Human intervertebral disc degeneration, sex, and aging increase Alpha-1 Antitrypsin expression

Helen Lin[1], Neharika Bhadouria[2], James C. Iatridis[2], Nilsson Holguin[2]
[1]The Bronx High School of Science, New York, NY
[2]Leni & Peter W. May Department of Orthopedics, Icahn School of Medicine at Mount Sinai, New York, NY
Neharika.Bhadouria@mssm.edu

Disclosures: Helen Lin (N), Neharika Bhadouria (N), James C. Iatridis (N), Nilsson Holguin (N).

Introduction: Low back pain is most commonly associated with intervertebral disc degeneration (IVDD) and is a leading cause of disability worldwide [1]. Current treatments for IVDD are primarily focused on symptom management rather than tissue repair. Conservative approaches such as physical therapy, non-steroidal anti-inflammatory drugs, and corticosteroid injections provide temporary relief, but do not address the underlying condition. Surgical interventions are reserved for severe IVDD and carry the risk of complications [2]. Inflammatory and immune processes, particularly regarding neutrophil activity, play a central role in intervertebral disc (IVD) matrix modeling and IVDD [3]. Alpha-1-antitrypsin (A1AT), encoded by the *SERPINA1* gene, an immunomodulatory protein secreted by the liver, acts as a serine protease inhibitor of neutrophil elastase and recruitment [4]. The presence and regulation of neutrophils have been associated with the chronic nature of low back pain, where dysregulated or insufficient neutrophil responses impair resolution of inflammation and promote persistent low back pain [5]. However, the regional and sex-specific protein expression of A1AT in human IVDD and IVD aging remains unclear. We hypothesized IVDD and IVD aging will be associated with greater IVD protein expression of A1AT in men and women.

.

Methods: Lumbar IVD were obtained from 16 cadaveric donors (n=9 female) ranging from 9-93 years old in age. IVDD was previously scored using a modified Thompson scoring system (Grades 1-5); all samples were collected from levels L2-L3 and L3-L4 for consistency [6]. Regions of interest (ROIs) were defined using NDP.view2 software, with the outer 10% of the IVD length designated as the annulus fibrosus (AF), the adjacent 15% as the AF-nucleus pulposus (NP) boundary, and the midpoint as the NP (Figure 1). Eleven ROIs were analyzed per IVD. A1AT protein expression was quantified in each ROI from stained sections using ImageJ thresholding of brown, A1AT stained regions. Left and right ROIs of the same region were averaged to account for orientation. Statistical analyses were performed using two-way ANOVA to assess the effects of IVDD grade and region on A1AT protein expression. A T-test compared A1AT protein expression by sex and age (mature [9-40 years] vs aged [47-93 years]).

Results: IVDD was associated with increased A1AT protein expression (main effect, p=0.0004) by 363% (G5 vs G1-G4), irrespective of region (Figure 2). There was no interaction between IVDD grade and IVD region (IVDD grade x region, p=0.9349). By sex, A1AT protein expression was greater in male IVDs than female IVDs by 318% (p=0.047). Aging trended to increase (314%, p = 0.06) A1AT protein expression in IVD.

Discussion: Our study shows that A1AT protein is present throughout the IVD and that its expression may be regulated by IVDD, age and sex. Immunohistochemistry data of human and mouse models showing decreased A1AT staining in IVDD. Notably, these immunohistochemical analyses of human IVD were limited to IVD with degeneration scores up to grade 4, whereas in our cohort, grade 5 IVD exhibited significantly higher A1AT expression than all other groups [7]. Elevated A1AT protein expression in late-stage male IVDD may reflect a response to greater interleukin-6 (IL-6) driven inflammation, as IL-6 is a principal inducer of A1AT synthesis during the acute-phase response [8]. This aligns with evidence that males exhibit stronger IL-6 mediated inflammatory activity following injury, contributing to poorer trauma outcomes [9]. Aging trended to be associated with greater A1AT expression, corroborating established research, though the differences could be attributed to IVDD severity rather than age [10]. Taken together, our findings suggest that the upregulation of A1AT within IVDD represents an adaptive attempt to regulate neutrophil elastase and recruitment.

Significance/Clinical relevance: These findings indicate that A1AT is upregulated in severe IVDD potentially inhibiting immune cell recruitment or preventing elastin degradation from immune cell recruitment. Understanding A1AT's function could inform future protease-inhibitory therapies in IVDD and associated low back pain

References V2: [1] Zhang C. et al., Frontiers Public Health. 2025; [2] Guo T. et al., Frontiers Bioengineering and Biotechnology. 2022; [3] Feng P. et al., Frontiers Immunology. 2023; [4] Xiang S. et al., Cells. 2025; [5] Parisien M. et al., Science Translational Medicine. 2022; [6] Liu X. et al., European Cells & Materials. 2018; [7] Yang X. et al., Frontiers in Cell and Developmental Biology. 2023; [8] Janciauskiene S. et al., Frontiers in Immunology. 2022; [9] Sperry L J. et al., 2008; [10] Tam V. et al., eLife. 2020

Acknowledgements: We would like to thank Damien M Laudier for his invaluable technical support with the histology work.

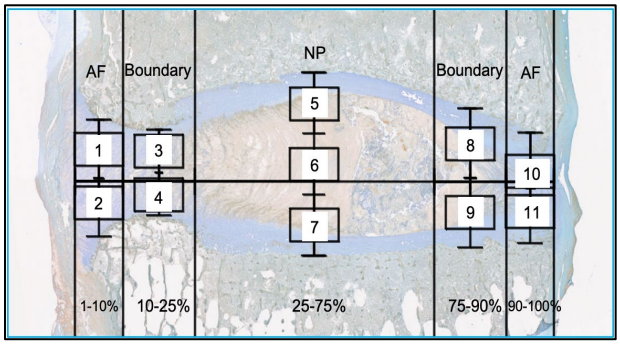

Figure 1. Schematic of regions of interest (ROIs) for histological analysis of A1AT expression in intervertebral discs (IVD). ROIs 1, 2, 10, 11 represent the annulus fibrosus (AF) region, ROIs 3, 4, 8, 9 represent the AF-nucleus pulposus (NP) boundary region, and ROIs 5, 6, 7 represent the NP region.

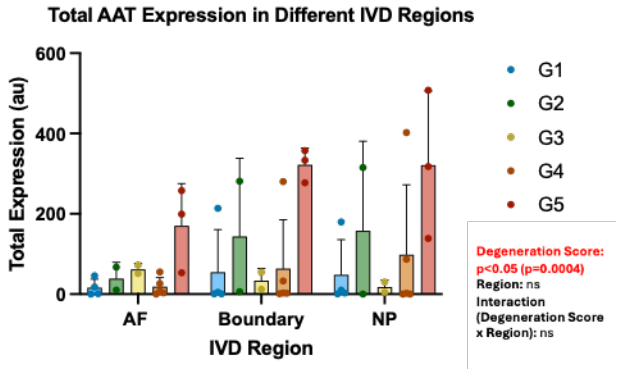

Figure 2. Total A1AT expression across the annulus fibrosus (AF), boundary, and nucleus pulposus (NP) regions increased significantly (p=0.0004) with degeneration score.