Re-expression of RAGE in damaged skeletal muscles: RAGE$^{-/-}$ mice show delayed muscle regeneration

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RAGE (receptor for advanced glycation end products) is a multiligand receptor of the immunoglobulin superfamily playing an important role in innate immunity and in endothelial cell activation and vascular smooth muscle proliferation in atherosclerosis and inflammation (*J Clin Invest 108:949-55, 2001; J Mol Med 83:876-86, 2005*). RAGE is expressed during development, repressed at completion of development and re-expressed in the course of certain pathological conditions (*J Clin Invest 108:949-55, 2001; J Mol Med 83:876-86, 2005*). The expression of RAGE in several cell types during development suggests that RAGE might not be regarded simply as a transducer of inflammatory cues. RAGE is expressed in skeletal myofibers during prenatal and postnatal development being repressed thereafter (*Mol Cell Biol 24:4880-94, 2004*). Also, RAGE is expressed in proliferating myoblasts and myotubes, and once activated by its ligand, HMGB1, it transduces a promyogenic, pro-apoptotic and anti-proliferative signal in myoblasts via a Rac1/Cdc42/MKK6/p38 MAPK pathway (*Mol Cell Biol 24:4880-94, 2004; J Biol Chem 281:8242-53, 2006; Am J Pathol 171:947-61, 2007*). We show here that following damage, RAGE becomes expressed in skeletal muscle satellite (i.e., Pax7^{+}) cells (SCs) and is found in regenerating myofibers (likely as a result of expansion of activated SCs and fusion of RAGE/myogenin-expressing SCs, in the latter case), becoming repressed at completion of regeneration, and that deletion of RAGE results in an elevated SC basal number, a strong infiltration of undamaged tissue with activated SCs at early and late regeneration phases, and delayed muscle regeneration. Also, primary RAGE$^{-/-}$ myoblasts exhibit high Pax7 levels, enhanced proliferation, migration and invasiveness and defective differentiation compared to wild-type myoblasts, and transfection of RAGE$^{-/-}$ myoblasts with full-length RAGE, but not a dominant negative RAGE rescues their myogenic potential. HMGB1/RAGE represses Pax7 expression via a p38 MAPK/myogenin axis in myoblasts with myogenin binding to four (in growth medium) and six (in differentiation medium) recognition sites in the Pax7 promoter and stimulating proteosomal degradation of Pax7. Collectively, our results suggest that HMGB1/RAGE might physiologically contribute to muscle regeneration.

Key words
RAGE, muscle satellite cells, HMGB1, Pax7, myogenin, regeneration