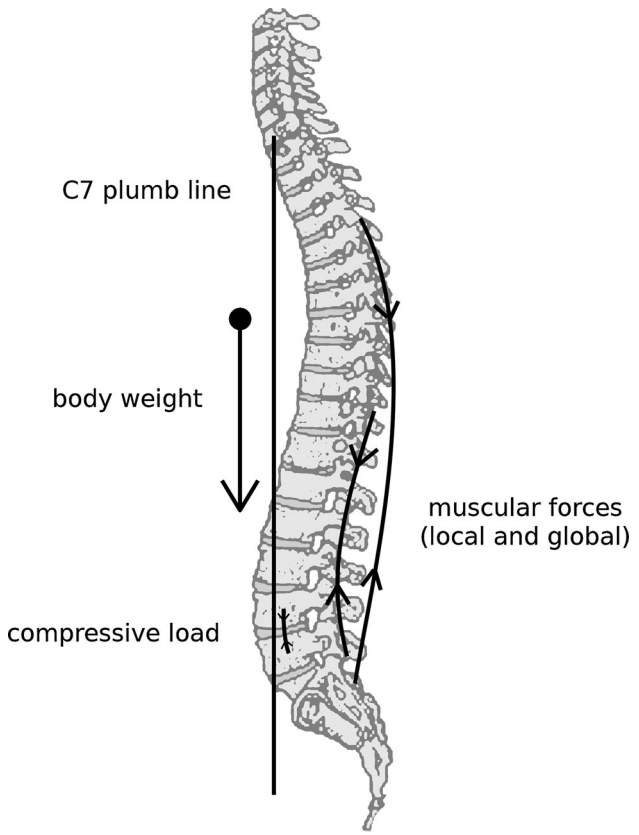


Fig. 1 Sagittal balance of the spine. The centre of gravity of the upper body lies in front of the spine, while the vertical plumb line passing through C7 is more posterior. The muscular forces necessary to maintain equilibrium sum up to the body weight, resulting in high compressive loads acting on the spine

cages for vertebral body replacements [84, 85, 88] communicating with an external console via telemetry, have been used to assess the spinal loads in different motions and daily activities. Despite the inherent limitations of this approach, e.g. related to the influence of the fixation itself on spinal biomechanics and the load sharing between the instrumentation and the native spinal structures, this approach has allowed for the estimation of an extensive set of force and moment values acting in the different anatomical planes.

Another approach for the calculation of spinal loads, developed by Wilke et al. [102], was based on the integration of in vivo intradiscal pressure data (Fig. 2) and in vitro tests simulating equilibrium in specific postures. Results were in good agreement to those measured with instrumented fixators. A similar but less refined method was used previously by Sato et al. [90], who estimated an axial load of 800 N acting in the lumbar spine during standing and of 1,000 N during sitting, based on in vivo intradiscal pressure measurement.

Optimization-based mathematical models have also been widely employed to estimate spinal loads, for both various static postures and body motion [1, 11, 25]. These models can be easily coupled with motion analysis and electromyographic data [4, 17]. They could also overcome the described limitations of the measurements with the instrumented spinal fixators, but at the price of introducing modelling assumptions and the need for validation.

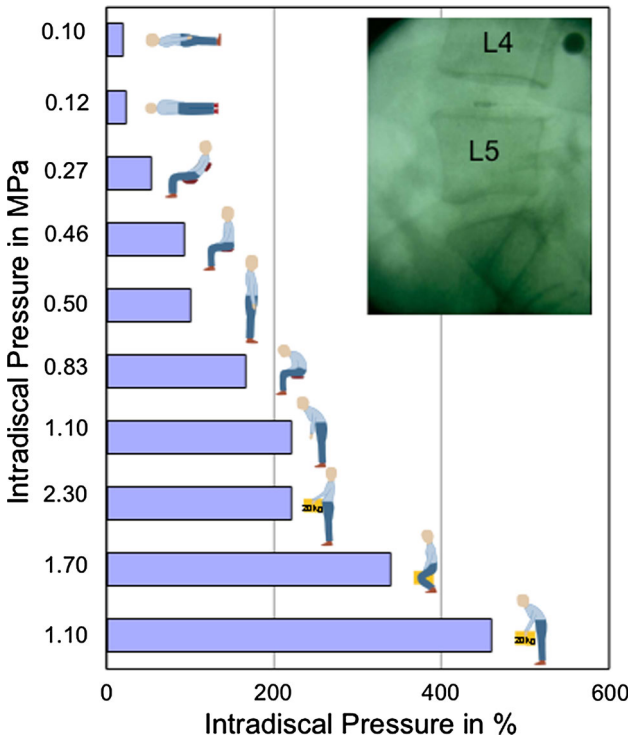


Fig. 2 In vivo values of intradiscal pressure in different postures and daily activities, measured with a pressure sensor implanted into the disc L4/5 of a volunteer [82]. The intradiscal pressure was measured in prone position (0.1), side posture (0.12), and in different sitting and standing positions (with or without carrying a weight) as shown by the simplified person above each bar

Stresses in the intervertebral disc

External loads on the spine result in intense stresses that act on the IVD. Due to the inherent inhomogeneous nature of the disc, stresses are irregularly distributed and peculiarly different in the nucleus and in the annulus.

Due to the high water content of the NP, the stress is predominantly hydrostatic and can, therefore, be well characterised by a pressure value [2]. This intradiscal pressure has been measured in vivo by means of needle pressure transducers in healthy subjects performing various daily activities [58, 90, 101]. A baseline intradiscal pressure value around 0.1–0.2 MPa was measured in supine rest, due to the combined effect of muscle loads and osmotic potential of the disc. During standing pressure, values around 0.5 MPa were measured [101]. Marked pressure increases were found for various activities, up to a peak of 2.3 MPa while carrying a weight in a flexed position. Due to recent findings discouraging the use of needle disc puncture due to the risk of disc degeneration initiation [9], new experimental campaigns on a wider number of healthy subjects should not be expected in the future.

In vitro experiments have been carried out to measure the spatial stress distribution along the midsagittal diameter of the IVD, usually named "stress profile" (Fig. 3) [55]. These experiments were limited by the fact that the applied loads were simplified in comparison to the in vivo condition, but they provided useful and unique data about the different load-bearing function of the annulus with respect to the nucleus. Stress profilometry uses a calibrated pressure transducer mounted on a needle that is able to estimate the compressive stress in the sagittal and transverse planes if appropriately rotated [55]. However, tensile and shear

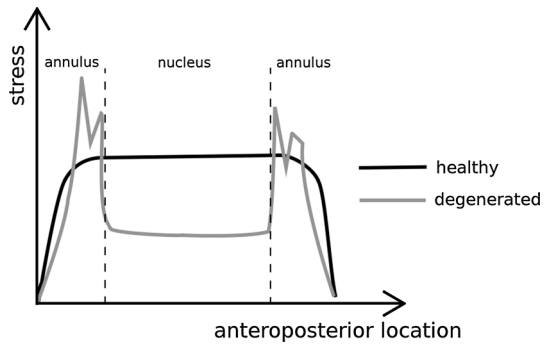


Fig. 3 Representative stress profiles in the sagittal midplane of cadaveric lumbar IVDs in healthy and degenerative conditions

stresses cannot be measured with this technology. Experiments were shown to be reproducible and results linearly scaled up with the applied load [54]. Considering a healthy disc (reviewed in [2]), stress showed to be hydrostatic and uniform in the nucleus and in the inner portions of the annulus, but direction-dependent and decreasing in the outer annulus (Fig. 3). Stresses were found to be dependent on posture, with the anterior or posterior part of the disc being more stressed in flexion and extension, respectively. In the healthy lumbar nucleus, stresses are uniform regardless of posture.

Internal displacements and strains of the intervertebral disc under application of physiological loads have also been investigated. O'Connell et al. [65] evaluated the strain field of human lumbar disc specimens subjected to a compressive load in combination with fixed flexion, extension and neutral positions, by means of magnetic resonance imaging and image correlation. The authors observed non-homogeneous strains, with peaks in the endplates at the fibre insertion sites and significant radial strain of the inner annulus, depicting a possible displacement of the nucleus in compression.

Changes in external loads due to ageing and degeneration

The IVD degeneration at a single level or in a short spinal segment should not be expected to drastically change the external loads acting on the spine. However, severe degenerative phenomena may alter the sagittal and/or coronal balance of the spine and, therefore, alter the loads acting on the single motion segments. Disc degeneration and facet arthritis may induce loss of the curvature of the lumbar spine (lordosis), resulting in anterior sagittal imbalance [39]. This may induce compensatory mechanisms related to altered muscle activation (Fig. 1), such as increase of curvature of the upper lumbar spine, decrease of the thoracic kyphosis and retrovision of the pelvis (decreased sacral slope), and knee flexion in the most severe cases [6]. The increased lordosis of the adjacent segment, i.e. hyperextension, may result in some cases in an initiation of degenerative phenomena in these segments, namely compensatory discopathy [6].

Changes in internal stresses due to ageing and degeneration

The IVDs showing signs of degeneration are subjected in many cases to a drop in the fluid content, which is replaced by fibrotic tissue [7]. This dehydration, together with the observed increased collagen cross-linking, may lead to a less uniform stress distribution inside the disc, in both the nucleus and the annulus [3]. Stress profilometry has shown that degenerative changes usually induce local stress concentrations along the midsagittal line (Fig. 3). The nucleus becomes depressurised and multiple stress peaks appear in the annulus, especially in the posterior region, which may be related to annular tears and disruptions. Due to the so-called "stone-in-the-shoe" principle, these stress concentrations are believed to be responsible for discogenic pain [2]. Conversely, ageing discs without degenerative signs usually do not, or only in a minor way, show peaks in the stress profile [3]. It should, however, be noted that stress profilometry in degenerated and ageing discs is technically more demanding and less reliable than in healthy discs [54]. These findings obtained with stress profilometry were corroborated by investigations conducted with magnetic resonance imaging and image correlation [66].

Mechanobiology of the disc

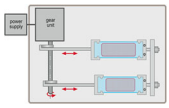
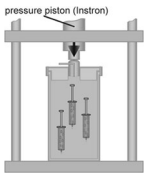
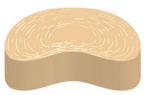
Loads acting on a cellular level

From a mechanical point of view, cells embedded in the different disc areas are exposed to wide ranges of mechanical loads: in the central NP, which has a very high water content, the predominant mechanical load is hydrostatic pressure. In contrast, annulus fibrosus cells are exposed predominantly to tensile strain. The discs are enclosed axially by the cartilaginous endplates at the interface between the disc and the adjacent vertebrae. This tissue has a cartilage-like structure and is predominantly influenced by compression.

The IVD as a load-bearing structure is exposed to daily recurring loads [14]. The biological response to these influences varies according to the IVD cell type and the type, magnitude, frequency and duration of loading [41, 92].

The loads that the cells in the different disc tissue areas are exposed to strongly depend on the mechanical properties of these tissue areas. As the disc tissue is bulged during the different exercises of the spine, the concentric lamellae of the annulus fibrosus underlie alterations of tension and pressure, which influence the cells that are embedded within the annulus lamellae [91]. Thus, the predominant physiological stimulus to the cells in the annulus lamellae is tensile strain and shear, both within and between lamellae. Focussing on cells in NP tissue, the major types of in vivo loading are compressive and shear stress, as well as hydrostatic pressure due to the swelling properties of NP tissue [64]. Nevertheless, studies about internal deformation of the disc showed that nucleus cells may also be subjected to tensile and shear deformation during compression of the disc, whereas annulus cells may also be compressed, especially in the anterior annulus

Table 1 Disc mechanobiology studies

Model	Mechanical stimulus	Species	Reference (examples of studies)
Monolayer 	Cyclic strain	Human	Gilbert et al. [19]
			Neidlinger-Wilke et al. [60]
			Wuertz et al. [104]
		Calf	Li et al. [44]
		Rabbit	Rannou et al. [78]
		Rat	Sowa et al. [94]
			Miyamoto et al. [57]
			Sowa et al. [93]
3D-culture 	Hydrostatic pressure	Human	Le Maitre et al. [40]
			Mietsch et al. [56]
			Rinkler et al. [81]
		Calf	Neidlinger-Wilke et al. [61]
		Pig	Kasra et al. [35]
		Rabbit	Kasra et al. [34]
	Compression	Calf	Korecki et al. [37]
		Pig	Fernando et al. [15]
			Salvatierra et al. [89]
Organ culture 	Compression	Human	Le Maitre et al. [42]
		Calf	Haglund et al. [23]
			Illien-Juenger et al. [32]
			Korecki et al. [38]
			Lee et al. [43]
		Sheep	Walter et al. [99]
			Gantenbein et al. [18]
		Pig	Illien-Juenger et al. [31]
			Oshima et al. [68]
Animal models 	Compression	Rabbit	Guehring et al. [22]
		Rat	Omlor et al. [67]
			Grivas et al. [21]
			Iatridis et al. [30]
			MacLean et al. [48]
			Nakamura et al. [59]
			Stokes et al. [95]
			Yurube et al. [106]
		Mouse	Court et al. [12]

Examples of experimental studies investigating mechanical influences on disc cells, disc organ cultures or discs in their native in vivo environment. The different mechanical stimuli and species used in the cited studies are shown

fibrosus [65]. Indeed, all these loading types will occur simultaneously leading to very complex loading combinations in vivo.

Several in vitro studies have been published investigating cell responses to loads using isolated cells in monolayer, three-dimensional culture systems or in vivo systems. Table 1 shows some representative studies applying mechanical loads.

In 2002, Lotz et al. [46] reviewed results of the in vivo disc-loading model. Experiments using static compression in a mouse-tail system revealed that static compression leads to disc degeneration in a dose-dependent fashion and that the mechanical response of the disc changes with degeneration. Furthermore, the authors reported experiments using computational models and the application of cyclic loading, which demonstrated that dynamic stimulation is able to balance anabolic and catabolic processes in a time, frequency and load-depending manner. Similar results were obtained using a mechanical stimulation in a rat-tail model [30]. Several studies demonstrated that overload as well as immobilisation caused disc degeneration by affecting mRNA expression levels [5, 37, 38, 47, 96, 103]. The results of these in vivo studies suggest the existence of a window of loading ranges within which no, or only little, changes in matrix turnover occur, thereby supporting a balance in matrix turnover. Excessive loading,

however, supports up-regulation of matrix-degrading enzymes and might, therefore, rather be a stimulus for matrix degradation.

In 2004 and 2006, Setton and Chen [91, 92] reviewed the diverse biological responses to mechanical influences which IVD cells exhibit depending on loading type, magnitude, duration and cell type in combination with environmental changes during disc degeneration. Furthermore, they emphasised that the majority of what is known about disc mechanobiology pertains to the regulation of extracellular matrix production and degradation. However, little is known about the mechanisms transducing mechanical stimuli to a cellular response. Mechanisms like Ca^{2+} influx and the reorganization of cytoskeletal elements are discussed. In a review in 2010, Hsieh and Twomey [28] focused on the cell mechanobiology of the immature NP and the interlamellae annulus fibrosus and their potential contribution to health and function of the IVD.

Several investigators applied external loads to IVD cells in vitro in three-dimensional cultures to analyse IVD cell reactions to mechanical stimulation [34, 35, 60, 63, 80] and reported positive influences on matrix synthesis. However, our own studies pointed out that the chemical environment has greater effects on cell reactions than mechanical stimulation [61, 81, 104]. Positive influences of hyperosmotic conditions on cellular metabolic activity and matrix gene expression have also been demonstrated in a rabbit IVD culture system [27]. A more recent study investigated cyclic strain effects on the organisation and expression of cytoskeletal elements on bovine IVD cells [44]. The authors showed an F-actin reorganization, as well as an increase in β-tubulin, but an inhibition of vimentin expression in annulus fibrosus cells due to mechanical stimulation. NP cells were less responsive. As cytoskeletal elements are involved in mechanotransduction this could be a mechanism of disc cells to differently respond to mechanical influences at variations of the osmotic environment. This could both play a role in the diurnal balance of disc matrix turnover and also contribute to the regulation of pathologic matrix degradation in degenerated discs. Another study comparing human annulus fibrosus cells from healthy and degenerated tissue and the involvement of interleukins IL-1 and IL-4 in the response to cyclic strain demonstrated differences in signal transduction [19]. Whereas IL-1 and IL-4 seem to be involved in mechanotransduction in healthy tissue, there is no involvement of these factors in degenerated tissue, indicating different mechanisms. Furthermore, it was shown recently that there is no reduced response capacity to mechanics comparing porcine annulus fibrosus cells from young and old animals [10]. Basal mRNA levels for collagen type 2 and aggrecan are lower in older animals but the capability to respond to mechanical loads is unaltered.

Cellular cytoskeleton, in parallel to its supporting function, plays a major role in mechanosensing and in mechano-signalling pathways [44]. Cytoskeleton is a dynamic structure characterised by a continuous reorganization as to fulfil its mechanosensing role in a continuously changing environment. Especially in the IVD, changes in the cytoskeleton are not only important as to respond to mechanical deformations, but also to osmotic changes.

These findings point out the importance of further increasing our knowledge in understanding intracellular mechanisms of mechanotransduction pathways and they raise the question of how these signalling pathways are influenced by the degenerative environment.

Influences of the degenerative environment on disc cell responses to mechanical loading

The biochemical environment of the normal healthy avascular disc is characterised by low oxygen and nutrient supply and a quite high osmotic pressure of the proteoglycan-rich disc matrix [97]. Degeneration drastically changes disc biochemistry with a significant loss of proteoglycans that is responsible for a reduced osmotic pressure and an impaired water binding capacity of the disc matrix [98]. An impaired permeability of the endplates due to calcification can lead to a further decrease of nutrient supply and a fall in pH because the metabolites of anaerobic glycolysis accumulate in the disc matrix [75, 82]. In a recent study, Boubriak et al. [8] concluded that degenerative changes in blood vessel supply in the vertebral bodies as well as changes in the endplate architecture influence cell density in the intervertebral discs. This alteration may be influenced by changes in the biochemical environment of the disc cells. In the NP of normal healthy discs, an average osmolarity around 400 mOsm can be considered as normal; however, there are also diurnal variations of disc osmolarity, because of reversible hydration and dehydration of the disc. The purpose of our initial studies was to investigate the influence of mechanical loads on disc cells in such an altered biochemical environment. It was shown that IVD cells are very sensitive towards alterations of their biochemical environment [61, 81, 104]. Human IVD cells increased the expression of aggrecan and collagen type 2 under increasing osmolarity conditions that are above the estimated average level of 400 mOsm. In contrast, collagen type 1 expression was inhibited by high osmolarity (500 mOsm). Mechanical stimulation had only minor influences on gene expression of disc cells. However, the application of mechanical loads either up- or down-regulated collagen type 2 expression depending on the osmotic environment [104].

A simulation of low glucose, low pH and decreased osmolarity (300 mOsm) rather impaired the expression of

matrix-forming proteins and increased the expression of matrix metalloproteinases (MMPs) [61]. The greatest effects were seen for decreases in glucose concentration and pH, whereas low oxygen had only little influence. The influences on disc cell responses to mechanical loads were quite low with an alteration of some of these effects at the different environmental conditions [61, 81, 103].

Further studies investigated the effect of osmotic fluctuations on the proliferation and cell cycle regulation of NP cells. It has been shown that high osmolality has an anti-proliferative effect by delaying the cells at the G2/M and G0/G1 phases of the cell cycle. The G2/M arrest is a rapid response of the cells dependent on p38 mitogen-activated protein kinase (MAPK) activation, while the p53-mediated G1 arrest follows a hypertonicity-induced DNA damage [51].

In addition, it has been found that the hyperosmolality-provoked DNA damage and the responses of NP cells induced by this genotoxic stress most probably originate from cell volume alterations mediated by hypertonicity and not from increased intracellular ionic concentration [53].

Furthermore, it has been reported that exposure of cells to high osmolality firstly, restrained novel DNA synthesis induced by platelet-derived growth factor (PDGF) or insulin-like growth factor 1 (IGF-1) and secondly, reduced extracellular signal-regulated kinase (ERK) and Akt activation stimulated by serum or isolated growth factors, indicating that hyperosmolality retains a low proliferation rate of the IVD cells, while hypo-osmotic conditions that characterise degenerated discs may be more permissive for increased cellular proliferation [52, 72].

Another important aspect of the progressive disc degeneration is that at later and more severe stages also the ingrowth of nerves and blood vessels has been observed [33]. Disc neo-vascularization and innervation might further alter the biochemical environment in the disc tissue in association with a number of cytokines and growth factors (pleiotrophin, inflammation cytokines) that are assumed to influence disc matrix turnover. In addition, these factors may influence disc cell responses to mechanical load—an important and under-investigated aspect that is important for the understanding of the pathomechanism of disc degeneration and for the development of biological therapeutic strategies for degenerative spinal disorders.

Mechanotransduction

Several lines of evidence clearly indicate that mechanical stimulation plays a critical role in the development and maintenance of the cytoskeleton. The process by which cells sense mechanical loading and convert it to biochemical signals is termed mechanotransduction. It contains three coupled procedures, i.e. mechanosensing, activation of signal transduction pathways and effector-cell responses [16, 69, 70, 76]. All these processes have been well studied in both osteoblasts and chondrocytes and common mechanisms have been revealed which are expected to be similar in disc cells. The major mechanosensors seem to be transmembrane calcium ion channels, receptor tyrosine kinases (RTK) and integrins. However, the latter are part of a continuum including extracellular matrix components and focal adhesions, as well as cytoskeletal elements. Mechanosensors activate intracellular signalling pathways, with the most important being MAPK, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), as well as other signalling molecules, such as protein kinase A (PKA), inositol trisphosphate (IP3), nitric oxide (NO) and β-catenin, among others. In addition, mechanical stimulation can provoke the secretion of growth factors, such as PDGF, IGF, transforming growth factor-beta (TGF-β) or fibroblast growth factor (FGF) that can also stimulate several pathways, e.g. MAPK, PI3K/Akt or Smads, and thus regulate cellular homeostasis. The combined activation of the above-mentioned pathways regulates the expression and activation of transcription factors. Among these, most important for osteoblast and chondrocyte differentiation are runt-related transcription factor 2 (Runx2)/core-binding factor subunit alpha-1 (Cbfa1), Osterix, Sox9 and activator protein-1 (AP-1) [20, 36, 49, 71, 108].

As already mentioned, mechanical forces represent an integral part of IVD physiology. However, information on the pathways involved in this mechanotransduction is rather limited compared to the knowledge of mechanotransduction in bone, and, in many cases, experimental data only indirectly support the implication of certain transduction pathways in the effects of mechanical stress. For example, the involvement of certain integrin(s)—the authors suggest integrin α5β1—in the compressive loading-induced down-regulation of aggrecan gene expression in human NP cell cultures (in alginate constructs) was deduced from the reversal of aggrecan expression in cultures incubated with an RGD-inhibitory peptide prior to compression [41]. A signalling entity clearly implicated in mechanotransduction in IVD is NO. Changes in hydrostatic pressure have been shown to alter proteoglycan synthesis in human IVD tissue samples through NO production [45]. Furthermore, NO production has been shown to be induced in rabbit annulus fibrosus monolayer cell cultures in a period of 8–24 h following cyclic tensile stretching and to participate in the stretching-provoked inhibition of proteoglycan synthesis [79]. NO has also been implicated in the cyclic tensile stretching-induced apoptosis in rat annular cells through endoplasmic reticulum stress [107]. In another study, cyclic tensile stretching has been shown

to lead rabbit annular cells to apoptosis through the mitochondrial pathway, an effect reversed by the use of a caspase-9 inhibitor [77].

The functional effects of mechanical stress on IVD cells allow some speculations regarding the implication of several transduction pathways. For example, the fact that cyclic tensile stretching regulates the expression of pro-inflammatory cytokines, such as interleukins and tumour necrosis factor-alpha (TNF-α) in IVD cells [19, 57] warrants the speculation that the NF-κB and the p38-MAPK pathways are also affected [105]. The NF-κB and the MAPK pathways are also implicated in the regulation of various MMPs, which have been shown to be induced in response to mechanical stimuli in IVD cells [26, 62, 100]. Furthermore, the reported increase in the DNA synthesis rate of IVD cells subjected to cyclic tensile stretching [50] implies the contribution of one or more growth factors to this response. IVD cells have been shown to produce and respond to several growth factors [52, 72–74] and the MEK/ERK and PI3K/Akt pathways are of major importance for these responses. Actually, our unpublished observations support the idea that MAPK and Akt kinases are activated in response to cyclic tensile stretching of human annulus fibrosus cell cultures.

Conclusion

Disc cells are exposed to a wide range of mechanical loads and the biochemical environment influences their responses. Degeneration-associated alterations of the disc matrix change the biochemical environment of disc cells and also the mechanical properties of the disc matrix. Recent studies indicate that these factors interact and regulate disc matrix turnover. Not all aspects of alterations of the biochemical and mechanical environment of the disc cells can be taken into consideration in vitro and ex vivo experimental models, which can only be rather simplified compared to the complex in vivo conditions. However, the simplified models are extremely useful in shedding light in the reciprocal interactions between mechanical loading and disc homeostasis. Accordingly, these studies are important for a better understanding of the physiology of normal and degenerated discs and for the development of successful treatment strategies of disc degeneration.

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Conflict of interest None.

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