Title

Kynurenine and NAD^+ metabolism as PGC-1α-regulated mediators of stress pathology in the *mdx* mouse model of Duchenne muscular dystrophy

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Abstract

The *mdx* mouse model of Duchenne muscular dystrophy (DMD) exhibits pathophysiological responses to graded forms of psychological stress, with phenotypes ranging from transient hypotension and tonic immobility to sustained cardiac instability and lethality. Transgenic dystrophin or utrophin expression in skeletal muscle prevents *mdx* stress pathology, but the downstream dystrophin-dependent mechanism that mediates *mdx* stress vulnerability remains to be identified. Metabolic alterations in the kynurenine (KYN) pathway of tryptophan metabolism and the nicotinamide adenine dinucleotide (NAD^+) catabolic pathway catalyzed by cluster of differentiation 38 (CD38) are hypothesized to contribute to *mdx* stress pathology and inter-organ stress response signaling along the skeletal muscle-cardiovascular-central nervous system axis. We demonstrate that KYN and CD38 pathway dysregulation in *mdx* mice displays stress dependence, but show that genetic modulation of KYN and CD38 pathway activity in *mdx* mice does not prevent *mdx* stress pathology. Exploratory multi-omics investigation of protein and metabolic stress signaling factors will provide valuable new insights into the origin of dystrophinopathy-related stress susceptibility, which is translationally relevant to the substantial portion of the DMD community who face chronic life stressors and exhibit pathological responses to psychological stress.

Graphical Abstract