DISTINCT PATTERNS OF INFLAMMASOME SIGNALLING IN THE CARDIAC AND SKELETAL MUSCLE FROM MURINE MODELS OF DUCHENNE MUSCULAR DYSTROPHY

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The life-limiting complications of Duchenne muscular dystrophy (DMD) include cardiomyopathy, leading to chronic heart failure. The routine treatment for delaying disease progression both in the skeletal and cardiac muscle are glucocorticoids, supporting the hypothesis that inflammation may contribute to the manifestation of cardiac and skeletal muscle dysfunction. However, little is known about the inflammatory mechanisms during the course of the disease, particularly whether inflammatory processes involve both cardiac and skeletal muscle. Thus, the objective of our research was to characterize inflammasome activity in myocardium and skeletal muscle tissue at different time points in two murine models of DMD.
Skeletal muscle and left ventricular myocardial samples were collected from mdx mice and mdx rats (both carrying mutation or deletion in dystrophin gene which produces nonfunctional dystrophin protein) as well as from wildtype littermates. Inflammasome signaling [inflammasome sensors NLRP3, NLRC4 and AIM2, adaptor protein and effectors e.g. interleukin-1 beta (IL-1β), interleukin-18 (IL-18) and gasdermin D (GSDMD)] was assessed by immunoblotting in left ventricular myocardial and skeletal muscle samples collected from the animals at two different time points (month 3 and month 9-10).
Skeletal muscle samples from both species showed a tendency towards elevated expression of GSDMD irrespective of the animal age. Surprisingly, adaptor protein ASC was only elevated in mdx mouse skeletal muscle and heart, but not in mdx rats. Increased expression and cleavage of cytokines was observed in the skeletal muscle of mdx rats. Cytokine expression was not changed in the heart or skeletal muscle of mdx mice. No significant alterations were detected in the expression of inflammasome sensors and caspase-1.
Muscular dystrophy-related inflammatory responses are distinct between skeletal muscle and heart tissue of murine DMD models. Gasdermin D is identified as a robust inflammatory mediator during the disease progression, suggesting its potential as a late stage drug target. Generally, inflammation tends to decrease over time, supporting the clinical observations that the efficacy of anti-inflammatory therapies might be more prominent in the early stage of DMD.

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