Abstract EMDS 2019
Category: Homeostasis

A PIWI protein controls the replicative lifespan of alveolar macrophages

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Over time, self-renewing, long-lived cells such as macrophages are subjected to increasingly deleterious insults on cellular processes such as protein homeostasis, energy metabolism or the maintenance of genome integrity. Long-lived, self-renewing cells therefore require mechanisms to contain time-dependent damage and enable an extended lifespan.

PIWI proteins, a sub-family of the Argonaute proteins, are evolutionarily conserved in many long-lived self-renewing cells, particularly in stem cells of lower organisms. In mammals, PIWI function has so far only been demonstrated for spermatogonial stem and progenitor cells. Our study describes for the first time a role for PIWI proteins in mammalian differentiated cells.

We have discovered that a specific PIWI protein is necessary for the self-renewal and extended lifespan of alveolar macrophages in vivo and in vitro. Deletion of this protein shortens the replicative lifespan of alveolar macrophages and leads to a premature aging phenotype. This phenotype is characterized by the upregulation of senescence markers, an aging-specific gene signature and increased DNA damage and.

In conclusion, we show that alveolar macrophages ensure an extended lifespan by up-regulating mechanisms that promote genome integrity. The identification of a new mechanism regulating the lifespan of self-renewing macrophages might be of general importance for the function of resident macrophage populations.