Epigenetic Factors Related to Low Back Pain

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Low back pain (LBP) is one of the most common causes of pain and disability. Treatment and interventions for acute and chronic low back pain often fail to provide sufficient levels of pain relief, and full functional restoration can be challenging. Considering the significant socio-economic burden and risk-to-benefit ratio of medical and surgical intervention in low back pain patients, the identification of reliable biomarkers such as epigenetic factors associated with low back pain could be useful in clinical practice.

low back pain epigenetics spine

1. Introduction

Low back pain (LBP) is pain referred to the lumbar region of the spine and is one of the most common causes of pain, disability, and social cost in Italy and worldwide [1]. More than 40 ± 20% of the population suffers from LBP at least once in their lifetime; each year, up to 35% of adults experience this symptom, and its prevalence worldwide has increased more than 15% in 10 years [2][3]. The global prevalence of low back pain that limits daily activities was estimated at 7.3% in 2015, accounting for about 540 million people [4].This symptom is a leading cause of global years lived with disability [5], with other musculoskeletal conditions such as arthrosis, neck pain, depressive disorders, and migraine joining it in the top 10, with a lifetime prevalence of >80% [6]. Moreover, it represented the leading cause in 126 of the 195 countries and territories investigated in the GBD 2017 disease and injury incidence and prevalence study [5].

Low back pain includes three distinct sources of pain: axial, radicular, and referred [7]. Axial pain occurs in the vertebral or lumbosacral region, while radicular pain manifests as leg pain with metameric distribution secondary to the irritation of the spinal roots or the posterior ganglion of the spinal roots. Referred pain occurs in a region distant from its source but without metameric distribution [7].

Low back pain can present as acute (when the pain episode ends within 6 weeks), subacute (between 6 and 12 weeks), and chronic (beyond 12 weeks). While most non-chronic patients are acute, with self-limited pain at 6 weeks or less, 10–40% of patients develop symptoms that last longer than 6 weeks [8][9].

Many vertebral pathologies are involved, such as intervertebral disc (IVD) degeneration and herniation, spondyloarthropathies, central and foraminal stenosis, spondylolisthesis, facet arthropathies, sacroiliac joint pain, primary tumors, metastases, infections, and fractures [10][11].

Extra-vertebral low back pain can be caused by urologic [12], vascular [13], gynecologic [14], intestinal [15], prostatic [16], and psychiatric diseases [2].

The medical history is crucial for guiding the diagnostic hypothesis; therefore, the physician must assess all aspects, from family members to the type of work, from psychological behavior to socioeconomic status. He must be well-informed about the work patterns (sitting, standing, bending, lifting weights, driving, etc.); the physical activities practiced (sports, hobbies, etc.); and any underlying medical conditions of the patient. Thus, the physician can direct the diagnosis of low back pain to a vertebral or extra-vertebral cause and proceed with targeted physical examination and imaging.
At present, treatment and interventions for acute and chronic low back pain often fail to provide sufficient levels of pain relief, and full functional restoration can be challenging [2][17].

Barriers to the development of non-opioid pain medications include the lack of validated targets, the paucity of diagnostic markers for pain-related conditions, and the high degree of interindividual variation in response to interventions.

The clinical courses of acute and persistent low back pain typically differ: most cases of acute low back pain recover completely within 4–6 weeks, but persistent low back pain has a poor prognosis, with recovery unlikely.

If pain becomes persistent or chronic, an assessment of pain intensity, associated disability, and the patient's general condition needs to be carried out. This can be achieved via a physical examination; a detailed patient history; and, eventually, imaging.

Surgical intervention is currently the ultimate solution established for patients with severe chronic low back pain or with conservative treatment failure [17]. It can achieve powerful pain relief but it is characterized by high morbidity and intra- and/or post-operative complications [17].

Like many other conditions, low back pain is influenced by genetic and environmental factors [18][19][20]. Studies of monozygotic and dizygotic twins have evidenced that low back pain has a familial component and that environmental factors are responsible for the variability in pain perception [19]; these include physical and psychological stress, physically demanding work, anxiety, and depression. Moreover, symptoms of anxiety were associated with a higher prevalence of LBP in the total sample analysis [19].

The interaction between the environment and genetics leads to regulatory mechanisms based on gene expression modulation, both via overexpression and gene silencing. Indeed, in eukaryotes, genetic expression is dynamically regulated at the chromatin level by epigenetics, defined as the reversible and heritable changes in gene expression without alterations in the underlying DNA nucleotide sequence.

Epigenetic markers principally include DNA methylation and histone post-transcriptional modifications at specific aminoacidic residues (such as methylation, acetylation, phosphorylation, ubiquitination, and sumoylation) [21]. Epigenetic regulation acts through variations in chromatin accessibility influencing DNA transcription and gene

expression [22]. In the vast majority, but not all, cases, DNA methylation corresponds to gene silencing, whereas histone modifications can promote both gene activation or silencing (e.g., lysine acetylation providing transcriptional activation and lysine methylation inducing both activation and repression depending on the histone protein and genomic region).

The role of epigenetics in many pain conditions has been widely described in recent years as a process underlying the development of pathologies such as fibromyalgia [23][24], chronic postoperative pain [25], and low back pain [6].

2. Methylation-Regulated Epigenetic Markers Investigated on Intervertebral Disc Tissue

Tajerian et al. [26], in their retrospective case–control study, investigated the methylation status of the SPARC (Secreted Protein Acydic and Cystein Rich) protein promoter in intervertebral disc DNA from patients with chronic low back pain, controls, and preclinical models. MRI images and ODI scores from patients and pain-free controls were collected to objectively describe the clinical features. SPARC promoter methylation was analyzed by bisulfite mapping in chronic LBP patients and pain-free controls, and higher pain levels and a higher degree of IVD degeneration were found in lumbar MRI compared to controls ($p < 0.001$). Moreover, five out of the thirteen sites of the SPARC promoter had higher levels of methylation in patients compared to controls ($p < 0.05$). SPARC is known to affect collagen fibrillogenesis, bone remodeling, and wound healing [27]. In human IVDs, decreased SPARC expression has been linked to aging and degeneration [28]. Additionally, the targeted deletion of the SPARC gene causes accelerated disc degeneration in old mice and behavioral phenotypes that are similar to chronic LBP in humans. The long-term downregulation of SPARC expression may be crucial in the development of chronic LBP, according to genetic data from mice and clinical observations of its downregulation in humans with IVD degeneration [29][30][31]. This is consistent with decreased protein expression as a function of age and disc degeneration. The study suggests that the age-dependent methylation of the SPARC gene promoter induces SPARC silencing, thus contributing to disc degeneration and low back pain.

In an interesting study, Jiang et al. [32] evidenced the regulatory effect of EZH2 (a histone methyltransferase enhancer) on the expression of SOX9, a cartilage growth and transcriptional factor gene required for chondrogenesis. SOX9 is a disc-degeneration-related gene, preventing chondrocyte hypertrophy and thus inhibiting endochondral ossification, a process seen in IVD degeneration. EZH2's function is to suppress the expression of various genes, including SOX9, through Histone3 Lysine methylation (H3K27me3). EZH2 inhibition reduces the repressive marker H3K27me3, thus upregulating SOX9 expression and slowing down IVD degeneration, suggesting EZH2 as a possible target to slow down IVD degeneration.

A GWAS analysis of DNA methylation associated with human intervertebral disc degeneration (IVD degeneration) was performed by Ikuno et al. [33] on advanced compared to early degenerated nucleus pulposus tissues obtained from patients undergoing spine surgery for low back pain. They observed different methylomes in the two groups, with the hypermethylation of most loci in advanced degeneration cases, suggesting the involvement of DNA hypermethylation with consequent gene silencing in IVD degeneration. Interestingly, three of the hypermethylated

loci (CARD14, EFHD2, and RTNKN2) are involved in the regulation of the NFk-B pathway, known to play a pivotal role in inflammation. The silencing of these gene would contribute to NFk-B activation by inducing the transcription of proinflammatory genes such as TNF-, IL-1, IL-6, and IL-8, as well as disc degeneration by upregulating the expression of matrix-degrading enzymes such as MMPs and ADAMTSs.

Nucleus pulposus cell (NPC) senescence is a critical process for IVD degeneration and, consequently, low back pain. Li et al. [34] observed that the upregulation of ALKBH (a demethylase of N6-methyladenosine in RNA molecules) can induce NPC senescence. Under the epigenetic regulation of histone H3K9me3, ALKBH5-mediated RNA demethylation could induce DNMT3B methyltransferase, which in turn methylates and consequently suppresses the expression of the E4F1 transcription factor, thus contributing to cell senescence through gene silencing.

3. Methylation-Regulated Epigenetic Markers Investigated on Peripheral Blood

Studies on epigenetic factors regulating LBP performed on peripheral blood cells are mostly genome-wide studies comparing global DNA methylation in patients compared to control groups. These studies frequently highlight different global methylation patterns in patients with the involvement of different cellular pathways or single genes.

Williams et al. [35] reported for the first time a large-scale genome-wide association meta-analysis to identify variants associated with lumbar disc degeneration (LDD) in LBP patients based on a GWA meta-analysis of five Northern European cohorts. They identified a variant in the PARK2 gene associated with LDD. Data were obtained from peripheral blood cell DNA from a subset of 38 individuals (four monozygotic twin pairs, eight dizygotic twin pairs, and fourteen unrelated individuals) investigated for differential DNA methylation levels in the PARK2 (Parkinson Protein 2) promoter. The authors found a positive correlation between cgc15832436 site methylation in the PARK2 promoter and LDD ($\beta = 8.74 \times 10^{-4}$, SE = 2.49×10^{-4}, $p = 0.006$), suggesting that epigenetic regulation may influence the degeneration of intervertebral discs. PARK2 encodes a protein called parkin, a component of a multiprotein E3 ubiquitin ligase complex mediating the targeting of unwanted proteins for proteasomal degradation. In LDD patients, the hypermethylated PARK2 promoter and the related inhibited PARK2 expression can reduce proteasomal degradation, thus altering the normal cellular environment in intervertebral disc cells, with the increased degradation of intervertebral disc tissue.

The prospective cohort study of chronic pain epigenetics performed by Sukenaga et al. [36] highlighted the importance of TRPA1 (potential ankyrin 1 transient receptor) gene methylation status. The authors harvested peripheral blood samples from 12 LBP patients or postherpetic neuralgia patients and measured their pain status via DN4 (Douleur Neuropathique 4) and the SF-MPQ (Short-Form McGill Pain Questionnaire). After a whole-blood array-based methylation analysis, the authors found a significant correlation between an increase in DNA methylation level at the CpG island of the TRPA1 gene (inducing TRPA1 transcription suppression) and an increase in DN4 scores ($p = 0.001$; $r = -0.82$), which represent the diversity of neuropathic pain symptoms. The authors also described a significant correlation between a decrease in TRPA1 expression and an increase in DN4

scores (p = 0.04; r = −0.65) [37]. Increased TRPA1 promoter methylation and decreased TRPA1 expression in whole blood cells were shown to be related to a reduced heat pain threshold in an investigation of human monozygotic twins [31]. TRPA1 appears to play a pivotal role in the development of chronic pain in humans, and it is included in the functional changes of neuro-immune interactions.

Another study from Grègoire et al. [6] used a genome-wide methylation approach to search for methylation signatures in human T cells. They analyzed the methylation status of 850,000 CpG sites in women and men with chronic low back pain compared to pain-free controls. The authors revealed sex-specific DNA methylation signatures in human T cells discriminating chronic LBP participants from healthy controls. In women, the percentage of methylation at position cg07420274 was 39.5 ± 2.7% vs 49.7 ± 3.2% in the control and low back pain groups, respectively (p < 0.05), with a significant association between methylation and low back pain (OR = 1.05, 95% CI: 1.01–1.11, p = 0.03). In men, a significant association was found between LBP and cg21149944 methylation (OR = 0.89, 95% CI: 0.82–0.95, p = 0.0015), as well as cg22831726 methylation (OR = 0.89, 95% CI: 0.84–0.96, p = 0.0036). In conclusion, the authors identified a polygenic DNA methylation sex-specific score from circulating T cells with only three differentially methylated loci, whose methylation allowed the categorization of pain status. Although LBP affects both sexes, these results highlight the striking sex difference in DNA methylation signature, suggesting fundamentally different underlying mechanisms and the possibility of sex-specific epigenetic biomarkers and sex-specific therapeutic approaches.

The results of Gregoire et al. [6] were consistent with those of Dorsey et al.'s study [38], wherein the authors performed a whole-transcriptome analysis, collecting peripheral blood from pain-free individuals, acute LBP patients, and chronic low back pain patients at baseline and at 6 months. The transition from acute to chronic low back pain showed a significant upregulation of mRNAs in the blood coding for genes involved in antigen presentation pathways (MHC class I and II). MHC class II gene upregulation has been associated with other chronic pain conditions including lumbar disc herniation, low back pain, and complex regional pain syndrome.

These results were also consistent with Goodin et al.'s [27] findings, obtained from an epigenome-wide association study (EWAS) on peripheral blood DNA from chronic LBP patients compared to pain-free controls. The study aimed at understanding the differences in the DNA methylation landscape in chronic LBP patients related to efficient or inefficient conditioned pain modulation (CPM). The results suggested the existence of characteristic epigenetic signatures of efficient or inefficient CPM. The authors identified 6006 differently methylated CpG sites in the low back pain cohort, most of them hypomethylated and annotated to genes of relevance for pain such as OPRM1, CACNA2D3, and LPL. New pathways of relevance for pain were enriched only in the chronic LBP group and not in the controls, including MAPK-Ras signaling pathways, suggesting their role in chronic LBP through differential methylation (p = 0.004).

By reduced representation bisulfite sequencing (RRBS), Aroke et al. [39] compared the methylation status of non-specific chronic LBP patients to pain-free controls and found 159 differentially methylated regions, enriched in inflammatory pathways and bone maturation, suggesting the role of epigenetics in the pathophysiology of non-specific chronic LBP.

The same group investigated differences in DNA methylation levels between chronic LBP patients of different ethnicities (non-Hispanic White and non-Hispanic Black patients). They identified 2873 differentially methylated loci, many of which were annotated to genes involved in nociception and pain progression (such as Corticotropine, realizing hormone signaling, and the GABA receptor signaling pathway), possibly contributing to the more severe pain and disability observed in the non-Hispanic Black group [40].

Bortsov et al. [41] tried to characterize the molecular and cellular pathways related to chronic versus acute LBP by GWAS and found a substantial genetic contribution to chronic but not acute back pain related to genes expressed in the central nervous system. The authors performed an epigenetic analysis by evaluating SNPs in linkage disequilibrium overlapping with epigenetic features to identify genes and pathways correlated to chronic but not acute LBP heritability.

Eller et al. [42] investigated global DNA methylation and H4 histone acetylation in peripheral blood cells collected from acute and chronic LBP patients at low back pain onset. Participants were also subjected to BPI (Brief Pain Inventory) and SF-MPQ assessments and a quantitative sensory test. DNA methylation levels and H4 acetylation levels were compared to the expression of 84 candidate genes with a possible role in pain onset and modulation. The authors findings showed higher levels of H4 acetylation in participants with LBP compared to controls ($p < 0.05$, $t = 2.261$). Moreover, H4 acetylation was also positively correlated with somatosensory hypersensitivity. Global DNA methylation levels were lower in chronic compared to acute LBP patients and controls ($p < 0.05$), suggesting the role of hypomethylation in the expression of genes contributing to pain chronicity. In particular, methylation levels were positively correlated with several genes involved in pain control (CX3CR1, GCH1, P2RX, PTGES3, and TNF) and negatively correlated with IL2 expression (lower expression in chronic patients).

4. Epigenetic Regulation through microRNA Signaling

Some of the investigated LBP and epigenetics studies were dedicated to microRNAs, small noncoding RNAs that participate in the regulation of bone metabolism and osteoclast and osteoblast function [43]. These molecules are epigenetic factors involved in the control of specific molecular pathways in bone-related disorders. MicroRNA activity is expressed through the silencing of gene targets whose mRNA is complementary to the miRNA sequence.

By performing an miRNA expression profile analysis on $CD4^+$ T cells harvested from the peripheral blood of chronic LBP patients (divided into therapy responders and non-responders) and healthy volunteers, Luchting et al. [44] described *miRNA124a, miRNA150n*, and *miRNA155* as putative biomarkers of low back pain, since they were significantly upregulated in chronic low back pain patients when compared to healthy volunteers (MiRNA-124a: patients 0.79 ± 0.63 vs. healthy volunteers 0.30 ± 0.16, $p < 0.001$; miRNA-150: patients 0.75 ± 0.21 vs. healthy volunteers 0.56 ± 0.20, $p = 0.025$; and miRNA-155: patients 0.55 ± 0.14 vs. healthy volunteers 0.38 ± 0.16, $p = 0.017$). Moreover, after a multidisciplinary treatment program, patients who responded to the treatment showed only an increase in *miRNA124a* expression (before treatment 0.54 ± 0.26 vs. after treatment 1.05 ± 0.56, $p = 0.007$), suggesting that *miRNA-124a* upregulation is associated with therapy response.

In X. D. Fa et al.'s study [45], the miR-133a-5p/FBXO6 axis was shown to be involved in IVD degeneration, one of the main contributors to LBP. MiR-133a-5p expression aggravates IVD degeneration by targeting and inhibiting FBXO6, a protein highly expressed in healthy discs and progressively downregulated in relation to disc degeneration severity. FBXO6 suppression inhibits cell proliferation, enhances apoptosis, suppresses extracellular matrix synthesis, and accelerates extracellular matrix degradation.

In summary, the hypomethylation of some DNA regions; the hypermethylation of some gene promoters (*SPARC, PARK2*); and the overexpression of some miRNAs (*miR-124a, miR-150, miRNA155,* and *miR133a-5p*) are associated with low back pain and its chronic or acute forms.

References

1. Hoy, D.; Bain, C.; Williams, G.; March, L.; Brooks, P.; Blyth, F.; Woolf, A.; Vos, T.; Buchbinder, R. A Systematic Review of the Global Prevalence of Low Back Pain. Arthritis Rheum. 2012, 64, 2028–2037.
2. Hartvigsen, J.; Hancock, M.J.; Kongsted, A.; Louw, Q.; Ferreira, M.L.; Genevay, S.; Hoy, D.; Karppinen, J.; Pransky, G.; Sieper, J.; et al. What Low Back Pain Is and Why We Need to Pay Attention. Lancet 2018, 391, 2356–2367.
3. Manchikanti, L.; Singh, V.; Falco, F.J.E.; Benyamin, R.M.; Hirsch, J.A. Epidemiology of Low Back Pain in Adults. Neuromodulation 2014, 17, 3–10.
4. Vos, T.; Allen, C.; Arora, M.; Barber, R.M.; Brown, A.; Carter, A.; Casey, D.C.; Charlson, F.J.; Chen, A.Z.; Coggeshall, M.; et al. Global, Regional, and National Incidence, Prevalence, and Years Lived with Disability for 310 Diseases and Injuries, 1990–2015: A Systematic Analysis for the Global Burden of Disease Study 2015. Lancet 2016, 388, 1545–1602.
5. James, S.L.; Abate, D.; Abate, K.H.; Abay, S.M.; Abbafati, C.; Abbasi, N.; Abbastabar, H.; Abd-Allah, F.; Abdela, J.; Abdelalim, A.; et al. Global, Regional, and National Incidence, Prevalence, and Years Lived with Disability for 354 Diseases and Injuries for 195 Countries and Territories, 1990–2017: A Systematic Analysis for the Global Burden of Disease Study 2017. Lancet 2018, 392, 1789–1858.
6. Grégoire, S.; Cheishvili, D.; Salmon-Divon, M.; Dymov, S.; Topham, L.; Calderon, V.; Shir, Y.; Szyf, M.; Stone, L.S. Epigenetic Signature of Chronic Low Back Pain in Human T Cells. Pain Rep. 2021, 6, e960.
7. Urits, I.; Burshtein, A.; Sharma, M.; Testa, L.; Gold, P.A.; Orhurhu, V.; Viswanath, O.; Jones, M.R.; Sidransky, M.A.; Spektor, B.; et al. Low Back Pain, a Comprehensive Review: Pathophysiology, Diagnosis, and Treatment. Curr. Pain Headache Rep. 2019, 23, 23.

8. Heuch, I.; Foss, I.S. Acute Low Back Usually Resolves Quickly but Persistent Low Back Pain Often Persists. J. Physiother. 2013, 59, 127.
9. Atlas, S.J.; Deyo, R.A. Evaluating and Managing Acute Low Back Pain in the Primary Care Setting. J. Gen. Intern. Med. 2001, 16, 120–131.
10. Knezevic, N.N.; Candido, K.D.; Vlaeyen, J.W.S.; Van Zundert, J.; Cohen, S.P. Low Back Pain. Lancet 2021, 398, 78–92.
11. Kraft, D.E. Low Back Pain in the Adolescent Athlete. Pediatr. Clin. N. Am. 2002, 49, 643–653.
12. Santoro, D.; Satta, E. Pain in Renal Disease. J. Pain Palliat. Care Pharmacother. 2014, 28, 409–411.
13. Verhagen, A.P.; Downie, A.; Popal, N.; Maher, C.; Koes, B.W. Red Flags Presented in Current Low Back Pain Guidelines: A Review. Eur. Spine J. 2016, 25, 2788–2802.
14. Troyer, M.R. Differential Diagnosis of Endometriosis in a Young Adult Woman with Nonspecific Low Back Pain. Phys. Ther. 2007, 87, 801–810.
15. Malik, T.F.; Aurelio, D.M. Extraintestinal Manifestations of Inflammatory Bowel Disease; StatPearls Publishing: Treasure Island, FL, USA, 2022.
16. de Oliveira Sá, M.V.B.; Pacheco, F.J.S.; Barretto, F.J.T. Elderly Patient with Prostate Cancer and Back Pain. Eur. J. Intern. Med. 2020, 72, 88–89.
17. Foster, N.E.; Anema, J.R.; Cherkin, D.; Chou, R.; Cohen, S.P.; Gross, D.P.; Ferreira, P.H.; Fritz, J.M.; Koes, B.W.; Peul, W.; et al. Prevention and Treatment of Low Back Pain: Evidence, Challenges, and Promising Directions. Lancet 2018, 391, 2368–2383.
18. Dario, A.B.; Ferreira, M.L.; Refshauge, K.M.; Lima, T.S.; Ordoñana, J.R.; Ferreira, P.H. The Relationship between Obesity, Low Back Pain, and Lumbar Disc Degeneration When Genetics and the Environment Are Considered: A Systematic Review of Twin Studies. Spine J. 2015, 15, 1106–1117.
19. Pinheiro, M.B.; Ferreira, M.L.; Refshauge, K.; Colodro-Conde, L.; Carrillo, E.; Hopper, J.L.; Ordoñana, J.R.; Ferreira, P.H. Genetics and the Environment Affect the Relationship between Depression and Low Back Pain: A Co-Twin Control Study of Spanish Twins. Pain 2015, 156, 496–503.
20. Patterson, T.G.; Carvalho-e-Silva, A.P.; Aquino, D.; Ferreira, M.; Ferreira, P. Factors Associated with Care-Seeking for Low Back Pain When Genetics and the Familial Environment Are Considered. Musculoskelet. Sci. Pract. 2021, 53, 102365.
21. Fitz-James, M.H.; Cavalli, G. Molecular Mechanisms of Transgenerational Epigenetic Inheritance. Nat. Rev. Genet. 2022, 23, 325–341.

22. Klemm, S.L.; Shipony, Z.; Greenleaf, W.J. Chromatin Accessibility and the Regulatory Epigenome. Nat. Rev. Genet. 2019, 20, 207–220.
23. Ciampi De Andrade, D.; Maschietto, M.; Galhardoni, R.; Gouveia, G.; Chile, T.; Victorino Krepischi, A.C.; Dale, C.S.; Brunoni, A.R.; Parravano, D.C.; Cueva Moscoso, A.S.; et al. Epigenetics Insights into Chronic Pain: DNA Hypomethylation in Fibromyalgia—A Controlled Pilot-Study. Pain 2017, 158, 1473–1480.
24. D'Agnelli, S.; Arendt-Nielsen, L.; Gerra, M.C.; Zatorri, K.; Boggiani, L.; Baciarello, M.; Bignami, E. Fibromyalgia: Genetics and Epigenetics Insights May Provide the Basis for the Development of Diagnostic Biomarkers. Mol. Pain 2019, 15.
25. Mauck, M.; Van De Ven, T.; Shaw, A.D. Epigenetics of Chronic Pain after Thoracic Surgery. Curr. Opin. Anaesthesiol. 2014, 27, 1–5.
26. Tajerian, M.; Alvarado, S.; Millecamps, M.; Dashwood, T.; Anderson, K.M.; Haglund, L.; Ouellet, J.; Szyf, M.; Stone, L.S. DNA Methylation of SPARC and Chronic Low Back Pain. Mol. Pain 2011, 7, 65.
27. Chmielewska, M.; Janusz, P.; Andrusiewicz, M.; Kotwicki, T.; Kotwicka, M. Methylation of Estrogen Receptor 2 (ESR2) in Deep Paravertebral Muscles and Its Association with Idiopathic Scoliosis. Sci. Rep. 2020, 10, 22331.
28. Brekken, R.A.; Sage, E.H. SPARC, a Matricellular Protein: At the Crossroads of Cell-Matrix Communication. Matrix Biol. 2001, 19, 816–827.
29. Gruber, H.E.; Ingram, J.A.; Leslie, K.; Hanley, E.N. Cellular, but Not Matrix, Immunolocalization of SPARC in the Human Intervertebral Disc: Decreasing Localization with Aging and Disc Degeneration. Spine 2004, 29, 2223–2228.
30. Gruber, H.E.; Sage, E.H.; Norton, H.J.; Funk, S.; Ingram, J.; Hanley, E.N. Targeted Deletion of the SPARC Gene Accelerates Disc Degeneration in the Aging Mouse. J. Histochem. Cytochem. 2005, 53, 1131–1138.
31. Millecamps, I.; Tajerian, M.; Sage, E.H.; Stone, L.S. Behavioral Signs of Chronic Back Pain in the SPARC-Null Mouse. Spine 2011, 36, 95–102.
32. Williams, F.M.K.; Bansal, A.T.; Van Meurs, J.B.; Bell, J.T.; Meulenbelt, I.; Suri, P.; Rivadeneira, F.; Sambrook, P.N.; Hofman, A.; Bierma-Zeinstra, S.; et al. Novel Genetic Variants Associated with Lumbar Disc Degeneration in Northern Europeans: A Meta-Analysis of 4600 Subjects. Ann. Rheum. Dis. 2013, 72, 1141–1148.
33. Aroke, E.N.; Joseph, P.V.; Roy, A.; Overstreet, D.S.; Tollefsbol, T.O.; Vance, D.E.; Goodin, B.R. Could Epigenetics Help Explain Racial Disparities in Chronic Pain? J. Pain Res. 2019, 12, 701–710.

34. Jiang, C.; Guo, Q.; Jin, Y.; Xu, J.J.; Sun, Z.M.; Zhu, D.C.; Lin, J.H.; Tian, N.F.; Sun, L.J.; Zhang, X.L.; et al. Inhibition of EZH2 Ameliorates Cartilage Endplate Degeneration and Attenuates the Progression of Intervertebral Disc Degeneration via Demethylation of Sox-9. EBioMedicine 2019, 48, 619–629.

35. Ikuno, A.; Akeda, K.; Takebayashi, S.I.; Shimaoka, M.; Okumura, K.; Sudo, A. Genome-Wide Analysis of DNA Methylation Profile Identifies Differentially Methylated Loci Associated with Human Intervertebral Disc Degeneration. PLoS ONE 2019, 14, e0222188.

36. Eller, O.C.; Glidden, N.; Knight, B.; McKearney, N.; Perry, M.; Bernier Carney, K.M.; Starkweather, A.; Young, E.E.; Baumbauer, K.M. A Role for Global DNA Methylation Level and IL2 Expression in the Transition from Acute to Chronic Low Back Pain. Front. Pain Res. 2021, 2, 744148.

37. Bell, J.T.; Loomis, A.K.; Butcher, L.M.; Gao, F.; Zhang, B.; Hyde, C.L.; Sun, J.; Wu, H.; Ward, K.; Harris, J.; et al. Differential Methylation of the TRPA1 Promoter in Pain Sensitivity. Nat. Commun. 2014, 5, 2978.

38. Dorsey, S.G.; Renn, C.L.; Griffioen, M.; Lassiter, C.B.; Zhu, S.; Huot-Creasy, H.; McCracken, C.; Mahurkar, A.; Shetty, A.C.; Jackson-Cook, C.K.; et al. Whole Blood Transcriptomic Profiles Can Differentiate Vulnerability to Chronic Low Back Pain. PLoS ONE 2019, 14, e0216539.

39. Sukenaga, N.; Ikeda-Miyagawa, Y.; Tanada, D.; Tunetoh, T.; Nakano, S.; Inui, T.; Satoh, K.; Okutani, H.; Noguchi, K.; Hirose, M. Correlation between DNA Methylation of TRPA1 and Chronic Pain States in Human Whole Blood Cells. Pain Med. 2016, 17, 1906–1910.

40. Aroke, E.N.; Overstreet, D.S.; Penn, T.M.; Crossman, D.K.; Jackson, P.; Tollefsbol, T.O.; Quinn, T.L.; Yi, N.; Goodin, B.R. Identification of DNA Methylation Associated Enrichment Pathways in Adults with Non-Specific Chronic Low Back Pain. Mol. Pain 2020, 16, 1744806920972889.

41. Du, X.F.; Cui, H.T.; Pan, H.H.; Long, J.; Cui, H.W.; Chen, S.L.; Wang, J.R.; Li, Z.M.; Liu, H.; Huang, Y.C.; et al. Role of the MiR-133a-5p/FBXO6 Axis in the Regulation of Intervertebral Disc Degeneration. J. Orthop. Transl. 2021, 29, 123–133.

42. Aroke, E.N.; Jackson, P.; Meng, L.; Huo, Z.; Overstreet, D.S.; Penn, T.M.; Quinn, T.L.; Cruz-Almeida, Y.; Goodin, B.R. Differential DNA Methylation in Black and White Individuals with Chronic Low Back Pain Enrich Different Genomic Pathways. Neurobiol. Pain 2022, 11, 100086.

43. Li, D.; Liu, J.; Guo, B.; Liang, C.; Dang, L.; Lu, C.; He, X.; Cheung, H.Y.S.; Xu, L.; Lu, C.; et al. Osteoclast-Derived Exosomal MiR-214-3p Inhibits Osteoblastic Bone Formation. Nat. Commun. 2016, 7, 10872.

44. Goodin, B.R.; Overstreet, D.S.; Penn, T.M.; Bakshi, R.; Quinn, T.L.; Sims, A.; Ptacek, T.; Jackson, P.; Long, D.L.; Aroke, E.N. Epigenome-Wide DNA Methylation Profiling of Conditioned Pain Modulation in Individuals with Non-Specific Chronic Low Back Pain. Clin. Epigenetics 2022, 14, 45.

45. Luchting, B.; Heyn, J.; Hinske, L.C.; Azad, S.C. Expression of MiRNA-124a in CD4 Cells Reflects Response to a Multidisciplinary Treatment Program in Patients with Chronic Low Back Pain. Spine 2017, 42, E226–E233.