P038 Premature aging in mice activates a pro-survival metabolic response involving autophagy induction

Guillermo Mariño, Ignacio Varela, Juan Cadiñanos, José M.P. Freije and Carlos López-Otín
Departamento de Bioquímica y Biología Molecular, Facultad de Medicina, Instituto Universitario de Oncología, Universidad de Oviedo, 33006-Oviedo, Spain

Autophagy is a highly regulated intracellular process involved in the turnover of most cellular constituents and in the maintenance of cellular homeostasis. It is well-established that the basal autophagic activity of living cells decreases with age and contributes to the accumulation of damaged macromolecules during aging. Conversely, the activity of this catabolic pathway is required for lifespan extension in animal models such as Caenorhabditis elegans. In this work, we describe the unexpected finding that Zmpste24-null mice with accelerated aging derived from nuclear lamina alterations exhibit an extensive basal activation of autophagy instead of the characteristic decline in this process occurring during normal aging. We also show that this autophagic increase is part of a protective systemic strategy which largely resembles a series of situations reported to prolong lifespan. These metabolic alterations observed in Zmpste24-/- mice are linked to substantial changes in circulating blood parameters, such as leptin, glucose, insulin or adiponectin which in turn lead to peripheral LKB1-AMPK activation and mTOR inhibition and finally, to the marked increase of basal autophagy found in these progeroid mice. On the basis of these results, we propose that nuclear abnormalities causing premature aging in Zmpste24-/- mice trigger an anti-aging metabolic response involving the activation of autophagy. However, the chronic activation of this highly regulated catabolic pathway turns an originally intended pro-survival strategy into a pro-aging mechanism and contributes to the systemic degeneration and weakening observed in progeroid mice.