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- Ramírez-Pardo I, Campanario S, Chavda B, Santiago-Fernández O, Flández M, Grima-Terrén M, Cisneros A, Calls-Cobos A, Itzhak DN, Ngo B, Janaki-Raman S, Kantz ED, Ortet L, Diaz A, Lindenau K, Doménech-Fernández J, Gómez-Cabrera MC, Camafeita E, Vázquez J, Martinez-Vicente M, Serrano AL, Perdiguero E, Isern J, Cuervo AM, Muñoz-Cánoves P. Chaperone-mediated autophagy sustains muscle stem cell regenerative functions but declines with age. **Nat Metab.** 2025 Dec;7(12):2571-2588. doi: 10.1038/s42255-025-01411-w. Epub 2025 Dec 3. PMID: 41339968.

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Abstract:

Proteostasis supports stemness, and its loss correlates with the functional decline of diverse stem cell types. Chaperone-mediated autophagy (CMA) is a selective autophagy pathway implicated in proteostasis, but whether it plays a role in muscle stem cell (MuSC) function is unclear. Here we show that CMA is necessary for MuSC regenerative capacity throughout life. Genetic loss of CMA in young MuSCs, or failure of CMA in aged MuSCs, causes proliferative impairment resulting in defective skeletal muscle regeneration. Using comparative proteomics to identify CMA substrates, we find that actin cytoskeleton organization and glycolytic metabolism are key processes altered in aged murine and human MuSCs. CMA reactivation and glycolysis enhancement restore the proliferative capacity of aged mouse and human MuSCs, and improve their regenerative ability. Overall, our results show that CMA is a decisive stem cell-fate regulator, with implications in fostering muscle regeneration in old age.