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Advances in Programmed Cell Death Research in Intervertebral Disc Degeneration

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Abstract: One of the primary causes of chronic low back pain and functional impairment is intervertebral disc degeneration. Various modes of programmed cell death such as apoptosis, pyroptosis, necroptosis, and ferroptosis and novel modes such as cupric death, disulfide bond death, and alkaline death contribute to the progressive loss of cells in the nucleus pulposus intervertebral discs and the establishment of an inflammatory microenvironment. Holistic processes such as PANoptosis reveal that programmed cell death is not mutually exclusive. The setting out of programmed cell death and intervertebral disc degeneration is also coordinately governed by upstream stimulus transduction. Recent technological breakthroughs in genome editing tools, individual cell transcriptomics, and biomaterials have not only deepened our understanding of programmed cell death pathways but have also opened novel avenues of intervertebral disc therapy. Targeting multiple modes of programmed cell death seems to have a greater advantage with regard to restoring the homeostatic balance of intervertebral discs to their original state. Nonetheless, there still remain matters related to precise intradiscal target delivery, human-scale modeling, and dynamic monitoring. Noting the elaborate programmed cell death network provides a theoretical framework for designing novel intervertebral disc precision medicine.

Keywords: Intervertebral Disc Degeneration; Programmed Cell Death; PANoptosis; Apoptosis; Pyroptosis; Necroptosis; Ferroptosis.

1. Introduction

1.1. Intervertebral Disc Degeneration Epidemiology and Disease Burden

Intervertebral disc degeneration (IVDD) is one of the primary pathologic foundations of chronic low back pain (LBP)[1]. As a common progressive musculoskeletal disease, IVDD causes spinal instability and biomechanics dysfunction, which can generate chronic pain, neurological dysfunction, and chronic disability[2, 3]. In addition to its pathologic effects on patients with spinal diseases, there is a large socioeconomic burden of this disease because of its high incidence rate and the lack of efficacious treatment strategies. Clinical data have shown that with the acceleration of world aging rates, the decreased workforce productivity and associated health care expenses because of IVDD continue to rise[4, 5]. The primary pathologic changes in the disease include the apoptosis of nucleus pulposus cells (NPCs) and intervertebral disc structure disorder. These changes can be accelerated or induced by mechanical pressure and oxidative injury[6, 7].

1.2. The Central Role of Programmed Cell Death in Degenerative Diseases

Programmed cell death, as a tightly controlled biological process, is known to have a vital role in intervertebral disc degenerative disease pathophysiology[8]. A large body of evidence suggests that the occurrence and development of IVDD are tightly related to the disorderly activation of multiple PCD modalities like apoptosis, pyroptosis, necroptosis, and ferroptosis[9, 10]. Among them, the over-activation of NPCs apoptosis had been confirmed to contribute to the decreased synthesis of the extracellular matrix (ECM) and disc dysfunction finally occurred[11]. In recent studies, it has been shown that the antioxidant inflammatory responses can trigger endoplasmic reticulum stress (ESR) to activate multiple cell death pathways to induce perinuclear cells programmed necrosis[7, 12]. All above-mentioned pieces of evidence have confirmed the crucial role of programmed cell death in intervertebral disc disease pathophysiology[9, 13].

1.3. The Mechanistic Advancements of Multimodal PCD in IVDD: From Single Pathways to Integrated Networks

Traditional research mainly explored the role of a single programmed cell death pathway in the pathogenesis of IVDD. But current evidence reveals that there is a dynamic transition between those programmed cell death pathways[14]. For example, the RIPK1/RIPK3 pathway mediates not only the activation of the inflammasome and subsequent pyroptosis but also the occurrence of necroptosis[15, 16]. The overall regulating role of such complex multimodal PCD pathways provides a novel insight into the pathogenetic mechanism of IVDD[17]. More crucially, the inflammatory microenvironment of the intervertebral disc is created through the interaction of multiple modes of PCD. This not only modulates macrophage activation concurrently but also modulates the metabolism of the extracellular matrix. This is because it ultimately promotes the progressive nature of the disease[18, 19]. These path-breaking findings have established a theoretical basis for the combined treatment strategy involving multiple pathways of cell death [20].

2. Principal Processes and Mechanisms of Intervertebral Disc Degeneration-Related Programmed Cell Death

2.1. Apoptosis: From Morphological Characteristics to Core Pathways

Apoptosis of NPCs is a universal form of cellular loss in IVDD and is one of the crucial factors in its pathologic process[21]. Cell atrophy, chromatin condensation, and apoptotic body formation are typical histologic changes associated with it and are directly related to mitochondrial dysfunction and oxidative stress[22]. These pathways have two chief mechanisms: the death receptor (or extrinsic) pathway and the mitochondrial (or intrinsic) pathway. An increased Bax/Bcl-2 ratio, activation of caspase-9, accumulation of reactive oxygen species (ROS), and loss of mitochondrial membrane potential are hallmarks indicative of mitochondrial activation and form a vital part of the intrinsic mechanism[23, 24]. These pathways are again regulated by SIRT1 signaling pathways, NF-κB, and PI3K/AKT. NF-κB activation is pro-apoptotic, and PI3K/AKT inhibition or SIRT1 inhibition is pro-apoptotic[25]. By activating the Wnt/NF-κB pathway, it promotes the extrinsic pathway released by death receptor activation. This is associated with caspase-8 activation and increase in Fas L[26, 27]. These pathways meet at caspase-3 to carry out programmed cellular lysis[10]. Recent reports have found that VNS inhibits increased apoptosis of NPCs and is modulated through cholinergic anti-inflammatory pathways. This provides a novel target for treatment to counteract disc degeneration[22].

2.2. Pyroptosis: Inflammatory Cascades of Classical and Non-Classical Pathways

The inflammatory form of gasdermin protein-initiated programmed cell death during intervertebral disc degeneration is named pyroptosis. It involves caspase-1 activation in the inflammasome and results in the processing of gasdermin D (GSDMD) to generate pores to liberate proinflammatory cytokines like IL-1β and IL-18[28, 29]. Apart from the above mechanism, there is evidence of GSDME participation in the non-classical mechanism. This involves caspase-3 activation to process GSDME to generate apoptosis with transition to pyroptosis. The metabolic status of cells is directly associated with the mechanism. Unbalanced fatty acid metabolism and increased glucose metabolism in nuclear fibroblasts serve as upstream pathways to trigger intervertebral disc pyroptosis[30, 31].

2.3. Necroptosis: Signal Transduction and Pathological Propagation

The degenerative mechanism in intervertebral discs involves a form of necrotic cell death known as necroptosis. This type of cell death is mainly mediated by the RIPK1-RIPK3-MLKL pathway and is known to have close links with inflammatory reactions and degradation of the extracellular matrix[9, 22]. More importantly, it is apparent that necroptosis can be transferred between cells with the prion-like transfer mechanism to increase the rate of degeneration in discs[10]. Regulatory analyses suggest that it has a protective role when the pathways of this form of cell death are inhibited[32]. Indeed, it is shown that although heme oxygenase-1 (HO-1) inhibits necrotic apoptosis and prevents degeneration through its anti-inflammatory and antioxidant effects[33], it acts as a protective mechanism.

2.4. Ferroptosis and Lipid Peroxidation Injury

Ferroptosis is an iron-dependent form of programmed cell death that causes the degeneration of NPCs through a lethal accumulation of lipid peroxides, thereby identifying the mechanism associated with iron-dependent programmed cell death in disc disease[34]. Ferroptosis is associated with the depletion of glutathione (GSH) and inactivation of glutathione peroxidase 4 (GPX4) expression, indicative of the breakdown of antioxidant defense machinery[35]. Results obtained through bioinformatics studies validate the pathologically altered expression of genes associated with ferroptosis in degenerated discs, which can potentially define the transcriptional regulative programs associated with such pathologic mechanisms[36, 37]. From such findings, there is evidence to support the role of numerous regulative factors like activating transcription factor 3 (ATF3) in slowing the progression of IVDD related to iron-dependent programmed cell death pathways associated with ferroptosis[38, 39].

2.5. Cuproptosis and Metabolic Reprogramming

Cuproptosis is a recently identified type of copper-dependent programmed cell death caused by ferredoxin-1 (FDX1), which accumulates copper in the mitochondria and causes proteotoxic stress by selectively targeting lipoylated proteins in the tricarboxylic acid cycle[40]. In IVDD, the NPCs' abnormal mitochondrial metabolism fosters an environment that is conducive to cuproptosis onset. Recent studies have examined the regulatory functions of cuproptosis-related signaling axes, such as MTF1/LIAS, in disc degeneration, opening up new possibilities for precision therapies that focus on metabolic dysfunction. Recent studies have shown that ferroptosis and cuproptosis share overlapping metabolic dependencies but differ mechanistically[41, 42]. Iron-dependent lipid peroxidation and GPX4 inactivation are the main causes of ferroptosis, whereas lipoylated-protein targeting (FDX1/LIAS axis) and mitochondrial copper accumulation cause cuproptosis[43]. The possibility that the two death modalities contribute sequentially or cooperatively is increased by the concurrent dysregulation of iron and copper homeostasis and mitochondrial metabolic abnormalities in IVDD[44]. Therefore, to experimentally differentiate between cuproptosis and ferroptosis in NP tissue, assays for tissue copper content and FDX1 expression/mitochondrial lipoylation should be used in addition to standard ferroptosis readouts (e.g., GPX4 levels, lipid peroxidation metrics)[45].

3. Crosstalk and Emerging Frontiers of Programmed Cell Death in Intervertebral Disc Degeneration

3.1. Integrated Regulatory Features of PANoptosis

An inflammatory form of programmed cell death that is regulated by the PANoptosome and that cannot be sufficiently explained by any one of the three death modalities alone, PANoptosis shares key features with pyroptosis, apoptosis, and necroptosis[46]. This particular mode of cell death has received a lot of attention in the study of IVDD. According to research, PANoptosis merges multiple death signaling

pathways to form an intricate regulatory network that may play a key role in IVDD development. Particularly in the creation and maintenance of the inflammatory microenvironment, PANoptosis may accelerate the death of NPCs and the disintegration of ECM by inducing a range of inflammatory mediators and death effectors [30]. New experimental studies and integrative analyses provide emerging empirical evidence for the involvement of PANoptotic programs in IVDD[47]. In vivo models and degenerated human discs, parallel activation of executioner caspases (caspase-3 cleavage), necroptotic effectors (e.g., RIPK3/MLKL phosphorylation), and canonical inflammasome components (e.g., caspase-1, IL-1β) has been noted[48]. In contrast to isolated single-pathway activation, these results are consistent with PANoptosome-mediated multimodal cell death. These findings emphasize the significance of coordinated readouts, such as simultaneous measurement of caspase-1 activity or GSDMD/GSDME processing along with caspase-3 cleavage and RIPK3/MLKL phosphorylation, to test PANoptotic involvement and resolve the temporal ordering of death signals in NPCs[49].

3.2. Crosstalk and Dynamic Switching among PCD

During intervertebral disc degeneration, various PCD modalities take part in complex crosstalk and dynamic transitions[35]. Instead of operating independently, apoptosis, pyroptosis, necroptosis, and ferroptosis all influence one another through shared signaling molecules and effector pathways. For example, ERS and mitochondria–ER interactions may simultaneously activate multiple PCD pathways[12]. Moreover, changes in autophagic activity can modify pyroptotic responses in NPCs, and ferroptosis, which is intimately associated with oxidative stress, may affect the activation of other PCD modalities[50]. These dynamic conversions and synergistic interactions among PCD types provide a substantial molecular basis for the progression of IVDD[8].

3.3. Status of Research on Other Potential Death Modalities

Along with more conventional forms of PCD, new death modalities such as disulfidptosis and alkaliptosis have begun to attract attention in the context of IVD[51]. Because these modes are associated with particular metabolic and redox alterations, they offer new insights into IVDD. Disulfidptosis is caused by disulfide-bond stress under glucose-deprivation conditions; its main mediator, SLC7A11, is aberrantly expressed in degenerated discs and leads to the collapse of the actin network, which accelerates NPC death by depleting NADPH[51]. Recent studies have shown that the scaffold protein IQGAP1 controls this process and modifies the immune milieu, which suggests that it could be a therapeutic target[52]. However, little is known about alkaliptosis, which is cell death caused by intracellular alkalinization (higher pH), and further study is required to completely comprehend its distinct regulatory networks and pathological roles in IVDD. Nonetheless, it is clear that these new death modalities present new avenues for disc degeneration treatment[53]. In human nucleus pulposus cells, a glucose deprivation model revealed NADPH depletion, disulfide bond stress linked to SLC7A11, and subsequent actin cytoskeletal collapse—events that are consistent with disulfide apoptosis mechanisms. The mechanism by which disulfide apoptosis results in nucleus pulposus cell death under metabolic stress has been directly elucidated by these additional investigations[54]. Single-cell and whole-transcriptome analyses of degenerative discs demonstrated aberrant expression of SLC7A11 and related redox regulators, specifically in NP subpopulations, confirming the pathophysiological relevance of disulfide apoptosis to IVDD. Alkaline apoptosis in disc degeneration, on the other hand, is still poorly supported by data and should be regarded as a theory that requires particular in vivo validation[55].

4. Key Regulatory Pathways and Molecular Interactions

4.1. Inflammation–Death Signal Crosstalk

In IVDD, there is a great deal of interaction between the PCD pathways and the inflammatory milieu. A substantial increase in macrophage infiltration is found in mechanically stressed disc tissues (msi-IVDD) according to single-cell transcriptome analyses; the macrophage-secreted protein SPP1 triggers NF-κB signaling, which in turn encourages inflammation and cell death[56]. NF-κB, a canonical inflammatory transcription factor, is a major regulator of ECM metabolic imbalance because it stimulates the expression of matrix-degrading enzymes like MMP3 and activates multiple PCD pathways[26]. Reactive oxygen species (ROS) generated by oxidative stress act as a vital molecular link between inflammation and PCD, triggering inflammasomes (like NLRP3) and ferroptosis-related lipid peroxidation at the same time, resulting in a vicious cycle of inflammation and death[57]. Notably, macrophages in the degenerative disc microenvironment secrete proinflammatory cytokines such as TNF-α, which not only directly induce NPCs apoptosis but also indirectly influence PCD processes by controlling nerve ingrowth and angiogenesis[14].

4.2. Mechanical Stress Transduction and PCD Activation

Through a number of mechanosensors, aberrant mechanical loading initiates PCD pathways, which is the main cause of disc degeneration. By translating changes in extracellular matrix stiffness into intracellular Ca2+ signals, increased expression of the mechanically sensitive ion channel Piezo1 in NP tissue initiates SIRT1-dependent apoptotic pathways[58, 59]. Compressive stress can cause ER stress (ERS) and the unfolded protein response (UPR), which can lead to mitochondria-dependent apoptosis by disrupting endoplasmic reticulum–mitochondria contact sites (MERCs) High-magnitude compression also inhibits primary cilium mechanosensing, accelerates endplate calcification, and promotes NPCs death by downregulating IFT88 expression[60]. By controlling actin cytoskeletal remodeling, non-muscle myosin II isoforms act as mechanotransduction effectors at the molecular level, mediating stress-induced cellular senescence[61]. Furthermore, changes in ECM stiffness can cause RIPK1/RIPK3-mediated necroptosis via integrin–FAK signaling; this mechanically induced PCD has important intercellular propagation characteristics[62]. In order to more accurately replicate the complex relationships between mechanical loading, nutrient gradients, and immune infiltration in IVDD, new disc-on-a-chip and ex vivo mechanically loaded organ culture platforms now enable controlled axial compression in combination with perfused immune compartments[63]. For mechanistic research and

therapeutic screening, these microphysiological systems are more physiologically relevant than acute needle-injury animal models. They also allow for temporally resolved interrogation of mechanotransduction-linked PCD, such as Piezo1-dependent Ca2+ signaling leading to apoptosis, or compression-induced RIPK1/RIPK3 activation[64].

4.3. Epigenetic Regulatory Networks

PCD in IVDD is controlled by a complex regulatory network that is influenced by epigenetic mechanisms. Mechanical overload affects NP cells' apoptotic threshold by altering the acetylation status of p53 and the activity of the histone deacetylase SIRT1[59]. Changes in DNA methylation patterns, especially aberrant promoter methylation of ferroptosis-related genes (e.g., GPX4, ACSL4), can be brought on by oxidative stress and impair antioxidant defense[10]. MicroRNA networks, such as miR-155 and miR-21, target death effector molecules like CASP3 and GSDME to establish dynamic balances between different PCD modalities. Mechanical stress can also influence NPCs' vulnerability to compression-induced ferroptosis by regulating ERK1/2 phosphorylation via long non-coding RNAs (e.g., MALAT1)[65]. Aberrant histone modifications, such as H3K27me3, can silence important autophagy genes, such as ATG7, which worsens mechanically induced proteotoxic stress and cell death. Together, these epigenetic modifications create a "molecular memory" of PCD pathways in disc degeneration and provide fresh opportunities for focused therapeutic intervention[66].

5. Advances in Targeted Therapeutic Strategies

5.1. Death Pathway–Specific Inhibitors

In recent years, significant progress has been made in the development of pathway-specific inhibitors that target different PCD mechanisms in IVDD. By preventing excessive NP cell apoptosis, disc degeneration can be effectively slowed, according to numerous studies in the field of apoptosis regulation[67]. A mechanistic foundation for innovative regulatory strategies is provided by the relationship between autophagy and pyroptosis: cellular homeostasis is maintained by moderate autophagy, whereas pyroptosis is promoted by its dysregulation[28]. Inhibiting pyroptosis has shown promise as a treatment for inflammatory death pathways. As a newly discovered regulated death mode, ferroptosis has opened up new therapeutic possibilities; ferroptosis inhibitors seem to be promising therapies for disc degeneration[50]. Furthermore, the ability of natural products to alter PCD networks and lower IVDD has attracted a lot of attention due to their multi-target characteristics[68].

5.2. Gene Editing, Cell Therapy, and Biomaterial Delivery Systems

The precise modulation of key gene expression to delay degeneration is made possible by CRISPR-based gene editing technologies, which has opened up new possibilities for IVDD cell and tissue engineering therapies[69]. Apoptotic vesicles derived from mesenchymal stem cells have been developed as systems that respond to dual pathologies in the extracellular vesicle field. These vesicles incorporate MMP13-responsive cell-penetrating peptides to concurrently intervene in PCD and cellular senescence[70]. These vesicles preserve the intrinsic regulatory functions of their parent cells and show promising clinical translation potential in addition to serving as carriers of therapeutic cargos (like proteins or miRNAs)[71]. Although the use of biomaterial-assisted cell transplantation is limited by post-transplantation cell survival, advancements in materials science and tissue engineering continue to make it useful for disc repair[72]. Furthermore, miRNA-based treatments have progressed, and it has been shown that specific miRNAs can effectively postpone degeneration through intradiscal delivery, opening up a non-cellular therapeutic option[73]. Recent translational advances have highlighted engineered extracellular vesicles and multi-responsive biomaterials as promising intradiscal delivery platforms. For example, MMP-responsive apoptotic vesicles (MR-ApoVs) and ROS-sensitive hydrogels have been demonstrated in preclinical models to enhance targeted cargo release, prolong intradiscal retention, and concurrently modify cellular senescence and programmed death pathways. In light of the current gaps in scale-up and long-term biosafety data, we recommend using an evidence ladder (in vitro→small animal→large animal→clinical) to report therapeutic evidence when evaluating engineered delivery systems. Additionally, translational statements should specifically address manufacturing reproducibility and immunogenicity[70].

5.3. Synergistic Effects of Combined Interventions

Because of IVDD's complex pathophysiology, combined intervention strategies exhibit synergistic advantages over monotherapies. According to studies, intervertebral disc regeneration requires simultaneously treating the inflammatory microenvironment and reversing excessive NPCs apoptosis[67]. Senescence and PCD are two important pathological processes that can be simultaneously regulated by systems that target multiple pathologies, like MR-ApoVs[70]. By simultaneously treating structural flaws, microenvironmental degradation, and cell loss, biomaterial-based treatments seek to stop the disease's progression[5]. To modulate the multifaceted pathology of degeneration, the macrophage-modulating methods have potential effects on NPC function, ECM turnover, angiogenesis, and nerve innervation simultaneously. In order to tackle the complex pathological network associated with IVDD, the combined methods above offer promising avenues[74].

6. Development of Diagnostic Biomarkers and Translational Challenges

6.1. Death-Specific Molecular Signatures

Different patterns of PCD during IVDD have unique molecular profiles. Ferroptosis can be discriminated by glutathione (GSH) levels and lipid peroxide accumulation[35], with crucial regulating genes such as ATF3 profoundly up-regulated in degenerated discs [29]. Pyroptosis can be confirmed by inflammatory body activation products like IL-1β or GSDME fragments, and then necrosis can be identified by markers of phosphorylations within the RIPK1/RIPK3 pathway. Single-cell RNA sequencing analyses have discovered particular profiles of gene expression related to cell death among nucleus pulposus cellular subtypes[51], while particular extracellular small RNA-containing EVs like miR-155 have been used as a bio-

marker for intercellular cell death. Even if such particular molecular markers of cell death have been identified to provide potential targets for early detection, spatiotemporaly dynamic markers of varied patterns of cell death still pose a challenge[75].

6.2. Imaging and Multi-Omics Integrated Markers

Traditional T2-weighted MRI can detect the water content in the disc but fails to differentiate between kinds of cell death[3]. More recent techniques such as chemical exchange saturation transfer (CEST) MRI can detect variations in glutathione among the cells in the disc[76], and another recent technique named quantitative susceptibility mapping (QSM) can detect iron accumulation caused by ferroptosis[50]. Results obtained through multi-omics integration analyses show that there is a marked correlation between oxidized lipids in the metabolism of degenerative intervertebral discs and ferroptosis genes such as ACSL4 and GPX4[36]. While metagenomic sequencing has revealed metabolites derived from the gut microbiota that may influence IVDD through death signaling pathways[74], proteomics has identified molecules such as TNFAIP3 as nodes within the death–inflammation cross-network[77]. The creation of machine-learning models that link imaging features with molecular markers holds promise for precise IVDD subtyping based on dominant death modalities. The potential of quantitative MRI techniques to noninvasively assess redox and metal homeostasis in disc tissues has been shown by preclinical and early translational studies. These techniques include quantitative susceptibility mapping (QSM) for the quantification of relative iron and chemical exchange saturation transfer (CEST) for the mapping of glutathione[78]. These techniques can help link imaging phenotypes to molecular death-mode signatures (e.g., FDX1 for cuproptosis, GPX4/ACSL4 for ferroptosis) when paired with spatial transcriptomics or single-cell sequencing. This enables the creation of multi-scale biomarker panels for subtype classification and therapy stratification. Prospective studies should prioritize cross-validation of imaging biomarkers with molecular assays in the same specimens.

6.3. Technologies for Dynamic Monitoring of the Microenvironment

The three primary technical barriers to dynamic monitoring of the disc microenvironment are the spatiotemporal heterogeneity of death signals, which necessitates the development of implantable sensors for real-time detection of pH, ROS, and other parameters[79], the selective associations between macrophage polarization states and death modes, which could be evaluated using CD86/CD206 dual-label flow-cytometry techniques[14], and the feedback loops between ECM degradation and death signaling, which necessitate the use of microfluidic platforms that can concurrently monitor MMP activity and death markers[67]. Novel nanosensors, like GSH-responsive fluorescent probes, can dynamically visualize ferroptotic regions, and PET-CT in combination with pyroptosis-specific tracers (e.g., 18F-DPA-714) has shown promise in small-animal validation studies[76]. Organ-on-a-chip technologies can model the relationship between mechanical stress and death-signal transduction, but they must overcome in vitr–in vivo discrepancies caused by the complexity of the human tissue microenvironment[80].

7. Conclusion

In summary, one of the biggest research challenges regarding intervertebral disc degeneration is still the explanation of complex dynamic shifting between different modalities of PCD. It's impossible to fully describe complicated spatiotemporal cell interactions of apoptosis, pyroptosis, necroptosis, and ferroptosis through methods of single-channel detection, making it essential to have sophisticated methods of dynamic monitoring. Moreover, inconsistencies of animal and human research, caused by differences of degeneration mechanism, physiological characteristics, and gene expression, can be serious barriers of translational research relevance. To overcome these disparities, an overarching framework of precision medicine is required, and this would involve stratified patient profiling, intelligent therapeutic delivery, combinations, and predictive translational systems. By leveraging multi-omics analysis, biomaterial delivery system approaches, and/or organoid or large animal model development, one can usher into clinical translational research of relevance more effectively and more quickly into multimodal PCD studies focused on intervertebral disc degeneration treatments, as a whole "stratification, delivery, combinations, and prediction" framework would attest towards this end.

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