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Absence of RAGE in an animal experimental model of Duchenne muscular dystrophy results in reduced muscle necrosis and inflammation

Roberta Sagheddu - Sara Chiappalupi - Laura Salvadori - Francesca Riuzzi - Guglielmo Sorci - Rosario Donato

Università degli Studi di Perugia, Dipartimento di Medicina Sperimentale, Perugia, Italia

Duchenne muscular dystrophy (DMD) is a lethal X-linked neuromuscular disorder characterized by progressive muscle degeneration due to lack of dystrophin, a protein essential for the integrity of sarcolemma during contraction. Chronic inflammation is a hallmark of muscles in DMD subjects, and contributes to progressive muscle wasting. RAGE (receptor for advanced glycation end-products) is a multiligand receptor of the immunoglobulin superfamily involved in physiological and pathological processes including inflammation and myogenesis [1]. While absent in healthy adult muscle tissue, RAGE is expressed in regenerating myofibers during muscle regeneration [2,3], in dystrophic muscles and activated immune cells. To have information about the role of RAGE in the pathophysiology of DMD we generated a double mutant mouse lacking dystrophin and RAGE (mdx/Ager–/– mouse) by cross-breeding dystrophic (mdx) mice with RAGE-null (Ager-/-) mice. Comparison of Quadriceps femoris of mdx and mdx/Ager–/– mice at different ages (i.e., 2, 3, 4 and 5 weeks, and 6 and 12 months of age) showed that the absence of RAGE in dystrophic mice did not affect the onset of the pathology. However, compared with age-matched mdx mice, muscles of 5 week- and 6 and 12 month-old mdx/Ager–/– mice showed i) significantly reduced numbers of necrotic myofibers, ii) a shift towards higher values of the cross-sectional areas (CSA) of myofibers, which was also evident in regenerating (centrally-nucleated) myofibers, and iii) reduced areas of immune cell infiltrate. The expression of MAC3, a marker of activated macrophages, was strongly reduced in muscles of mdx/Ager–/– mice compared with mdx mice. Moreover, muscles of mdx/Ager–/– mice exhibited significantly reduced PAX7+ve and myogenin+ve cell numbers, suggesting a reduced recruitment of muscle precursor cells and more efficient regeneration in dystrophic mice lacking RAGE. Our results suggest that RAGE may sustain inflammatory and degenerative processes in dystrophic muscles, and the inhibition of its expression/activity might represent a potential therapeutic approach in DMD patients.

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References

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Keywords

Duchenne muscular dystrophy; muscle inflammation; RAGE; mdx mice; Ager–/– mice.